- Altered conscious state
- Papilloedema

Other

- Focal neurological signs such as hemiplegia, dysphasia, ataxia
- Seizures (30%)
- Fever (may be absent)
- Signs of sepsis elsewhere, e.g. teeth, endocarditis

Investigations

- MRI (if available) or CT scan
- FBE, ESR/CRP, blood culture

  Note: Lumbar puncture is contraindicated.
- Consider endocarditis

Management

Management is urgent neurosurgical referral. Aspiration or biopsy is essential to guide antimicrobial treatment, which may (empirically) include metronidazole IV and a cephalosporin, e.g. ceftriaxone IV. Nocardiosis is treated with other antibiotics.

Spinal subdural or epidural abscess[9]

These uncommon focal infections can be extremely difficult to diagnose so an index of suspicion is required to consider such an abscess. The usual organism is *Staphylococcus aureus*.

Clinical features[6]

- Back pain (increasing) ± radiculopathy
- Percussion tenderness over spine
- Evolving neurological deficit, e.g. gradual leg weakness and sensory loss ± fever (may be absent)

Causes

- Associated infection: furuncle, decubitus ulcer, adjacent osteomyelitis, discitis, other

- Back trauma with haematoma
- Post-subdural or epidural anaesthetic block
- One-third is spontaneous

Investigations

- Blood culture
- MRI scan to localise abscess and spinal cord pressure

Management

Urgent neurosurgical referral. Empirical therapy while awaiting culture results may include di/flucloxacillin IV + gentamicin IV or vancomycin IV.

Prion-transmitted diseases[10,11]

Prions are proteinaceous infectious particles devoid of nucleic acid that can present with a wide spectrum of neurological presentations. The feature is transmissible spongiform encephalopathy (TSE), with Creutzfeldt–Jakob disease being the classic example. Other examples of TSE forms affecting humans are variant CJD, kuru (New Guinea) and fatal familial insomnia.

Creutzfeldt–Jakob disease

There are three distinct forms of CJD: sporadic (80–85%), familial (15%) and iatrogenic (1%). The annual incidence is one per million people. Usual transmission is from contaminated human tissue (e.g. corneal graft), cadaver pituitary human gonadotrophin or eating contaminated beef. There is no specific treatment for the disease.

DxT fatigue + psychiatric symptoms + myoclonus → CJD

Clinical features

- Progressive dementia (starts with personality change and memory loss—eventual loss of speech)
- Myoclonus/muscle spasms
- Fatigue and somnolence
- Variable neurological features (e.g. ataxia, chorea)

Diagnosis

- MRI: high signal intensity in thalami
- CSF: positive 14-3-3 protein immunoassay
- EEG
- Brain biopsy after death (ultimate confirmation)

Management

- Supportive: no proven specific treatment

Poliomyelitis[11]

Polio is a highly contagious enterovirus (picornavirus) transmitted through the faeco-oral route and is a specific spinal cord anterior horn cell enterovirus. It remains endemic in the tropics. Most infections (95%) are asymptomatic. *Note:* Myelitis means inflammation of the spinal cord.

Clinical features

- Flu-like syndrome, with fever and sore throat, then
- 'Pre-paralytic' stage: nausea and vomiting, headache, stiff neck (meningeal irritation)
- Paralytic (0.1%): LMN lesion (flaccid paralysis)—may include spinal polio especially of lower limbs and/or bulbar polio ± respiratory failure. No sensory loss.

There are 2 levels of polio: minor (recovery in a few days) and major.

Diagnosis

- Viral studies of throat and faeces—culture and PCR
- Serology
- CSF: leucocytosis, esp. lymphocytes

Management

Symptomatic paralytic patients should be referred to hospital. Prevention is through vaccination.

Post-polio syndrome

Many years after the primary infection (usually 20–40 years) this may present with new muscle weakness and pain as dysfunction of surviving motor neurones develops. Refer to specialist unit.

Non-viral causes of flaccid paralysis[12,13]

- *Borrelia burgdorferi* (Lyme disease), *Mycoplasma*, diphtheria, botulism, transverse myelitis, syphilis

Syphilis

Neurosyphilis can present at any stage of syphilis. The main syphilitic syndromes affecting the CNS are:

- Asymptomatic syphilis: present during the interval between the secondary and tertiary stages of syphilis.
- Meningitis including acute basal meningitis and meningovascular syphilis. The latter can present with a cerebrovascular accident.
- Tabes dorsalis causing meningoradiculitis with degeneration of the parenchyma of the spinal columns of the spinal cord and involvement of the pupils. Features include lightning pains, Charcot joints, ataxia and neurotrophic ulcers, Argyll Robertson pupils.
- General paralysis of the insane with marked personality change, dementia, dysarthria and seizures.

Other infections that can involve the CNS

Tuberculosis

Neurological TB may include tuberculosis meningitis, tuberculoma (presenting as a cerebral abscess), spinal arachnoiditis and spinal involvement (Pott disease). Treatment with multiple antimicrobial agents is usually complex and prolonged.

Human immunodeficiency virus

HIV involvement may be direct with primary infection causing encephalopathy ('AIDS' dementia), myelopathy or acute atypical meningitis in addition to secondary opportunistic infection. The latter include CNS toxoplasmosis, cytomegalovirus, herpes simplex myelitis, varicella zoster and others (see CHAPTER 19).

Helminthic infections

Worm infestations that can (rarely) cause intracerebral lesions through the formation of cysts or granulomas include cysticercosis (tapeworms, e.g. Taenia solium), *Echinococcus* (hydatid) and *Schistosoma.*

Other infections may present with seizures. These include:

- Botulism (see CHAPTER 19)
- Tetanus (see CHAPTER 19)
- Rabies (see CHAPTER 129)
- Hansen disease (leprosy) (see CHAPTER 129)

Patient education resource

Hand-out sheet from *Murtagh's Patient Education* 8th edition:

- Bacterial meningitis and meningococcus

Resource

Central nervous system infections [published 2019]. In: *Therapeutic Guidelines* [digital]. Melbourne: Therapeutic Guidelines Limited; 2019. www.tg.org.au, accessed January 2020.

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21 Connective tissue disease and the systemic vasculitides

In its more aggravated forms diffuse scleroderma is one of the most terrible of all human ills. Like Tithonus to 'wither slowly' and like him to be 'beaten down and marred and wasted', until one is literally a mummy, encased in an ever shrinking, slow contracting skin of steel, is a fate not pictured in any tragedy.

SIR WILLIAM OSLER 1898

The inflammatory connective tissue diseases and the related vasculitides are groups of disorders that are difficult to classify because their causation is generally unknown. They all cause joint and soft tissue inflammation and multiple other possible manifestations that create diagnostic difficulties.

Autoimmune diseases[1]

These are disorders in which the body's immune system damages its own specific organs or systems. The connective tissue diseases are a classic subgroup of autoimmune disease. Rheumatoid arthritis is the most common autoimmune disease. Organ-specific autoimmune diseases include diabetes type 1, Hashimoto thyroiditis, pernicious anaemia, IgA glomerulonephritis, Graves disease, autoimmune hepatitis and myasthenia gravis.

It is convenient to consider a working classification of joint pain (see TABLE 21.1) that includes apparent joint pain (arthralgia), as some of the inflammatory disorders cause problems in the soft tissues around joints (e.g. giant cell arteritis and hydroxyapatite crystallopathy of the tendons around the shoulder joint).

Table 21.1 A classification of rheumatological pain

Hyperacute (red hot) joints	Crystals	Urate: gout Calcium pyrophosphate;

		hydroxyapatite
	Pus	Example: staphylococcal septic arthritis
Inflammation of joints	Symmetrical	Example: rheumatoid arthritis
	Asymmetrical	Example: spondyloarthropathies
Non-inflammatory joint disorder	Typical	Primary osteoarthritis (e.g. in hands)
	Atypical	Example: post-trauma, haemochromatosis
Joint and soft tissue inflammation	Connective tissue disorders	SLE
		Scleroderma
		Polymyositis/dermatomyositis
		Polyarteritis nodosa
	Vasculitides	Giant cell arteritis
		Polymyalgia rheumatica
Non-articular (soft tissue) inflammation	Generalised	Examples: fibrositis, fibromyalgia, polymyalgia
	Localised	Examples: plantar fasciitis, epicondylitis

Source: Dr Stephen Hall, personal communication

Vasculitis is, in fact, a condition common to the connective tissue disorders and to the so-called vasculitides (see TABLE 21.2).

Table 21.2 List of connective tissue disorders and systemic vasculitides

Connective tissue disorders

Rheumatoid arthritis

SLE

Systemic sclerosis/limited scleroderma

Polymyositis/dermatomyositis

Mixed connective tissue disease

Sjögren syndrome
Raynaud phenomenon (including Raynaud syndrome)
Systemic vasculitides
Large vessel predominantly: • giant cell arteritis/temporal arteritis/polymyalgia rheumatica • Takayasu arteritis • Behçet syndrome
Medium vessel (mainly affects visceral vessels): • polyarteritis nodosa • Kawasaki disease • Buerger disease
Small vessel (mainly): • immunoglobulin A vasculitis (Henoch–Schönlein purpura) • hypersensitivity vasculitis • essential cryoglobulinaemia
Antineutrophil cytoplasmic antibody (ANCA) associated: • granulomatosis with polyangiitis (Wegener granulomatosis) • eosinophilic granulomatosis polyangiitis (Churg–Strauss vasculitis) • microscopic polyangiitis

Source: Reproduced with permission from Dr Stephen Hall, personal communication.

A major concern to all is that the diagnosis of these conditions is elusive and often delayed.

Inflammatory connective tissue disease

The term ‘connective tissue disease’ (CTD) is a generic label applied to a group of disorders characterised by systemic inflammation, presumed initiated by an autoimmune response to an autoantigen and perpetuated by unknown factors (both genetic and environmental).[2] If serological markers such as positive ANA and ENA are present they are termed seropositive CTDs. The vasculitides are a variety of CTD.

The CTDs comprise three classic conditions, namely systemic lupus erythematosus (SLE), systemic sclerosis (scleroderma) and the inflammatory muscular conditions polymyositis/dermatomyositis (see FIG. 21.1).[1]

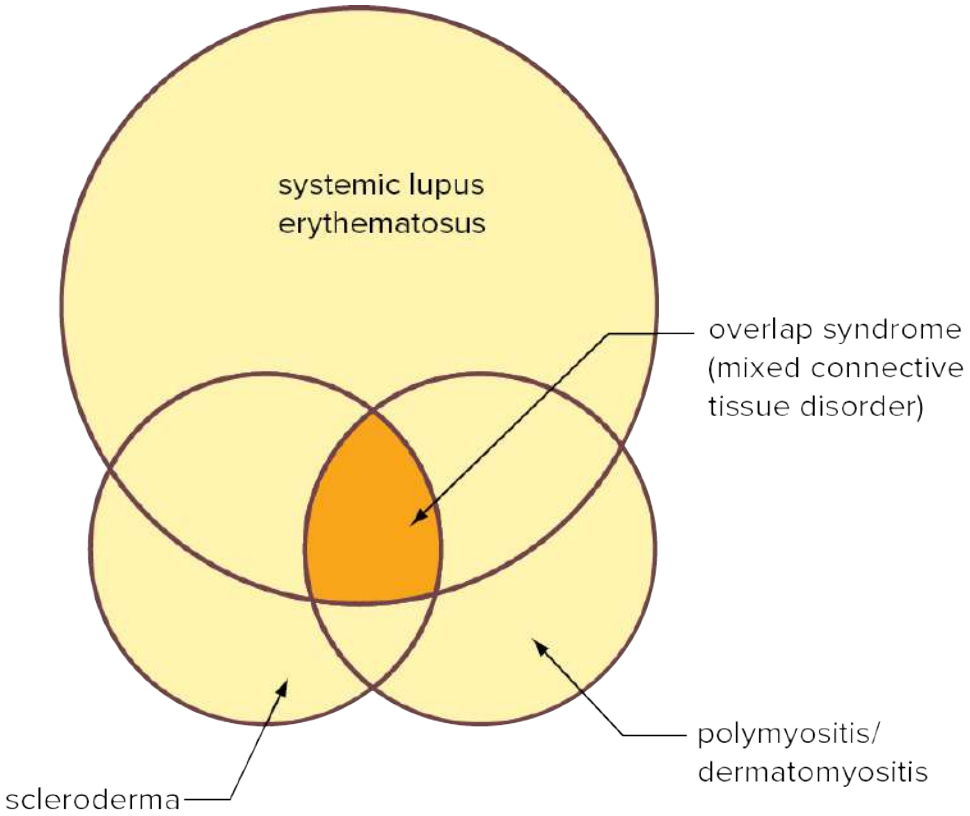

FIGURE 21.1 The classic connective tissue disorders

Mixed connective tissue disorder includes features of all three disorders and is sometimes referred to as ‘overlap’ syndrome. Other related disorders classified as CTDs include sicca syndromes such as Sjögren syndrome and Raynaud syndrome. Rheumatoid arthritis and the spondyloarthropathies are also immune mediated.

Common features include:

- fatigue
- arthralgia or arthritis
- multisystem involvement
- vasculitis
- immunological abnormalities
- sicca (dry skin and mucous membranes)
- Raynaud phenomenon

Investigations in connective tissue disease

The diagnosis is based on the clinical assessment. The rapidly growing list of investigations, particularly those of autoantibodies, can be confusing. Baseline investigations to consider are FBE, ESR, C-reactive protein and rheumatoid factor. The rheumatoid factor can be positive in a great range of disorders, including rheumatoid arthritis, SLE, systemic sclerosis, Sjögren syndrome, chronic liver disease and various viral (e.g. hepatitis), bacterial (e.g. tuberculosis) and parasitic (e.g. malaria) infections. There is usually a low titre, except in rheumatoid arthritis. X-rays and HLA-B_{27} tests are not recommended.

TABLE 21.3 summarises the majority of autoantibodies that can be tested. The antinuclear antibody (ANA) test is a generic term for autoantibodies to several different cellular antigens. It is very sensitive for SLE, but not absolutely specific (false positives occur with viral arthritis and others, e.g. Sjögren). It is especially useful in the young female presenting with fatigue, small joint arthralgia and dermatological features of SLE.

Table 21.3 Autoantibodies in connective tissue disease[2]

Antinuclear antibody (ANA)	High sensitivity 95%, low specificity for SLE
Anti-dsDNA	High sensitivity and specificity for SLE (60%): found in rheumatoid arthritis
Antibodies to extractable nuclear antigens (ENA)	
Smith (Sm)	Highly specific for SLE
U1 RNP	Common in mixed connective tissue disease, SLE
Ro (SSA)	Common in Sjögren syndrome and SLE
La (SSB)	Common in Sjögren syndrome, SLE (15%)
Scl-70 (antitopoisomerase)	Common in 20–30% of patients with scleroderma
Jo1	Common in 30% of patients with polymyositis
Anticentromere Ic	High sensitivity and specificity for CREST syndrome
Antineutrophil cytoplasm (ANCA)	High sensitivity and specificity for Wegener granulomatosis
Antiphospholipids	Diagnostic in antiphospholipid syndrome
Anticardiolipin	
Anti-β_2-GP1 antibodies	

Lupus anticoagulants	Present in 5–10% of SLE
1gM × 1gG aPL	

The more specific antibodies for SLE, namely to double-stranded DNA (dsDNA) and extractable nuclear antigens (ENA), should only be ordered if there is a significantly positive ANA.

Antiphospholipid antibody syndrome

This syndrome may occur with SLE or in isolation and is responsible for recurrent arterial and/or venous thromboembolism, recurrent spontaneous abortions or thrombocytopenia in the presence of antiphospholipid antibodies but without features of SLE. Livedo reticularis, skin ulcers and neuropsychiatric disturbances have also been noted. If suspected, commence aspirin 150–300 mg (o) daily and refer to a consultant, especially during pregnancy.

Systemic lupus erythematosus

SLE (lupus), which is the commonest of the connective tissue disorders, is described as the 'great pretender'.[3] It is a multisystem autoimmune disorder with a wide variety of clinical features that are due to vasculitis (see FIG. 21.2). Arthritis is the commonest feature of SLE (90% of cases). Milder manifestations outnumber more severe forms.

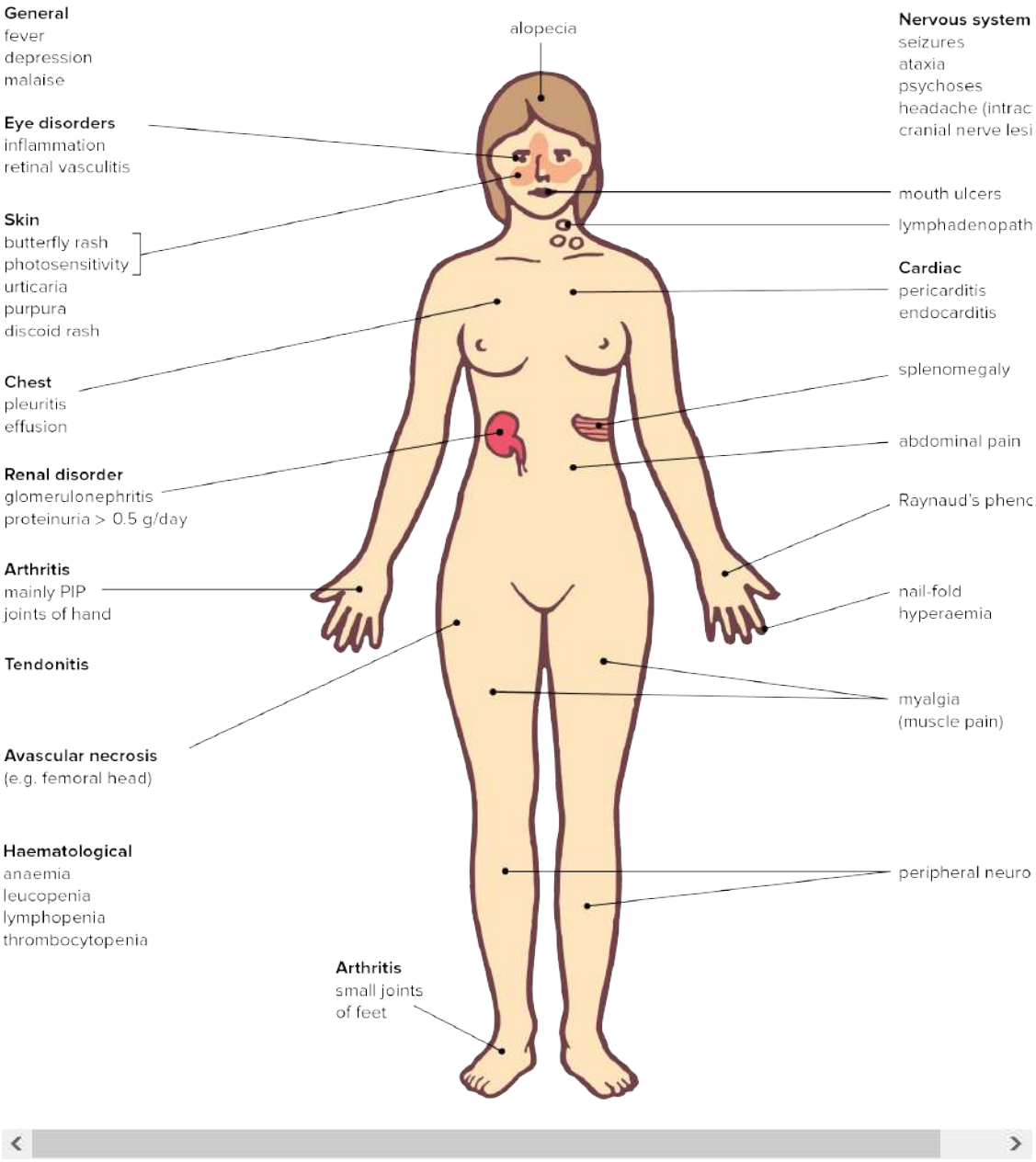

FIGURE 21.2 Clinical features of SLE

Clinical features[4]

- Prevalence about 1 in 1000 of population
- Mainly affects women in 'high oestrogen' period (90% of cases)
- Peak onset between 15 and 45 years

- Fever, malaise, tiredness common
- Multiple drug allergies, e.g. sulfonamides
- Problems with oral contraceptive pill and pregnancy
- Course of remission and flares

DxT polyarthritis + fatigue + skin lesions → SLE

Classification criteria

(SLE = four or more of these 11 criteria)

- Malar (butterfly) rash
- Discoid rash
- Photosensitivity
- Arthritis (symmetric non-erosive arthritis in ≥2 peripheral joints)
- Oral ulcers (usually painless)
- Serositis (pleurisy or pericarditis)
- Kidney features (proteinuria or cellular casts)
- Neurological features (intractable headache, seizures or psychosis)
- Haematological features (haemolytic anaemia, leucopenia, lymphopenia or thrombocytopenia)
- Immunological features (positive anti-dsDNA, antiphospholipid antibodies, anticardiolipin or anti-Sm tests and false-positive syphilis serology)
- Positive antinuclear antibody (ANA) test

Note: Drugs that can cause a lupus-like syndrome are discussed in CHAPTER 25 .

Diagnosis

- ESR/CRP—elevated in proportion to disease activity
- ANA test—positive in 95% (perform first) (key test) but poor specificity

- dsDNA antibodies—90% specific for SLE but present in only 60% (key test)
- ENA antibodies, especially Sm—highly specific
- Rheumatoid factor—positive in 50%
- LE cell test—inefficient and not used

The diagnosis cannot be made on blood tests alone. Supportive clinical evidence is necessary.

For suspected SLE, the recommended approach is to perform an ANA test. If positive, then order dsDNA and ENA antibodies.

Management[5]

- Appropriate explanation, support and reassurance, use of sunscreens (refer to CHAPTER 113)
- Refer to consultant rheumatologist for shared care in a multidisciplinary team: urgent if evidence of severe organ damage

Treatment[2]

Based on severity and organ involved.

- Mild: NSAIDs (for arthralgia)
- Moderate (especially skin, joint serosa involved): low-dose antimalarials (e.g. hydroxychloroquine up to 6 mg/kg once daily) (e.g. 400 mg (o) daily for 3 months, then 200 mg daily long term)

Rule: treat early and avoid long-term and unnecessary steroid use.

- Severe: corticosteroids are the mainstay (e.g. prednisolone initially 25–60 mg (o) daily then 7.5–15 mg (o) daily); immunosuppressive steroid-sparing drugs (e.g. azathioprine, methotrexate with folic acid, bDMARDs (e.g. rituximab, belimumab) may be used for severe arthralgia and IV or oral cyclophosphamide for organ damage
- Avoid drugs in those in clinical remission and with normal complement levels.
- Avoid excessive sunlight.
- Other treatments, such as plasma exchange and immunosuppressive regimens, are available for severe disease.
- Keep in mind antiphospholipid antibody syndrome, especially with recurrent fetal loss and

thrombotic episodes.

Prognosis

The course of SLE is usually chronic, relapsing and unpredictable.

Systemic sclerosis (scleroderma)

This can present as a polyarthritis affecting the fingers in 25% of patients, especially in the early stages. Soft tissue swelling produces a ‘sausage finger’ pattern. Scleroderma mainly affects the skin with fibrotic thickening. It presents with Raynaud phenomenon in over 85% of patients (see FIG. 21.3).

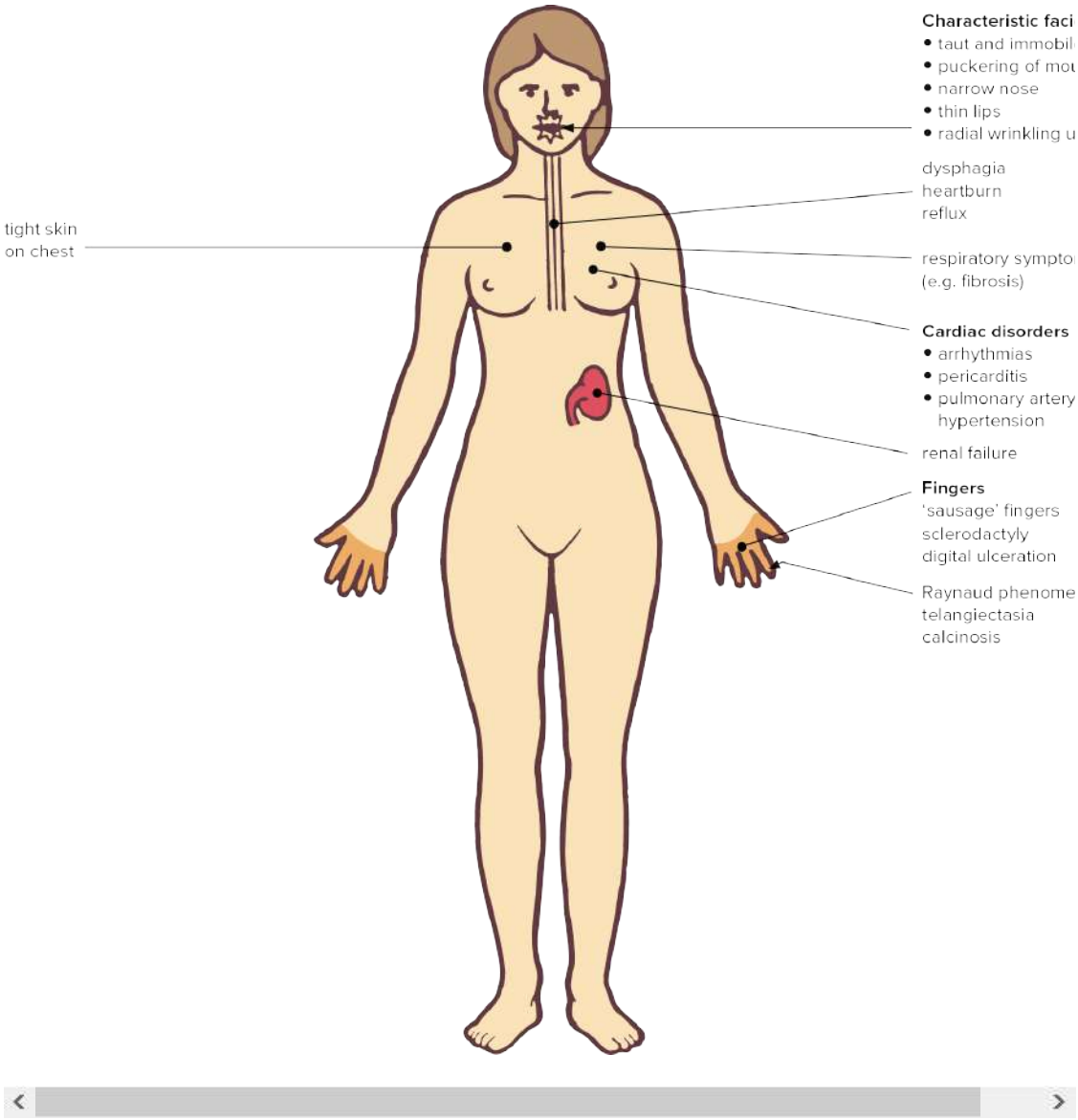

FIGURE 21.3 Clinical features of scleroderma

There are three clinical variants:

1 limited cutaneous disease, e.g. morphea

2 cutaneous with limited organ involvement (CREST)

3 diffuse systemic disease (systemic sclerosis)

Clinical features[2,6]

- Female to male ratio = 3:1
- A progressive disease of multiple organs
- Raynaud phenomenon
- Stiffness and tightness of fingers and other skin areas (see FIG. 21.4)
- 'Bird-like' facies (mouth puckered)
- Dysphagia and diarrhoea (malabsorption)
- Oesophageal dysmotility
- Respiratory symptoms: pulmonary fibrosis
- Cardiac symptoms: vasculopathy, pericarditis, pulmonary arterial hypertension, etc.
- Look for tight skin on chest (Roman breastplate)

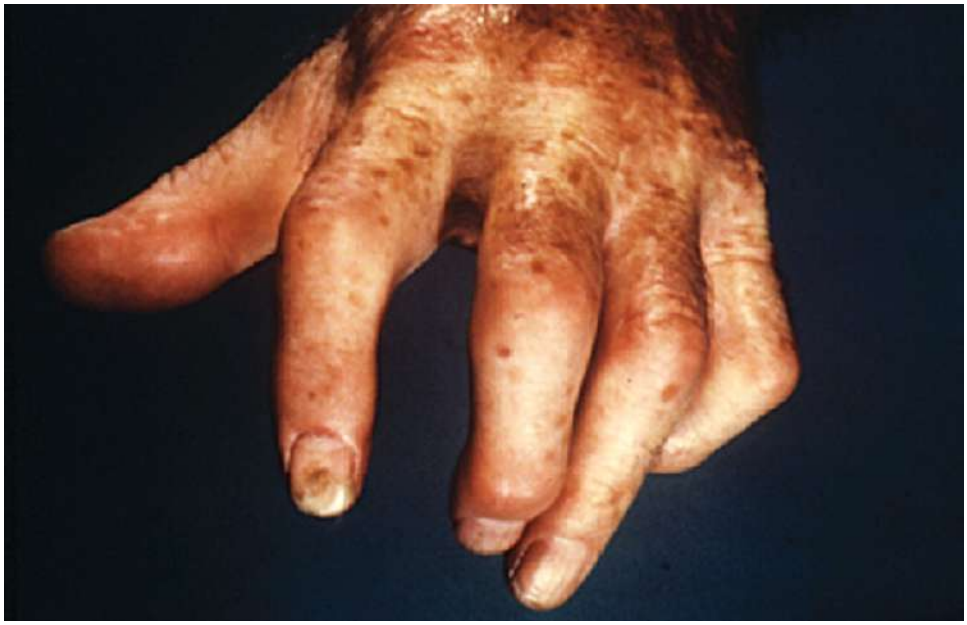

FIGURE 21.4 Scleroderma showing stiff, taut skin of fingers

DxT finger discomfort + arthralgia + GORD (± skin tightness) → scleroderma

Diagnosis[2,6]

- ESR may be raised
- Normocytic normochromic anaemia may be present
- ANA test—up to 90% positive (relatively specific)
- Rheumatoid factor—positive in 30%
- Anticentromere antibodies—specific (positive in 90% with limited disease and 5% with diffuse)
- Antitopoisomerase I (anti-Scl-70) antibody is specific but only positive in 20–30%
- Skin biopsy—increase in dermal collagen

Management

- Refer to consultant or specialised unit for shared and multidisciplinary care

- Empathic explanation, patient education
- Analgesics and NSAIDs for pain
- Avoid vasospasm (no smoking, beta blockers, ergotamine); calcium-channel blockers such as nifedipine may help Raynaud
- Monitor blood pressure
- Treat malabsorption if present; skin emollients
- D-penicillamine can help if there is significant systemic or cutaneous involvement[7]

Localised scleroderma

- Morphea—plaques of erythema with violaceous periphery, feels hard; mainly on trunk
- Linear—may be ‘en coup de sabre’ (a sabre stroke)

CREST syndrome

Clinical features

- Calcinosis
- Raynaud phenomenon
- Oesophageal dysmotility
- Sclerodactyly
- Telangiectasia
- Anticentromere antibody (invariably positive)

Polymyositis and dermatomyositis

Polymyositis is an uncommon systemic disorder with inflammation of skin and muscle whose main feature is symmetrical muscle weakness and wasting involving the proximal muscles of the shoulder and pelvic girdles.

Clinical features

- Any age group
- Peak incidence 40–60 years

- Female to male ratio = 2:1
- Muscle weakness and wasting proximal limb muscles
- Main complaint is weakness
- Muscle pain and tenderness in about 50%
- Arthralgia or arthritis in about 50% (resembles distribution of rheumatoid arthritis)
- Dysphagia in about 50% due to oesophageal involvement
- Raynaud phenomenon
- Consider associated malignancy: lung and ovary

DxT weakness + joint and muscle pain + violaceous facial rash → dermatomyositis

The rash

The distinctive rash shows features of photosensitivity. There is heliotrope (violet) discolouration of the eyelids (see FIG. 21.5), forehead and cheeks, and possible erythema resembling sunburn and peri-orbital oedema. A classic sign is a macular rash over the upper chest, back and shoulders. There is a characteristic rash on the hands, especially the fingers and nail folds. The knees and elbows are commonly involved.

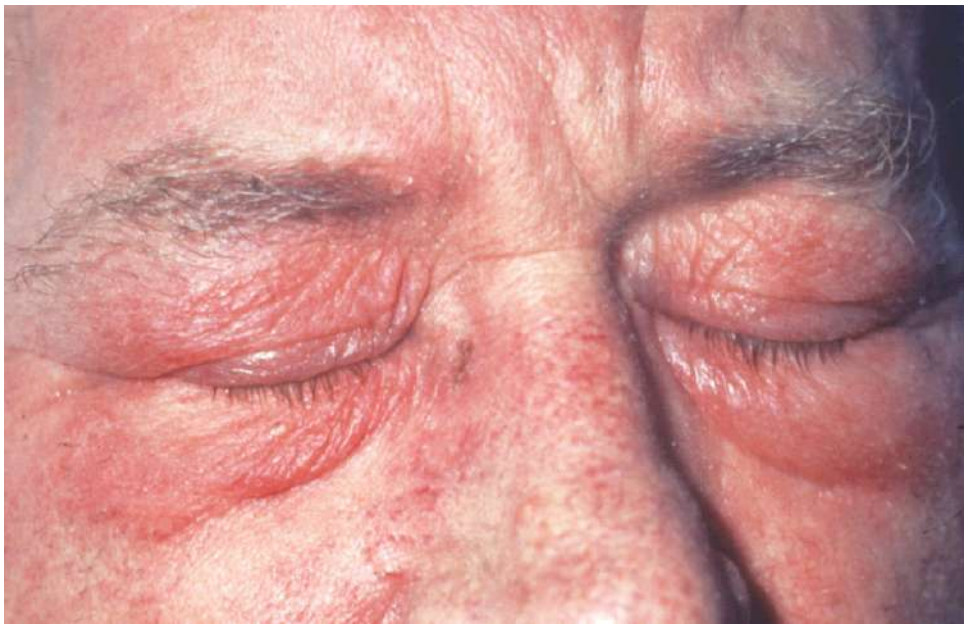

FIGURE 21.5 Heliotrope discolouration of eyelids in dermatomyositis

Differential diagnosis: statin-induced necrotising myositis (↑ CK levels).

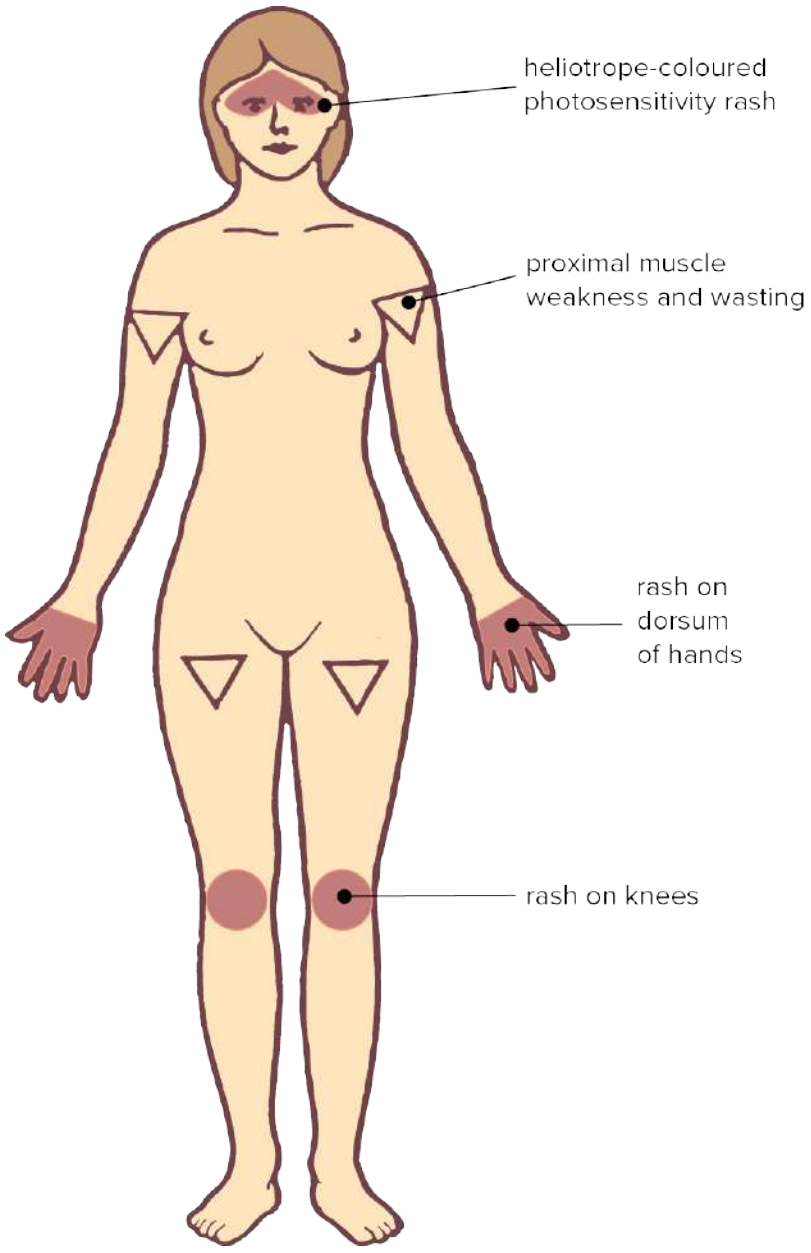

FIGURE 21.6 Heliotrope discolouration of eyelids in dermatomyositis

Diagnosis

- Muscle enzyme studies (serum creatine kinase and aldolase)
- Antibody associations, e.g. anti-Jo1

- Biopsies—skin and muscle
- EMG studies—show characteristic pattern

Treatment includes corticosteroids, hydroxychloroquine and cytotoxic drugs. Early referral is appropriate. Malignancy surveillance is important due to an increased risk of common cancers.

Sjögren syndrome

The underdiagnosed syndrome of dry eyes (keratoconjunctivitis sicca) in the absence of rheumatoid arthritis or any other autoimmune disease is known as primary Sjögren syndrome (SS). There is lymphoid infiltration of the exocrine glands:

- primary SS—limited or multisystem
- secondary SS—occurs in association with other CTDs including rheumatoid arthritis (accounts for 50%) or systemic sclerosis

Clinical features

- Fatigue
- Sicca (xerostomia, dry eyes, dry vagina)
- Difficulty swallowing food
- Increased dental caries; denture dysfunction
- Salivary gland enlargement; reduced salivation
- Xerotrachea → chronic dry cough; hoarseness
- Dyspareunia
- Arthralgia ± non-erosive arthritis

Although considered benign, it can transform into non-Hodgkin lymphoma (approx. 1 in 44 cases).

DxT dry eyes + dry mouth + arthritis → Sjögren syndrome

Diagnosis

- Autoantibody tests—positive ANA(ENA), Ro (SSA), La (ss-B)
- Elevated ESR, +ve RA factor, possibly anaemia

- Schirmer tear test (measures conjunctival dryness)

Management

- Referral to rheumatologist
- Treatment is symptomatic for dry eyes, mouth and vagina; arthralgia
- NSAIDs, hydroxychloroquine or steroids for arthritis

Raynaud phenomenon[2]

(Refer also to CHAPTER 53 .)

It is classified as either primary (without associated disease) or secondary (when associated with any CTD).

Patients with primary Raynaud may progress to a CTD but the likelihood is low (5–15%) and the delay to diagnosis is long (average of 10 years).[2] The more severe the Raynaud, the more likely it is to progress to systemic disease.

Raynaud is a clinical syndrome of episodic arteriolar vasospasm usually involving the fingers and toes (one or two at a time). It may also involve the nose, ear or nipple.

The vasculitides[2]

The vasculitides or vasculitis syndromes are a heterogeneous group of disorders involving inflammation and necrosis of blood vessels, the clinical effects and classification depending on the size of the vessels involved (see TABLE 21.2). They are a variety of CTD.

Small vessel vasculitis is the common type encountered in practice. Medium vessel vasculitis includes polyarteritis nodosa and large vessel vasculitis includes giant cell arteritis.

Symptoms suggestive of vasculitis include systemic (malaise, fever, weight loss, arthralgia), skin lesions (e.g. purpura, ulcers, infarction), respiratory (wheeze, cough, dyspnoea), ENT (epistaxis, sinusitis, nasal crusting), chest pain (angina), kidney (haematuria, proteinuria, CKF) and neurological (various, e.g. sensorimotor).

Small vessel vasculitis

This is associated with many important disorders, such as rheumatoid arthritis, SLE, bacterial endocarditis, Henoch–Schönlein purpura and hepatitis B. Skin lesions are usually associated with these disorders and the most common presentation is painless, palpable purpura, such as occurs with Henoch–Schönlein purpura.

Practice tip

Consider vasculitis in any unidentified multisystem disorder.

Rarer but deadly causes

The major vasculitides called systemic vasculitides are polyarteritis nodosa (PN), polymyalgia rheumatica (PR), giant cell arteritis (GCA), Takayasu arteritis, Behçet syndrome, Churg–Strauss vasculitis and Wegener granulomatosis (WG). Unfortunately, many patients die or become terminally ill before the diagnosis is suspected.

Practice tip

If a serious ANCA-associated disease is suspected, early diagnosis is life-saving because of sinister kidney damage. Perform a urine examination for haematuria and proteinuria. If positive, order an ANCA test. If positive, refer urgently.

Henoch–Schönlein purpura

More details are presented about this vasculitis disorder in CHAPTER 29 .

Takayasu arteritis[2]

Known as ‘pulseless disease’ or ‘aortic arch syndrome’, this vasculitis involves the aortic arch and other major arteries. It typically affects young Japanese female adults. Features include absence of peripheral pulses and hypertension.

Polyarteritis nodosa

The hallmark of PN is necrotising vasculitis of the small and medium arteries leading to skin nodules, infarctive ulcers and other serious manifestations. The cause is unknown but associations are found with drug abusers (especially adulterated drugs), B-cell lymphomas, other drugs and hepatitis B surface antigen. It should be suspected in any multisystemic disease of obscure aetiology.

Clinical features

- Young to middle-aged men
- Constitutional symptoms: fever, malaise, myalgia, weight loss

- Migratory arthralgia or polyarthritis
- Subcutaneous nodules along arterial lines
- Livedo reticularis and skin ulcers
- Kidney impairment and hypertension
- Cardiac disorders: arrhythmia, failure, infarction
- Diagnosis confirmed by biopsy or angiogram
- ESR raised
- Treatment is with corticosteroids and immunosuppressants. Refer for specialist care. Meticulous control of blood pressure is essential.
- Death is usually from kidney disease

 **DxT** arthralgia + weight loss + fever (± skin lesions) → polyarteritis nodosa

Giant cell arteritis and polymyalgia rheumatica

The basic pathology of this very important disease complex is GCA (synonyms: temporal arteritis, cranial arteritis). The clinical syndromes are polymyalgia rheumatica and temporal arteritis. The clinical manifestations of polymyalgia rheumatica invariably precede those of temporal arteritis, of which there is about a 50% association. The diagnosis is based on clinical grounds. No definite cause has been found.

Urgently refer any patient with giant cell arteritis.

Clinical features (polymyalgia rheumatica)

- Pain and stiffness in proximal muscles of shoulder and pelvic girdle, cervical spine (refer FIG. 21.7)
- Symmetrical distribution
- Typical ages 60–70 years (rare <50)
- Both sexes: more common in women
- Early morning stiffness lasting >45 minutes
- May be systemic symptoms: weight loss, malaise, anorexia, fever

- Painful restriction of movement of shoulders and hips (other joints not usually involved)
- Signs may be absent later in day
- ESR typically >40 but may be normal

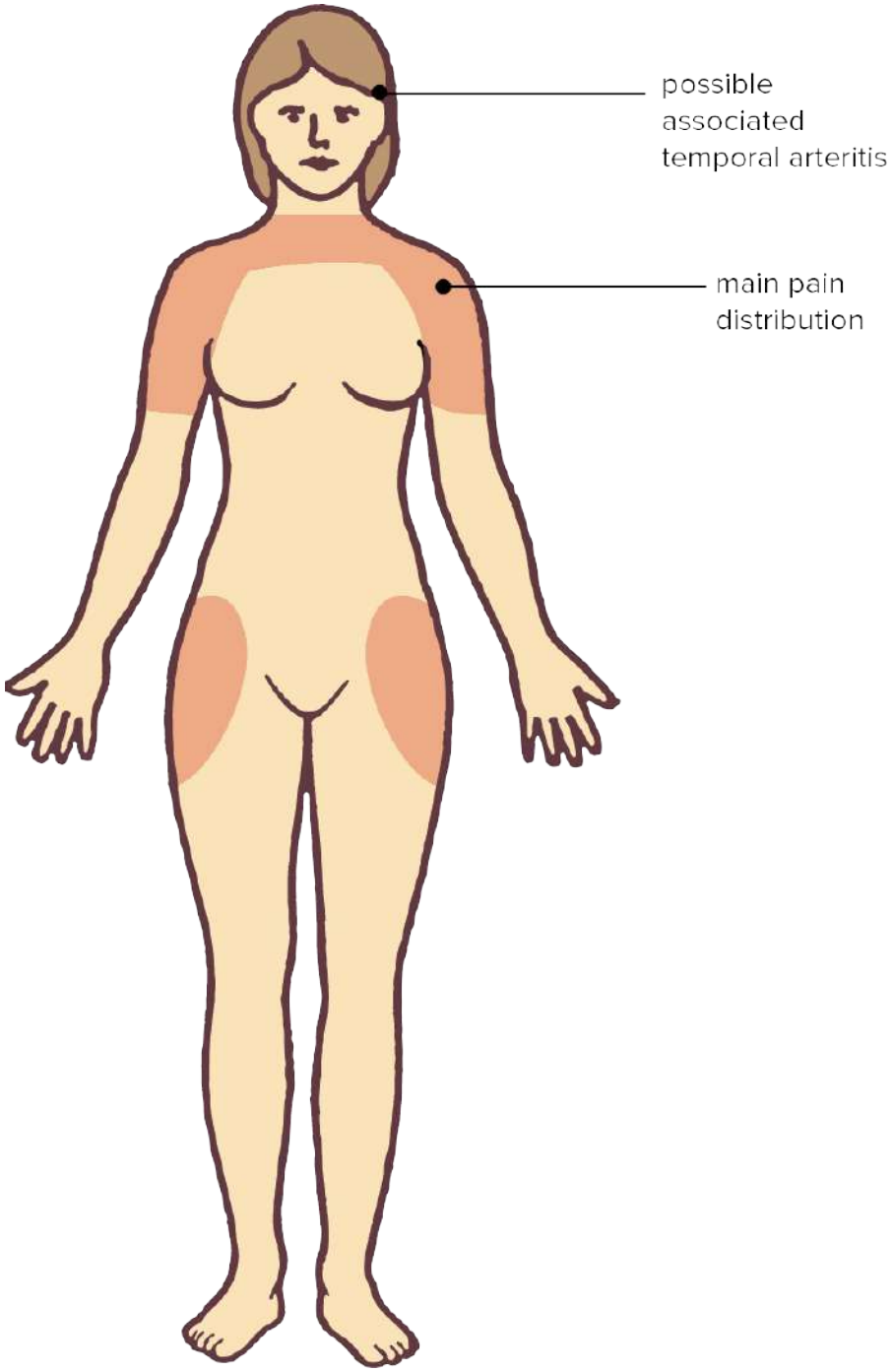

FIGURE 21.7 Polymyalgia rheumatica: typical sites of areas of pain and stiffness

Differential diagnosis: polymyalgic onset rheumatoid arthritis.

DxT malaise + painful shoulder girdle + morning stiffness (>50 years) → polymyalgia rheumatica

Clinical features (temporal arteritis)

- Age >50
- New headache—unilateral, throbbing (see CHAPTER 45)
- Visual symptoms, e.g. diplopia
- Temporal artery tenderness
- Polymyalgia rheumatica
- Loss of pulsation of temporal artery
- Jaw claudication
- Biopsy of temporal artery (5 cm) is diagnostic

DxT fatigue/malaise + headache + jaw claudication → temporal arteritis

Investigation

- No specific test for polymyalgia rheumatica
- ESR—extremely high, >50 mm/hr
- C-reactive protein—elevated
- Mild anaemia (normochromic, normocytic)

Treatment for uncomplicated disease[8]

Refer any patient with suspected GCA urgently.

Prednisolone

- Starting dose:

  temporal (giant cell) arteritis: 1 mg/kg (usually 60 mg) (o) daily initially for 4 weeks (+ aspirin 100 mg/day) then gradual reduction according to ESR/CRP

  polymyalgia rheumatica: 15 mg (o) daily for 4 weeks, then reduce daily dose by 2–5 mg every 4 weeks to 10 mg/day, then 1 mg every 4–8 weeks to zero

- Taper down gradually to the minimum effective dose (often <5 mg daily) according to the clinical response and the ESR and CRP. Aim for treatment for 2 years. Relapses are common.
- If complicated (e.g. evolving visual loss) give IV methylprednisolone for 3 days prior to oral agents.

Other drugs

- Azathioprine or methotrexate can be used as steroid-sparing agents.

> **Practice tip**
>
> In giant cell arteritis, a delay in diagnosis after presenting with amaurosis fugax and non-specific symptoms can have tragic consequences, in the form of ischaemic events such as blindness and strokes.

Behçet syndrome[2]

Behçet syndrome is a systemic (multiorgan) vasculitis of unknown aetiology, affecting veins and arteries of all sizes. The main feature is painful oral ulceration and the hallmark is the ‘pathergy’ reaction whereby simple trauma such as a pinprick can cause a papule or pustule to form within a few hours at the site.

Clinical features

- Male to female ratio = 2:1
- Recurrent oral and/or genital ulceration
- Arthritis (usually knees)
- Skin changes, e.g. erythema nodosum
- Ocular symptoms—pain, reduced vision, floaters (ocular inflammation)

There is no specific diagnostic test.

Associated problems/complications: repeated uveitis and retinitis → blindness, colitis, venous thrombosis, meningoencephalitis.

Treatment: high-dose steroids and specific ulcer treatment. DMARDs or bDMARDs may be required.

Practice tip

Patients with Behçet eye disease should be referred promptly for an ophthalmological opinion, which may be sight-saving.[2]

Granulomatosis[2] with polyangiitis

Previously called ‘Wegener granulomatosis’, this rare vasculitis of unknown cause has a classic triad: upper respiratory tract (URT) granuloma, fleeting pulmonary shadows (nodules) and glomerulonephritis. Without treatment it is invariably fatal and sometimes the initial diagnosis is that made at autopsy. It is difficult to diagnose, especially as the patient (usually young to middle-aged) presents with a febrile illness and respiratory symptoms, but early diagnosis is essential. It usually gets confused with benign nasal conditions.

Clinical features

- Adolescence to elderly, mean age 40–45 years
- Constitutional symptoms (as for PN)
- Lower respiratory tract (LRT) symptoms (e.g. cough, dyspnoea)
- Oral ulcers
- Upper respiratory symptoms: rhinorrhoea, epistaxis, sinus pain, nasal septum loss, ear dysfunction
- Eye involvement—orbital mass
- Polyarthritis
- Kidney involvement—usually not clinically apparent (about 75% get glomerulonephritis)
- Chest X-ray points to diagnosis—multiple nodes, cavitations
- Antineutrophil antibodies (c-ANCA) are a useful diagnostic marker (not specific)
- Diagnosis confirmed by biopsy, usually an open lung biopsy

- Better prognosis with early diagnosis and treatment with appropriate DMARD

DxT malaise + URTs (e.g. rhinitis, sinusitis) + LRTs (e.g. wheeze, cough) → granulomatosis with polyangiitis

DxT asthma + rhinitis + vasculitis + hypereosinophilia → Churg−Strauss vasculitis

Patient education resources

Hand-out sheets from *Murtagh's Patient Education* 8th edition:

- Rheumatoid arthritis
- Systemic lupus erythematosus

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22 Neurological dilemmas

The disease is of long duration; to connect, therefore, the symptoms which occur in its later stages with those which mark its commencement, requires a continuance of observation of the same case, or at least a correct history of its symptoms, even for several years.

JAMES PARKINSON (1755–1824), *AN ESSAY ON THE SHAKING PALSY*

In general practice there are many neurological problems that present a diagnostic dilemma, with some being true masquerades for the non-neurologist. This applies particularly to various seizure disorders, space-occupying lesions in the cerebrum and the cerebellum, demyelinating disorders, motor neurone disorders and peripheral neuropathies.

The most common pitfall that occurs with neurological disorders is misdiagnosis, and the most common reason for misdiagnosis is an inadequate history. Failure to appreciate the neurological meaning of points elicited during the history is another reason for misdiagnosis.

Some very important neurological disorders are presented in this section: Parkinson disease, which is common and can be easily misdiagnosed, especially when the classic ‘pill rolling’ tremor is absent or mild; multiple sclerosis (MS), because it is difficult to diagnose initially; and acute idiopathic demyelinating polyneuropathy (Guillain–Barré syndrome), because it can be rapidly fatal if misdiagnosed. MS can masquerade as almost anything—‘If you don’t know what it is, think of MS.’

Another brain teaser for the family doctor is to diagnose accurately the various types of epilepsy. The most commonly misdiagnosed seizure disorders are complex partial seizures or atypical generalised tonic–clonic seizures (see CHAPTER 43).[1] Even more difficult is the differentiation of real seizures from pseudo- or non-epileptic seizures. As a rule, neurological conditions should be referred early for specialist management.

Diplopia

The onset of diplopia (double vision) in adults is often acute, very distressing and invariably easy to diagnose. It is invariably binocular, which usually results from extraocular muscular imbalance or weakness. The type of binocular diplopia—vertical, horizontal or oblique—provides clues in identifying the affected muscle. Monocular diplopia is double vision that

occurs in one eye when the other is covered. It arises from the eye itself.

The diagnostic strategy model is outlined in TABLE 22.1 .

Table 22.1 Diplopia: diagnostic strategy model

Probability diagnosis?

Binocular:

- ocular nerve palsy (3, 4, 6)—various causes
- CVA/TIA
- opthalmoplegic migraine
- physiological (disparateness)
- drug effect, e.g. alcohol, benzodiazepines

Monocular:

- eye disorder, e.g. cataract, refractive error, cornea

Serious disorders not to be missed

Vascular:

- CVA/TIA

Infection:

- intra-ocular abscess
- sinusitis
- botulism
- HIV/AIDS

Tumour/cancer:

- involving 3, 4 or 6 cranial nerves

Other:

- facial bone trauma/head injury
- Guillain–Barré syndrome

Pitfalls (often missed)

Any orbital infiltration

Rarities:

- multiple sclerosis
- myasthenia gravis
- orbital myositis
- cavernous sinus thrombosis
- Wernicke encephalopathy

Seven masquerades checklist

Diabetes: mononeuritis
Drugs, e.g. sedatives, opioids, alcohol
Thyroid/other endocrine—hyperthyroid?

Is the patient trying to tell me something?

A consideration if nil findings
Some cases are idiopathic

Diagnosis

Diplopia should be differentiated from blurred vision, which is like ‘ghosting’ on a TV screen.

Office tests

Test for double vision with each eye occluded. If diplopia persists, it is uniocular. If, however, double vision disappears when either eye is covered, there is a defect of one of the muscles moving the eyeball. Determine whether diplopia occurs in any particular direction of gaze. It is most marked when moved in the direction of action of the weak muscle. Ask the patient to follow your finger, red pin or penlight with both eyes and move it in an H pattern.

- 3rd nerve—eye turned out: divergent squint
- 6th nerve—failure to abduct: convergent squint (see FIG. 22.1)

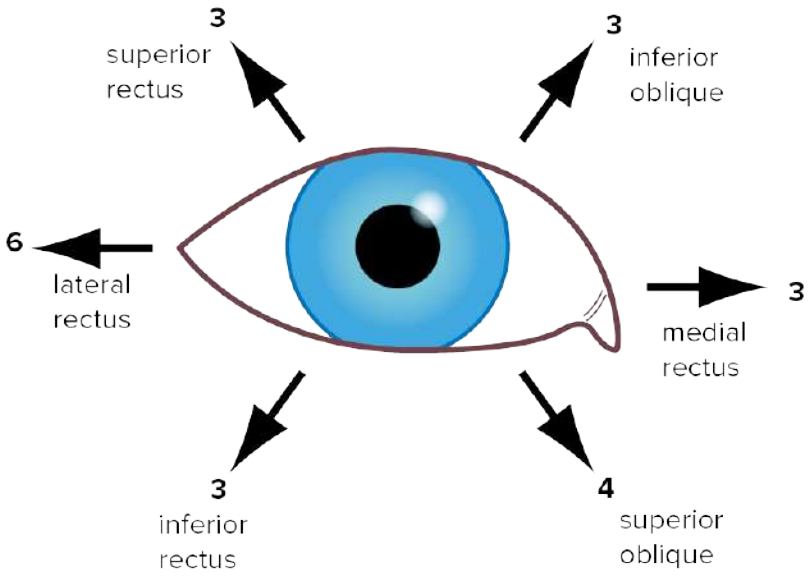

FIGURE 22.1 Direction of movement of the right eye indicating the responsible extraocular muscles and cranial nerves (3 = oculomotor, 4 =

trochlear, 6 = abducens)

Key investigations

- Nil for most cases
- First line: urinalysis, blood sugar, FBE, ESR/CRP (?arteritis)
- Consider: TFTs, imaging if indicated (refer)
- ESR (consider arteritis)

Note:

- Exclude 3rd and 6th nerve palsies as they may be secondary to life-threatening conditions.
- Refer urgently if diplopia is binocular, of recent onset and persistent.

Motor weakness

Muscle weakness is a common feature of many disorders ranging from neurogenic and myogenic disorders to metabolic and psychiatric. It is very important clinically to be able to differentiate upper motor neurone (UMN) signs from lower motor neurone (LMN) signs (see TABLE 22.2).

Table 22.2 Clinical differences between a lower motor neurone lesion and an upper motor neurone lesion

Manifestation	UMN	LMN
Weakness	Present	Present
Wasting	Absent or mild	Marked
Power	Reduced	Reduced
Tone	Usually increased (spastic paralysis) ± clonus	Absent or decreased (flaccid paralysis)
Fasciculations	Absent	May be present
Reflexes	Brisk tendon reflexes Abdominal absent Extensor plantar response	Absent or diminished Downgoing plantar response

Upper motor neurone lesions

UMN signs occur when a lesion has interrupted a neural pathway at a level above the anterior horn cell.[2] Examples include lesions in motor pathways in the cerebral cortex, internal capsule, brain stem or spinal cord.

Clinical examples include stroke (thrombosis, embolism or haemorrhage in the brain), tumours of the various pathways, demyelinating disease (e.g. multiple sclerosis) and infection (e.g. HIV).

Lower motor neurone lesions

LMN signs occur when a lesion interrupts peripheral neural pathways from the anterior horn cell, that is, the spinal reflex arc.

Clinical examples include peripheral neuropathy, Guillain–Barré syndrome, poliomyelitis and a thickened peripheral nerve (e.g. leprosy).

Note: A spinal cord lesion causes LMN signs at the level of the lesion and UMN signs below that level.

Neurogenic and myogenic muscle weakness

It is also important to distinguish between weakness caused by neurological conditions, especially those causing LMN lesions and muscular disorders. The features are compared in TABLE 22.3 . Myotonia is muscle stiffness with difficulty in relaxation after voluntary contraction, e.g. dystrophia myotonica (myotonic dystrophy) (see TABLE 22.7).

Table 22.3 Muscle weakness: main clinical differences between neurogenic and myogenic lesions

Myogenic weakness	Neurogenic weakness
Reflexes often present despite severe weakness	Reflexes often absent despite minimal weakness
Weakness out of proportion to wasting	Wasting out of proportion to weakness
Sensation normal	± Sensory changes
No fasciculation (polymyositis may cause fasciculation)	Fasciculation a feature

Motor neurone disease (MND)

MND is a progressive neuromuscular disorder resulting in muscular limb and bulbar weakness due to death of motor neurones in the brain, brain stem and spinal cord. The sensory system is

not involved, nor the cranial nerves to the eye muscles. Five to 10% of MND is inherited with an autosomal dominant pattern; the rest is sporadic. The three main patterns are:

1. amyotrophic lateral sclerosis (Lou Gehrig disease)—combined LMN muscle atrophy plus UMN hyper-reflexia, leading to progressive spasticity. This is the most common type.
2. progressive muscle atrophy—wasting beginning in the distal muscles; widespread fasciculation
3. progressive bulbar (LMN) palsy and pseudobulbar palsy (LMN lesions in the brain stem motor nuclei). Results in wasted fibrillating tongue, weakness of chewing and swallowing, and of facial muscles.

Symptoms and signs

- Weakness or muscle wasting—first noticed in hands (weak grip) or feet
- Stumbling (spastic gait, foot drop)
- Difficulty with swallowing
- Difficulty with speech, for example, slurring, hoarseness
- Fasciculation (twitching) of skeletal muscles and fibrillating tongue
- Cramps
- Emotional instability, depression
- ± Muscle pain

The diagnosis is clinical. There are no diagnostic tests, but neurophysiological tests and MRI of the brain and cord help differentiate from other conditions.

MND is incurable and progresses to death usually within 3–5 years from ventilatory failure/aspiration pneumonia.

No treatment is proven to influence outcome although riluzole, a sodium channel blocker, appears to slow progression slightly. Baclofen 10 mg bd may help symptoms of cramp. Botulinum toxin may help spasticity and propantheline or amitriptyline for drooling. Multidisciplinary care is essential. Management is supportive.

Tremor

Tremor is an important symptom to evaluate correctly. The diagnostic model, including causes is presented in TABLE 22.4 . A common pitfall in patients presenting with tremor is for Parkinson disease (PD) to be diagnosed as benign essential tremor and for benign essential tremor to be

diagnosed as PD, but the clinical distinction is not always easy and it must be remembered that as many as 20% will experience both concurrently.

Table 22.4 Tremor: diagnostic strategy model

Probability diagnosis

Benign essential (familial) tremor
Senility
Physiological
Parkinson disease (including drug-induced PD)
Functional or psychogenic, e.g. anxiety/emotional
Alcohol

Serious disorders not to be missed

Vascular:

- cerebral infarction → Parkinsonism

Infection:

- meningoencephalitis
- tertiary syphilis

Cancer/tumour:

- cerebral tumour (frontal lobe)

Other:

- toxicity from organ failure (kidney, liver, lungs)

Pitfalls often missed

Cerebellar disease
Multiple sclerosis
Fragile X sydrome
Alzheimer dementia
Uraemia of kidney failure
CO_2 retention of respiratory failure
Hepatic failure

Rarities:

- hepatolenticular degeneration (Wilson disease)
- lesion of midbrain (red nucleus)

Seven masquerades checklist

Drugs (withdrawal, e.g. opioids, stimulants, illicit agents, benzodiazepines, caffeine, alcohol; adverse reactions,

Key history

- Nature of the tremor: resting, intention, pill-rolling, flapping (asterixis)
- Family history of tremor
- Evidence of cognitive changes or other neurological problems
- Systems review: respiratory, cardiac, liver, kidneys

Key examination

- General appearance and vital signs
- Respiratory, cardiac, abdominal (esp. liver) and neurological examination

Key investigations

According to above:

- FBE and ESR
- thyroid function tests (hyperthyroidism), LFTs, pulse oximetry/blood gases
- drug screen
- MRI

e.g. sympathomimetics, β agonists, lithium, phenothiazines, valproate, amiodarone, alcohol) Thyroid/other endocrine (hyperthyroidism, hypoglycaemia, phaeochromocytoma)	**Diagnostic tips** • Essential tremor eased by a small quantity of alcohol • Triad of essential tremor: postural or action tremor, head tremor, positive family history • Look for Parkinson tetrad: resting tremor, bradykinesia, rigidity, postural instability • Look for cerebellar tetrad: intention tremor, dysarthria, nystagmus, ataxic gait • Typical drugs that induce Parkinsonism are phenothiazine, butyrophenones, reserpine
Is the patient trying to tell me something? Anxiety (esp. hyperventilation)	

Resting tremor—Parkinsonian

The tremor of PD is present at rest. The hand tremor is most marked with the arms supported on the lap and during walking. The characteristic movement is ‘pill-rolling’ where movement of the fingers at the metacarpophalangeal joints is combined with movements of the thumb. The resting tremor decreases on finger–nose testing. The best way to evoke the tremor is to distract the patient, such as focusing attention on the left hand with a view to ‘examining’ the right hand or by asking the patient to turn the head from side to side.

Action or postural tremor

This fine tremor is noted by examining the patient with the arms outstretched and the fingers apart. The tremor may be rendered more obvious if a sheet of paper is placed over the dorsum of the hands. The tremor is present throughout movement, being accentuated by voluntary contraction.

Causes

- Essential tremor (also called familial tremor or benign essential tremor)
- Senile tremor
- Physiological
- Anxiety/emotional
- Hyperthyroidism
- Alcohol
- Drugs, for example, drug withdrawal (e.g. heroin, cocaine, alcohol), amphetamines, lithium, sympathomimetics (bronchodilators), sodium valproate, heavy metals (e.g. mercury), caffeine, amiodarone
- Phaeochromocytoma

Intention tremor (cerebellar disease)

This coarse oscillating tremor is absent at rest but exacerbated by action and increases as the target is approached. It is tested by ‘finger–nose–finger’ touching or running the heel down the opposite shin, and past pointing of the nose is a feature. It occurs in cerebellar lobe disease, with lesions of cerebellar connections and with some medications.

Flapping (metabolic tremor)

A flapping or ‘wing-beating’ tremor is observed when the arms are extended with hyperextension of the wrists. It involves slow, coarse and jerky movements of flexion and extension at the wrists.

Note: Flapping (asterixis) is not strictly a tremor.

Causes

- Wilson syndrome
- Hepatic encephalopathy
- Uraemia
- Respiratory failure
- Lesions of the red nucleus of the midbrain (the classic cause of a flap)

Essential tremor

Essential tremor, which is probably the most common movement disorder (2–5% prevalence), has been variously called benign, familial, senile or juvenile tremor.

Clinical features

- Autosomal dominant disorder (variable penetrance)
- Often begins in early adult life, even adolescence
- Usually begins with a slight tremor in both hands
- May involve head (titubation), chin and tongue and rarely trunk and legs
- Interferes with writing (not micrographic), handling cups of tea and spoons, etc.
- Tremor most marked when arms held out (postural tremor); less evident at rest
- Tremor exacerbated by anxiety
- May affect speech if it involves bulbar musculature
- Relieved by alcohol
- Can swing arm and gait normal

Triad of features

- Positive family history
- Tremor with little disability
- Normal gait

Distinguishing essential tremor from Parkinson disease

This is not always easy as a postural tremor can be present in PD, although the hand tremor is most marked at rest with the arms supported on the lap. Parkinsonian tremor is slower at 4–6 Hz while essential tremor is much faster at around 8–13 Hz. Imaging is unnecessary.

A most useful way to differentiate the two causes is to observe the gait. It is normal in essential tremor but in PD there may be loss of arm swing and the step is usually shortened with stooped posture and shuffling gait.

Management

Most patients do not need treatment and all that is required is an appropriate explanation.[1] If

necessary, use propranolol (first choice) or primidone 62.5 mg nocte (up to 250 mg).[3] A typical starting dose of propranolol is 10–20 mg bd; many require 120–240 mg/day.[3] If the tremor is only intrusive at times of increased emotional stress, intermittent use of benzodiazepines (e.g. lorazepam 1 mg) 30 minutes before exposure to the stress may be all that is required. Modest alcohol intake (e.g. a glass of whisky) is very effective. A standard drink of alcohol often alleviates the tremor. Larger doses of alcohol have no additional effect. If drugs fail, deep brain stimulation to the thalamus can be used.

Parkinson disease

Parkinson disease (PD) is a disorder of the automatic processor of the brain which relies on dopamine to maintain movements at a selected size and speed. Loss of dopamine causes movements to become smaller and slower. The pathological features are loss of dopamine-producing neurones from the substantia nigra in the brain stem together with Lewy bodies in the neurones.[4] Genetic factors occur in 5% of individuals.

One of the most important clinical aspects of PD, which has a slow and insidious onset, is the ability to make an early diagnosis. Sometimes this can be very difficult, especially when the tremor is absent or mild, as occurs with the atherosclerotic degenerative type of Parkinsonism. The lack of any specific abnormality on special investigation leaves the responsibility for a diagnosis based on the history and examination. As a general rule of thumb the diagnosis of PD is restricted to those who respond to levodopa (L-dopa)—the rest are termed Parkinsonism or ‘Parkinson plus’.

The classic quintet of PD

1. Tremor (at rest)
2. Rigidity
3. Bradykinesia/hypokinesia
4. Postural instability
5. Gait freezing

≥2 signs = Parkinson disease

Key facts and checkpoints

- PD is a most common and disabling chronic neurological disorder. About 90% are idiopathic.
- The prevalence in Australia is 120–150 per 100 000.[5] Lifetime risk is 1 in 40.

- The mean age of onset is between 58 and 62 years.[5]
- The incidence rises sharply over 70 years of age (peak 65 years).[5]
- The diagnosis is based on the history and examination.
- Always think of PD in an older person presenting with falls.
- A reduced sense of smell is one of the first symptoms. Others that may precede PD include constipation, REM sleep disorders and orthostatic hypotension.
- Non-motor automatic dysfunctions: cognition, behaviour, mood.
- Hemi-parkinsonism can occur; all the signs are confined to one side and thus must be differentiated from hemiparesis. In fact, most cases of PD start unilaterally.
- Always consider drug-induced Parkinsonism. The usual drugs are phenothiazines, butyrophenones and reserpine. Tremor is uncommon but rigidity and bradykinesia may be severe.
- Other causes include vascular (atherosclerosis) and normal pressure hydrocephalus.

Refer to TABLE 22.5.

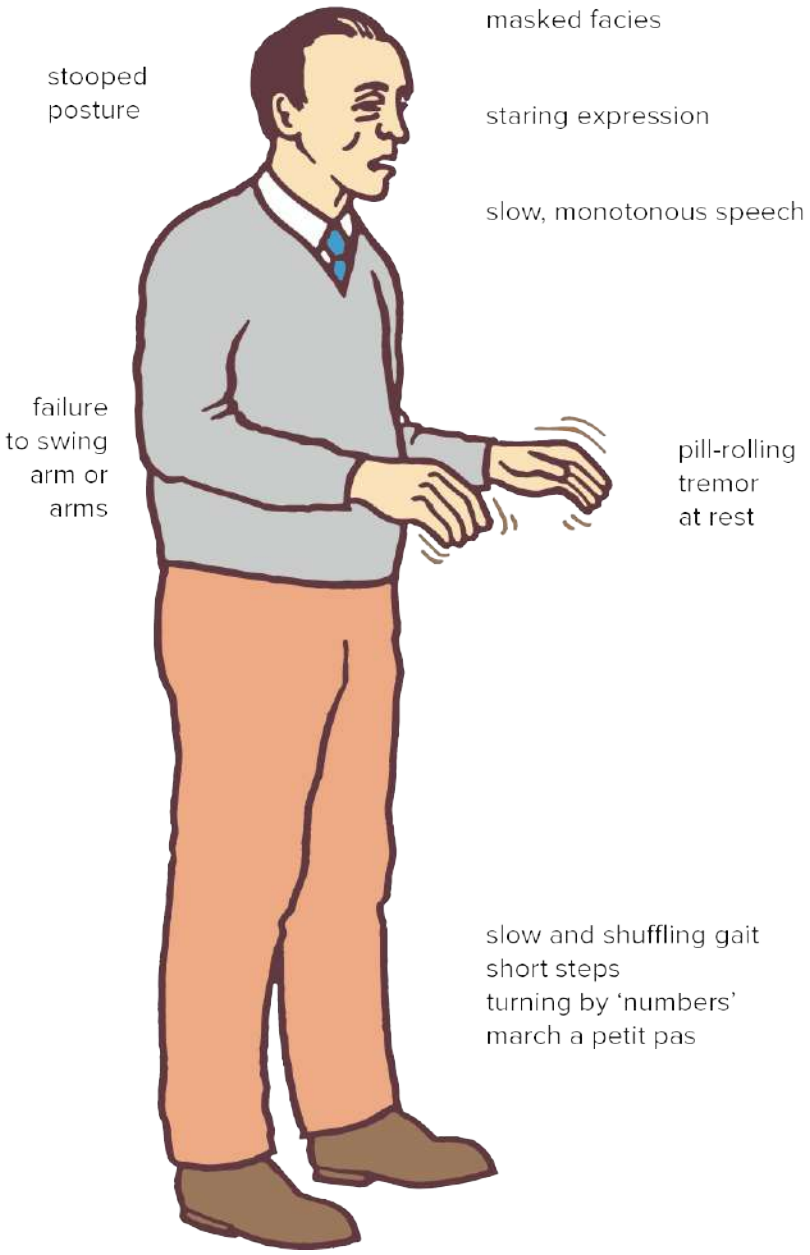

FIGURE 22.2 Basic clinical features of Parkinson disease[6]

Table 22.5 Parkinson disease: symptoms and signs (a checklist)

General	Tiredness
	Lethargy
	Restlessness

	Trouble getting out of chair or car and turning over in bed
Tremor	Present at rest
	Slow rate—4 to 6 cycles per second
	Alternating, especially arms
	Pill-rolling (severe cases)
	Note: may be absent or unilateral
Rigidity	'Cogwheel'—'juddering' on passive extension of the forearm—feels like going through cogs
	Lead pipe—limbs resist passive extension through movement (constant resistance)
Motor: bradykinesia/hypokinesia	Slowness of initiating a movement
	Difficulty with fine finger tasks
	Micrographia (see FIG. 22.3)
	Masked facies
	Relative lack of blinking
	Impaired convergence of eyes
	Excessive salivation (late)
	Swallowing problems (can aspirate)
	Difficulty turning over in bed and rising from a chair
	Slow, soft monotonous speech/dysarthria
Gait disorder	No arm swing on one or both sides
	Start hesitation
	Slow, shuffling and narrow based
	Short steps (petit pas)
	Slow turning circle ('turn by numbers')
	'Freezing' when approaching an obstacle
	Festination
Disequilibrium	Poor balance
	Impaired righting reflexes
	Falls—may be first thing that leads to presentation
Posture	Progressive forward flexion of trunk (stooped)

	Flexion of elbow at affected side
Autonomic symptoms	Constipation (common) Postural hypotension—may be induced by treatment
Neuropsychiatric	Depression (early), anxiety, sleep disorder Progressive dementia in 30–40% usually after 10 years[6] Hallucinations—either with Lewy body dementia or treatment

FIGURE 22.3 Micrographia, one of the signs of Parkinson disease

Signs

- Power, reflexes and sensation are usually normal.
- Muscle tone is increased: patients display cogwheel or lead-pipe rigidity when tested at wrist.
- The earliest abnormal physical signs to appear are loss of dexterity of rapid alternating movements and absence of arm swing, in addition to increased tone with distraction.
- Positive frontal lobe signs, such as grasp and glabellar taps (only allow three blinks), are more common with Parkinsonism.

Note: There is no laboratory test for PD—it is a clinical diagnosis. Hypothyroidism and depression, which also cause slowness of movement, may cause confusion with diagnosis.

Note: The Steele–Richardson–Olszewksi syndrome (also known as progressive supranuclear palsy—PSP parkinsonism, mild dementia and vertical gaze dysfunction) is worth considering.

Three major traps in missing early diagnosis:[5]

- Age: 10–15% are <50 years at onset

- Belief that it is a disease of men: M = F
- Absence of resting tremor (only 50% have it at onset)

Principles of management

- Provide appropriate explanation and education.
- Explain that PD is slowly progressive and is improved but not cured by treatment. It is associated with increased mortality (RR death compared with general population ranges 1.6 to 3). The question of whether treatment reduces mortality remains controversial.[7]
- Refer to a specialist for shared care—from outset.
- Support systems are necessary for advanced PD.
- Walking sticks (which spread the centre of gravity) with appropriate education into their use may be necessary to help prevent falls, and constant care is required. Admission to a nursing home for end-stage disease may be appropriate.
- Correct dopamine deficiency and/or block cholinergic excess in the brain.

Management (pharmacological)[8,9]

Avoid postponing treatment. It should be commenced as soon as symptoms interfere with working capacity or the patient's enjoyment of life. This will be apparent only if the correct questions are asked as the patient may accept impaired enjoyment without appreciating that it is due to PD. Start low—L-dopa 100/25 (½ tab bd) and go slow. There is usually no difference between the L-dopa preparations. The dosage should be tailored so that the patient neither develops side effects nor is on an inadequate dose of medication without significant therapeutic benefit (see TABLE 22.6). The dose usually progresses to 1 tab bd, then consider add-on therapy.

Table 22.6 Antiparkinson drugs[8,9]

Agent	Main adverse effects
Dopaminergic (standard and slow release)	
• L-dopa + benserazide • L-dopa + carbidopa	Nausea and vomiting (initially) Orthostatic hypotension Involuntary dyskinetic movements Psychiatric disturbances Compulsive behaviour/impulse control disorders (as below)

	On–off phenomena End-of-dose failure Constipation
Dopamine agonists	
Ergot derivatives (not recommended): • bromocriptine • cabergoline • pergolide	Nausea and vomiting Dizziness, fatigue, somnolence Compulsive behaviours (gambling, punding, overspending, hypersexuality) Orthostatic hypotension
Non-ergot derivatives: • pramipexole • ropinirole • rotigotine • apomorphine (SC injection)	Nausea, psychosis, dyskinesia
Anticholinergics • benzhexol • benztropine • biperiden	Dryness of mouth GIT upset Constipation Confusion in elderly Contraindicated in glaucoma and prostatism
COMT inhibitors • entacapone • combination entacapone/L-dopa-carbidopa (Stalevo)	Diarrhoea, discoloured urine Sleep problems
MAO-B inhibitors • selegiline • rasagiline	Dry mouth Neuropsychiatric disturbances Nausea Dizziness, fatigue Insomnia
Others • amantadine	Nausea and vomiting Insomnia Nightmares Neuropsychiatric disturbances Ankle oedema Livedo reticularis

The older drugs, such as anticholinergics and amantadine, still have a place in modern

management but L-dopa, which basically counters bradykinesia, is the best drug and the baseline of treatment. With the onset of disability (motor disturbances), L-dopa in combination with a decarboxylase inhibitor (carbidopa or benserazide) in a 4:1 ratio should be introduced. L-dopa therapy does not significantly improve tremor but improves rigidity, dyskinesia and gait disorder. It is preferred in those >70 years.[10] Consider benzhexol or benztropine if tremor is the feature, especially in young patients.

The new non-ergot derivative dopamine agonists (e.g. pramipexole and rotigotine) can be used in treatment, especially with the L-dopa 'on–off' phenomenon (fluctuations throughout the day), and also as first-line monotherapy in early PD in certain circumstances and with caution.[8] They are preferred to the ergot derivatives because of a superior adverse effect profile. They appear to be most effective when used in combination. The ergot derivatives can have serious adverse effects, including cardiac valve damage, and are no longer recommended. Selegiline is an effective second-line drug, especially in combination with Sinemet. If there is associated pain, depression or insomnia, the tricyclic agents (e.g. amitriptyline) can be effective.

Entacapone has the potential to increase 'on time' and reduce motor fluctuations in L-dopa treated patients who are beginning to experience end-of-dose failure. The initial dose is 200 mg and best used when combined with L-dopa.

Treatment strategy[8,9]

Mild (minimal disability):

- L-dopa preparation (low dose), e.g. L-dopa 100 mg + carbidopa 25 mg (½ tab bd—increase gradually as necessary to 1 tab (o) tds)

  or

- amantadine 100 mg (o) daily may help the young or the elderly for up to 12 months—if inadequate response

- selegiline up to 5 mg bd can be added to L-dopa if necessary

Moderate (independent but disabled, e.g. writing, movements, gait):

- L-dopa preparation

- selegiline 1 mg bd

  and/or

- add if necessary—non-ergot dopamine agent

  pramipexole start with 0.25 mg transdermally daily

  or

- rotigotine start with 2 mg daily

Severe (disabled, dependent on others):

- L-dopa (to maximum tolerated dose) + non-ergot dopamine agent
- add entacapone 200 mg (o) with each dose of L-dopa, e.g. Stalevo
- consider antidepressants

An example of a practical treatment algorithm is presented in FIGURE 22.4 .

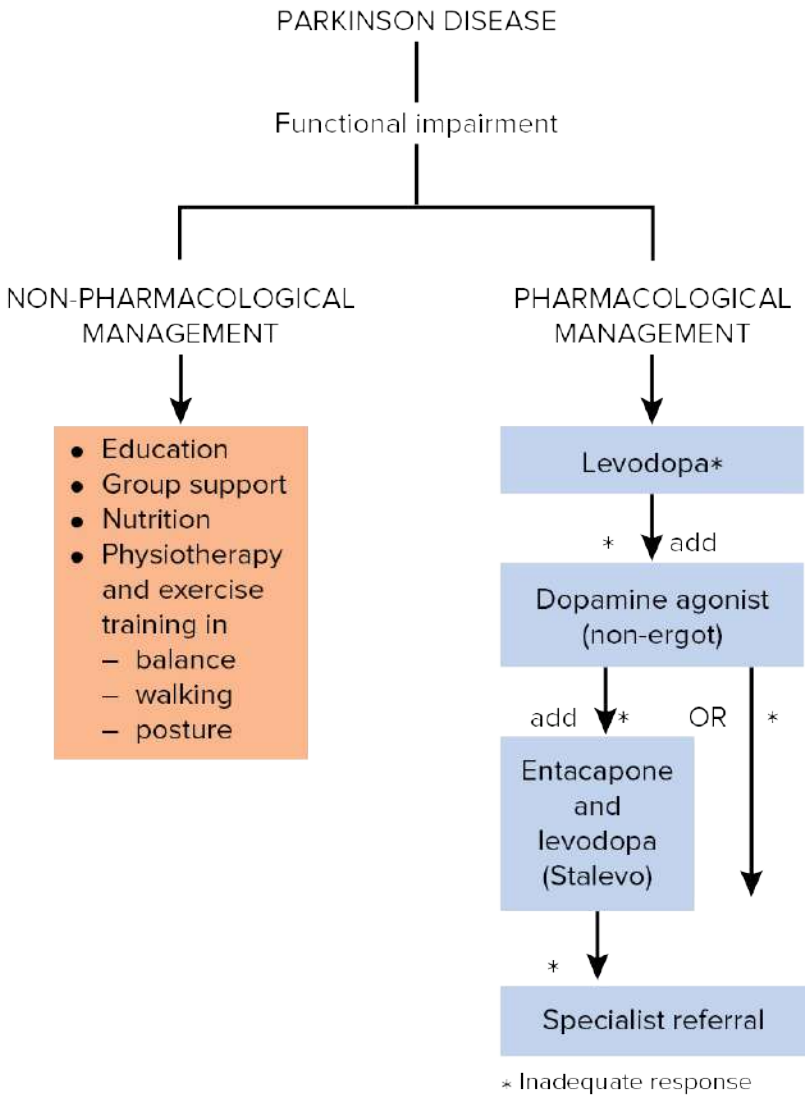

FIGURE 22.4 Management of early Parkinson disease: one possible pathway

Long-term problems

After 3–5 years of L-dopa treatment, side effects may appear in about one-half of patients:[5]

- involuntary movements—dyskinesia
- end-of-dose failure (reduced duration of effect to 2–3 hours only)—consider entacapone
- 'on–off' phenomenon (sudden inability to move, with recovery in 30–90 minutes)
- early morning dystonia, such as clawing of toes (due to disease—not a side effect)

Specialist advice is appropriate.

Advanced disease[8]

Under consultant and good home/nursing care:

- apomorphine can be used for severe akinesia not responsive to L-dopa
- for nausea and vomiting side effects: domperidone 20 mg (o) tds 24 hours prior to apomorphine
- better control may also be achieved with: amantadine 100 mg (o) bd
- duodopa—levodopa into jejunum

Contraindicated drugs

- Phenothiazines and other older antipsychotics
- Butyrophenones

Multidisciplinary care

This important strategy includes physiotherapy, occupational therapy, physical therapy, e.g. tai chi, and psychiatry/psychology, e.g. CBT, mindfulness.

Treatment (surgical)

The preferred method is high-frequency deep brain stimulation via electrodes into the subthalamic nucleus, which may benefit all major features of the disease. The indication for surgery such as thalamotomy is erratic and disabling responses to prolonged L-dopa therapy, especially for annoying dyskinesias. It is considered more appropriate for younger patients with a unilateral tremor.[8]

When to refer

If the diagnosis is unclear at the time of initial presentation, it is appropriate either to review the patient at a later date or to refer the patient for more neurological assessment.

Once diagnosed or highly suspected, it is best to refer to establish the diagnosis and to seek advice on initiation of treatment. Patients and families usually prefer this approach. In the initial years before motor fluctuations develop, management could be performed by the GP according to an overall plan developed in liaison with a neurological colleague. When fluctuations develop and end-stage diseases manifest (e.g. gait disorders), specialist supervision is appropriate.[1]

Parkinson Plus disorders and red flags in differential diagnosis[11]

Bilateral onset (PSP)

Poor response to L-dopa

Dysautonomia—bladder, orthostatic hypotension (MSA)

Dystonia (PSP)

Anterocollis (head flexed) (MSA)

Retrocollis (head extended) (PSP)

Myoclonus (CBD, CJD)

Early-onset dementia (LBD)

Abbreviations: CBD = corticobasal degeneration, CJD = Creutzfeldt–Jakob disease, LBD = Lewy body dementia, MSA = multiple system atrophy, PSP = progressive supranuclear palsy

Cognitive impairment with Parkinson disease[4,10]

This may be due to multiple factors including Parkinson-associated dementia, Lewy body dementia, Alzheimer disease and medication, all of which can induce psychosis, but L-dopa is the least likely. Neuropsychiatric symptoms, which can be varied and bizarre and usually worse in the evening, can occur. Factors contributing to psychosis are illustrated in FIGURE 22.5. Management is based on monotherapy with gradual build-up of L-dopa to maximum tolerated dose, for example, 450–600 mg/day.

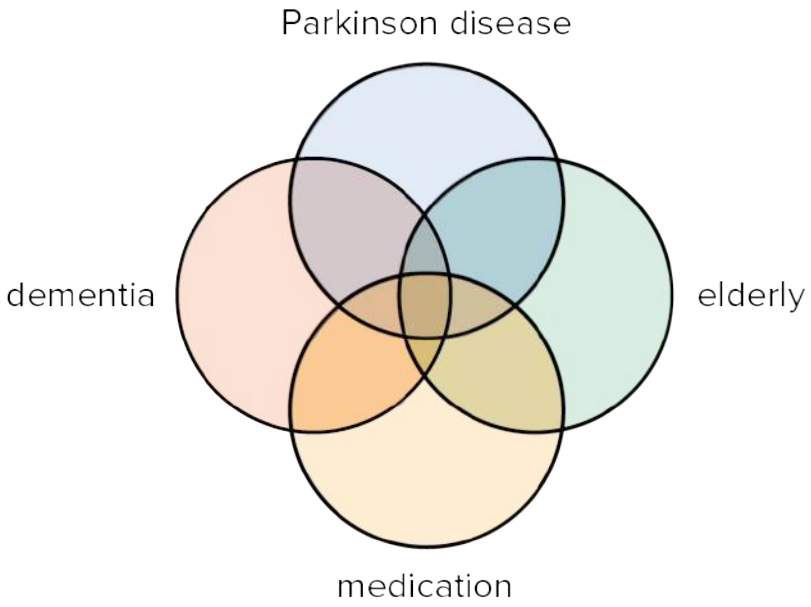

FIGURE 22.5 Factors contributing to psychosis

Management (psychotic problems)

- Treat as an inpatient
- Exclude and treat comorbidities, e.g. UTI
- Eliminate and wean off worst drugs
- Increase L-dopa slowly to 150 mg tds or qid
- Give low dose of quetiapine first line, or olanzapine at night-time

Practice tips for Parkinson disease

- One of the simplest diagnostic tools for PD, as compared with Parkinsonism, is a trial of therapy with L-dopa. The response is excellent while that for Parkinsonism is poor.
- L-dopa is the gold standard for therapy.
- Ensure that a distinction is made between drug-induced involuntary movements and the tremor of PD.
- Keep the dose of L-dopa as low as possible to avoid these drug-induced involuntary movements.

- In the elderly with a fractured hip always consider PD (a manifestation of disequilibrium).
- Remember the balance of psychosis and PD in treatment.
- Keep in mind the ‘sundown’ effect—patients often go psychotic as the sun goes down.
- Don’t fail to attend to the needs of the family, who often suffer in silence.
- If drugs are to be withdrawn they should be withdrawn slowly.

Paraesthesia and numbness

The diagnostic strategy model for paraesthesia and numbness is presented in TABLE 22.7 .

Table 22.7 Paraesthesia and numbness: diagnostic strategy model

Probability diagnosis

Diabetic peripheral neuropathy
Nutritional peripheral neuropathy, esp. alcohol, B12, folate
Hyperventilation with anxiety
Nerve root pressure, e.g. sciatica, cervical spondylosis
Nerve entrapment, esp. carpal tunnel syndrome

Serious disorders not to be missed

Vascular:

- CVA/TIA
- peripheral vascular disease

Infection:

- AIDs
- Lyme disease/suspected tick-borne disease
- leprosy
- some viral infections

Tumour/cancer:

- disseminated malignancy
- cerebral/spinal cord tumours

Other:

- uremia
- Guillain–Barré syndrome
- trauma to spinal cord
- marine fish toxins, e.g. toadfish, ciguatera

Pitfalls (often missed)
Migraine variant with focal signs
Multiple sclerosis/transverse myelitis
Hypocalcaemia
Rarities:
- chronic inflammatory polyneuropathy
- amyloidosis
- heavy metal toxicity, e.g. lead

Seven masquerades checklist?
Diabetes
Drugs, e.g. cytotoxic agents, interferon (see list)
Anaemia—pernicious anaemia
Thyroid/other endocrine—hypothyroid?
Spinal dysfunction

Is the patient trying to tell me something?
Consider conversion reaction (hysteria), severe anxiety disorder
Some cases may be idiopathic

Multiple sclerosis

Multiple sclerosis (MS) is the most common cause of progressive neurological disability in the 20–50 year age group.[11] It is generally accepted that MS is an autoimmune disorder. Genetic and environmental factors are believed to play a role.[12] Early diagnosis is difficult because MS is characterised by widespread neurologic lesions that cannot be explained by a single anatomical lesion, and the various symptoms and signs are subject to irregular exacerbations and remissions. The lesions are ‘separated in time and space’. The most important issue in diagnosis is the need for a high index of suspicion. The use of MRI has revolutionised the diagnosis of MS.

MS is a primary demyelinating disorder with demyelination occurring in plaques throughout the white and grey matter of the brain, brain stem, spinal cord and optic nerves. The clinical features depend on their location. There is a loss of brain volume.

There is a variety of types of MS—relapsing remitting (most common), secondary progressive, progressive relapsing and primary progressive—together with ‘benign’ and ‘malignant’ forms.

Clinical features

See FIGURE 22.6 .

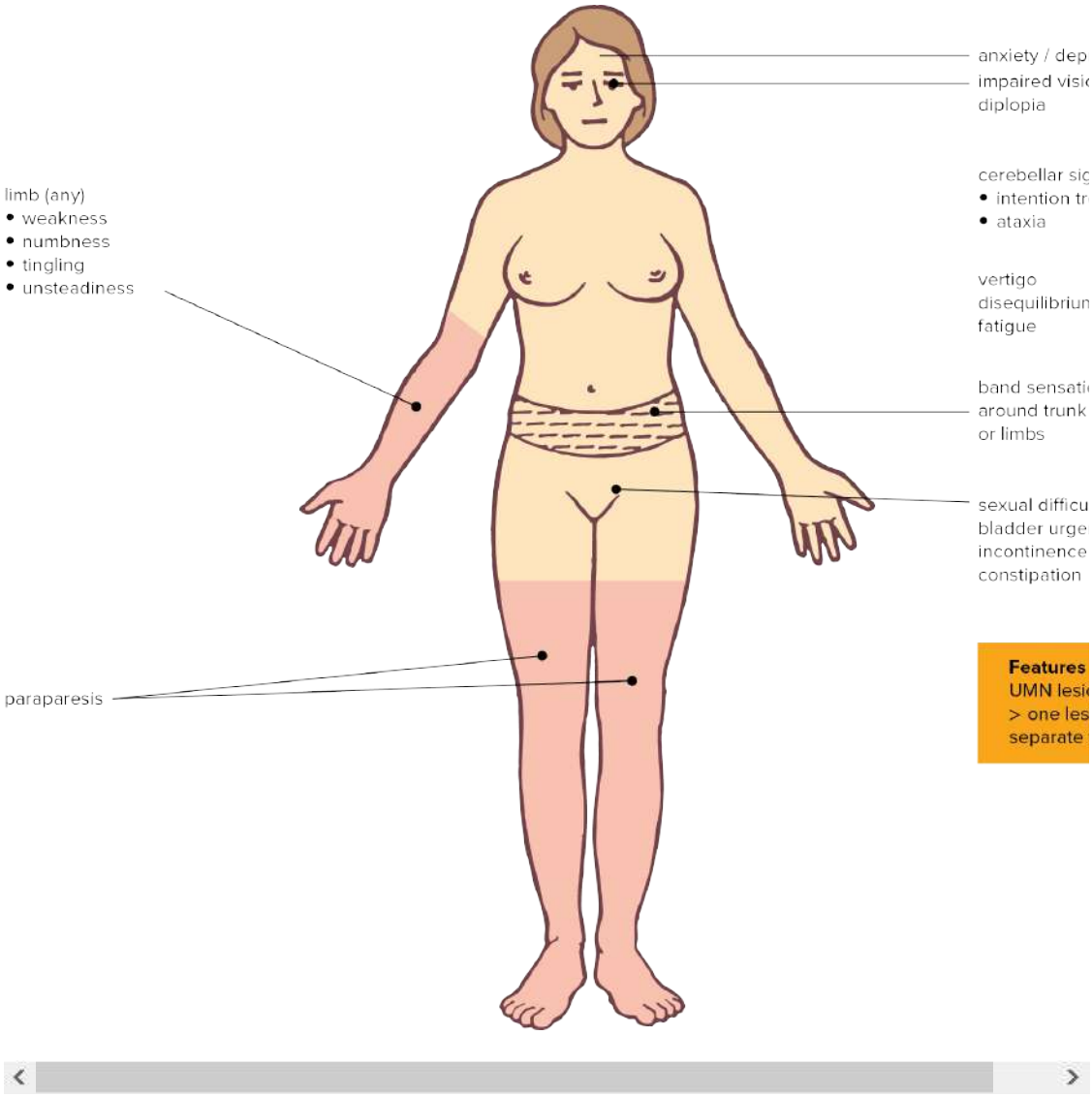

FIGURE 22.6 Basic clinical signs in multiple sclerosis

- More common in females (3:1)
- Peak age of onset is in the fourth decade
- Transient motor and sensory disturbances
- UMN signs
- Symptoms develop over several days but can be sudden
- Monosymptomatic initially in about 80%
- Only 20% have a benign disease

- Multiple symptoms initially in about 20%
- Common initial symptoms include:

  visual disturbances of optic neuritis (blurred vision or loss of vision in one eye—sometimes both); central scotoma with pain on eye movement (looks like unilateral papilloedema)

  diplopia (brain-stem lesion)

  weakness in one or both legs, paraparesis or monoparesis

  sensory impairment in the lower limbs and trunk: numbness, paraesthesia; band-like sensations; clumsiness of limb (loss of position sense); feeling as though walking on cotton wool

  vertigo (brain-stem lesion)
- Subsequent remissions and exacerbations that vary from one individual to another
- 80% have a relapsing remitting disease
- There is a progressive form, esp. in women around 50 years
- Anxiety, depression and other mood disorders are common

Symptoms causing diagnostic confusion

- Bladder disturbances, including retention of urine and urgency
- ‘Useless hand’ due to loss of position sense
- Facial palsy
- Trigeminal neuralgia
- Psychiatric symptoms

In established disease, common symptoms are fatigue, impotence and bladder disturbances.

Examination (neurological)

The findings depend on the site of the lesion or lesions and include optic atrophy, weakness, hyper-reflexia, extensor plantar responses, nystagmus (two types—cerebellar or ataxic), ataxia, incoordination and regional impairment of sensation.

Diagnosis

The diagnosis is clinical along with the MRI and depends on the following determinants:

- Lesions are invariably UMN.
- >1 part of CNS is involved, although not necessarily at time of presentation.
- Episodes are separated in time and space.
- Practically MS can only be diagnosed after a second relapse or when the MRI shows new lesions.[11]
- An early diagnosis requires evidence of contrast-enhancing lesions or new T2 lesions on the MRI indicating dissemination in time.
- The diagnostic criteria is based on the internationally accepted 2010 McDonald criteria (refer to: www.nice.org.uk).[12,13]

Other neurological disorders such as infections (e.g. encephalitis), malignancies, spinal cord compression, spinocerebellar degeneration and others must be excluded.

Investigation

- Lumbar puncture: oligoclonal IgG detected in CSF in 90% of cases[14] (only if necessary)
- Visual evoked potentials: abnormal in about 90% of cases
- MRI scan: usually abnormal, demonstrating MS lesions in about 90% of cases[14]

Course and prognosis

- The course is variable and difficult to predict. An early onset (<30 years) is usually ‘benign’ while a late onset (≥50 years) is often ‘malignant’.
- MS follows a classic history of relapses and remissions in 80–85% of patients.[14]
- The rate of relapse is about once in 2 years.
- About 20% have a progressive course from the onset with a progressive spastic paraparesis (applies mainly to late-age onset).
- The average duration of MS is about 40 years from diagnosis to death.[14]
- A ‘benign’ course occurs in about 30% of patients with 10–20% never suffering major disability.
- The median time to needing a walking aid is 15 years.[8]
- The likelihood of developing MS after a single episode of optic neuritis is about 60%.

Management principles

- All patients should be referred to a neurologist for confirmation of the diagnosis, which must be accurate.
- Explanation about the disorder and its natural history should be given.
- Acute relapses require treatment if causing significant disability.
- Depression and anxiety, which are common, require early treatment, e.g. paroxetine.
- CBT or mindfulness-based interventions.

Treatment (relapses)

Mild relapses

Mild symptoms, such as numbness and tingling, require only confirmation, rest and reassurance.

Moderate relapses

- Prednisolone—in outpatient setting

Severe relapses or attacks[8,15]

These attacks include optic neuritis, paraplegia or brain-stem signs. Admit to hospital for IV therapy:

- methylprednisolone 1 g in 200 mL saline by slow IV infusion (1 hour) daily for 3 days

  Plasma exchange may be used.

  Observe carefully for cardiac arrhythmias.

Drugs to prevent relapses[16]

Currently first-line immunomodulators are the interferons, glatiramer acetate and the monoclonal antibodies natalizumab and alemtuzumab, or others.

Interferon beta-1b (SC injection) and beta-1a (IM injection) appear to be effective (but expensive) for those with frequent and severe attacks.

New agents being evaluated include teriflunomide, siponimod, daclizumab, ocrelizumab and Biotin.

Treatment (symptoms)[7,16]

Spasticity

- Physiotherapy
- Baclofen 10–25 mg (o) nocte
- For continuous drug therapy: baclofen 5 mg (o) tds, increasing to 25 mg (o) tds + diazepam 2–10 mg (o) tds
- An alternative is dantrolene

Paroxysmal (e.g. neuralgias)

- Carbamazepine or gabapentin

Cannabis

The reported efficacy of the cannabis-based medicine Sativex for relaxation, pain and bladder function is still being debated. One RCT showed a positive effect on detrusor activity.[17]

See references 8 and 16 for treatment of other symptoms.

Peripheral neuropathy

Peripheral neuropathy (PN) refers to all conditions causing nerve damage outside the central nervous system. It can be a mononeuropathy, such as carpal tunnel syndrome; mononeuropathy multiplex involving multiple single nerves in an asymmetric pattern (as in vasculitides); or a polyneuropathy, which is a diffuse symmetric disorder best referred to as PN. It can be classified according to clinical progression as acute, subacute or chronic. The manifestations can be sensory, motor, autonomic or mixed (sensorimotor).

- Sensory symptoms: tingling, burning, numbness in extremities, unsteady gait (loss of position sense)
- Motor symptoms (LMN): weakness or clumsiness in hands, foot/wrist drop
- Signs: may be classic ‘glove and stocking’ sensory loss, sensory ataxia, LMN signs—distal muscle wasting, muscle weakness, reflexes absent or depressed, fasciculations

Causes

- Mostly sensory: diabetes mellitus, vitamin deficiency (folate, B1, B6, B12), alcohol, various neurotoxic drugs, leprosy, uraemia (CKF), amyloidosis, malignancy
- Mostly motor: lead poisoning, porphyria, various neurotoxic drugs, Charcot–Marie–Tooth syndrome (peroneal muscle atrophy), acquired inflammatory polyneuropathies—acute (Guillain–Barré syndrome) and chronic (chronic inflammatory demyelinating polyneuropathy)

Note: In many instances no cause is found despite a full history and examination.

Management

Refer to a suitably qualified consultant for diagnosis, particularly via electrophysiology.

Acute inflammatory polyradiculoneuropathy (Guillain–Barré syndrome)

Guillain–Barré syndrome, which is a rapidly progressive and treatable cause of PN or ascending radiculopathy, is potentially fatal. Early diagnosis of this serious disease by the family doctor is crucial as respiratory paralysis may lead to death. The underlying pathology is segmental demyelination of the peripheral nerves and nerve roots.

Clinical features

- Weakness in the limbs (usually symmetrical)
- Paraesthesia or pain in the limbs (less common)
- Both proximal and distal muscles affected, usually starts peripherally and moves proximally
- Facial and bulbar paralysis (rare)
- Weakness of extraocular muscles (rarely)
- Reflexes depressed or absent
- Variable sensory loss but rare

Within 3–4 weeks the motor neuropathy, which is the main feature, progresses to a maximum disability, possibly with complete quadriparesis and respiratory paralysis.[18]

Investigation

- CSF protein is elevated; cells are usually normal.
- Motor nerve conduction studies are abnormal.

Management

- Admit to hospital.
- Respiratory function (vital capacity) should be measured regularly (2–4 hours at first).
- Tracheostomy and artificial ventilation may be necessary.
- Physiotherapy to prevent foot and wrist drop and other general care should be provided.

- Treatment is with plasma exchange or IV immunoglobulin (0.4 g/kg/day for 5 days), which may need to be continued monthly.[8]
- Corticosteroids are not generally recommended.

Outcome

About 80% of patients recover without significant disability. Approximately 5% relapse.[18]

Chronic inflammatory demyelinating polyneuropathy[8,19]

This acquired immunological disorder is similar to Guillain–Barré syndrome except that it has a slower and more protracted course. Diagnosis is by nerve studies and treatment is with corticosteroids, plasmapheresis or IV immunoglobin.

Charcot–Marie–Tooth syndrome

This is an inherited autosomal dominant polyneuropathy with an insidious onset from puberty. Clinical features include weakness in the legs, variable distal sensory loss and muscle atrophy giving the 'inverted champagne bottle' appearance of the legs. The features vary according to the various subgroups. Refer for electrodiagnostic studies and specific genetic testing.

Familial periodic paralysis

An autosomal dominant skeletal muscle disorder. Clinical features:

- young patient (usually adolescent)
- day after vigorous exercise awakens with weakness in limbs (for 4–24 hours)
- flaccid paralysis/loss of deep tendon reflexes

Related to potassium levels—measure during symptoms. Classify as high, low or normal.

Myasthenia gravis

Myasthenia gravis (MG) is an acquired autoimmune disorder that usually affects muscle strength. Patients have fluctuating symptoms and variable distribution of muscle weakness. All degrees of severity, ranging from occasional mild ptosis to fulminant quadriplegia and respiratory arrest, can occur[20] (see TABLE 22.8). It is associated with thymic tumour and other autoimmune diseases, for example, RA, SLE, thyroid and pernicious anaemia.

Table 22.8 Clinical classification of acquired myasthenia gravis

Group I	Ocular MG
Group IIA	Mild generalised MG
Group IIB	Moderate to severe MG
Group III	Acute severe (fulminating) MG with respiratory muscle weakness
Group IV	Late (chronic) severe MG

Clinical features

- Painless fatigue with exercise
- Weakness also precipitated by emotional stress, pregnancy, infection, surgery
- Variable distribution of weakness:

  ocular: ptosis (60%) and diplopia (see FIG. 22.7); ocular myasthenia only remains in about 10%

  bulbar: weakness of chewing, swallowing, speech (ask to count to 100), whistling and head lolling

  limbs (proximal and distal)

  generalised

  respiratory: breathlessness, ventilatory failure

Note: The classic MG image is ‘the thinker’—the hand used to hold the mouth closed and the head up.

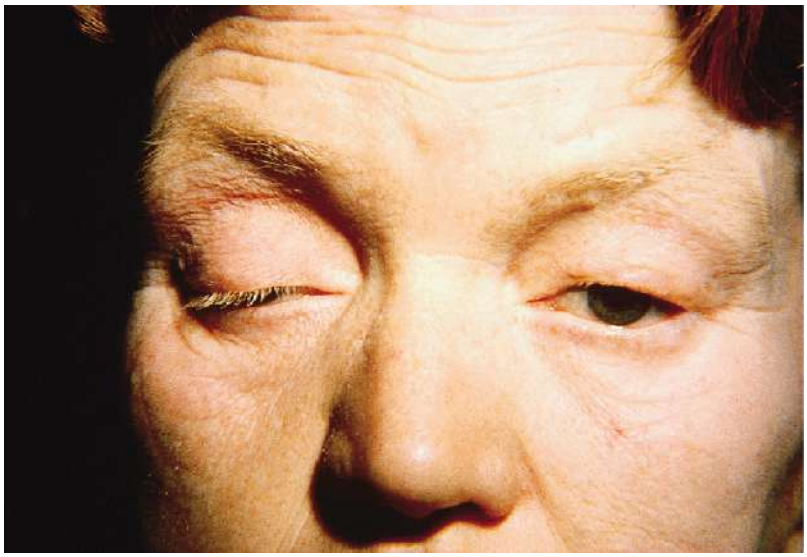

FIGURE 22.7 Myasthenia gravis in a 40-year-old woman with a 12-month history of increasing muscular weakness including drooping of the eyelids. Ptosis, especially on the right side, is apparent.

Diagnosis

- Serum anti-acetylcholine receptor antibodies
- Electrophysiological tests if antibody test negative
- CT scan to detect thymoma
- Edrophonium test still useful but potentially dangerous (atropine is the antidote)

Management principles[8,20]

- Refer for consultant management.
- Detect possible presence of thymoma with CT or MR scan of thorax. If present, removal is recommended.
- Thymectomy is recommended early for generalised myasthenia, especially in all younger patients with hyperplasia of the thymus, even if not confirmed preoperatively.
- Plasmapheresis is useful for acute crisis or where temporary improvement is required or patients are resistant to treatment.
- Avoid drugs that are relatively contraindicated.
- Pharmacological agents:

  anticholinesterase inhibitor drugs, first-line (e.g. pyridostigmine, neostigmine or distigmine), should be used only for mild-to-moderate symptoms

  corticosteroids are useful for all grades of MG (should be introduced slowly)

  immunosuppressive agents

Practice tips for myasthenia gravis

- The combination of ocular and facial weakness should alert the family doctor to the possibility of a neuromuscular disorder, especially MG or mitochondrial myopathy.[19] Look for weakness and fatigue.
- Beware of facioscapulohumeral dystrophy.

- Ptosis may develop only after looking upwards for a minute or longer.
- Smiling may have a characteristic snarling quality.

Ptosis

It is worth remembering that the four major causes of ptosis are:

1. 3rd cranial nerve palsy—ptosis, eye facing ‘down and out’, dilated pupil, sluggish light reflex
2. Horner syndrome—ptosis, miosis (constricted pupil), ipsilateral loss of sweating
3. Mitochondrial myopathy—progressive external ophthalmoplegia or limb weakness, induced by activity—no pupil involvement
4. Myasthenia gravis—ptosis and diplopia, no pupil involvement

Dystonia

Dystonias are sustained or intermittent abnormal repetitive movements or postures resulting from alterations in muscle tone. The dystonic spasms may affect one (focal) or more (segmental) parts of the body or the whole body (generalised).

Key facts and checkpoints

- Misdiagnosis is common as transient symptoms may be mistaken for an emotional or psychiatric disorder. Many cases take years to diagnose.
- Dystonias are often regarded as nervous tics.
- The cause is thought to be disorders of the basal ganglia of the brain, but mainly there is no known specific cause.
- Neuroleptic and dopamine receptor blocking agents (e.g. L-dopa, metoclopramide) can induce a severe generalised dystonia (e.g. oculogyric crisis) which is treated with benztropine 1–2 mg IM or IV.[8] However, L-dopa is the drug of choice in some L-dopa responsive dystonias.

Focal dystonias

- *Blepharospasm* is a focal dystonia of the muscles around the eye resulting in uncontrolled blinking, especially in bright light. This is best treated with botulinum toxin, type A.
- *Oromandibular dystonia* affects the jaw, tongue and mouth, resulting in jaw grinding movements and grimacing. Proper speech and swallowing may be disrupted.
- *Meige syndrome* is a combination of blepharospasm and oromandibular dystonia.

  Note: It must be differentiated from the buccal-lingual-facial movements of tardive dyskinesia.
- *Hemifacial spasm* involves involuntary, irregular muscle contractions and spasms affecting one side of the face. It usually starts with twitching around the eye and then spreads to involve all the facial muscles on one side. It is usually due to irritation of the facial nerve in its intracranial course and surgical intervention may alleviate this problem.
- *Writer's cramp, typist's cramp, pianist's cramp, golfer's cramp* are all occupational focal dystonias of the hand and/or forearm initiated by performing these skilled acts.
- *Cervical dystonia* or *spasmodic torticollis* is a focal dystonia of the unilateral cervical muscles. It usually begins with a pulling sensation followed by twisting or jerking of the head, leading to deviation of the head and neck to one side. In early stages patients can voluntarily overcome the dystonia.
- *Laryngeal* or *spastic dystonia* is a focal dystonia of the laryngeal muscles resulting in a strained, hoarse or creaking voice. It may lead to inability to speak in more than a whisper.

Treatment

The current treatment for focal or segmental (spread to an adjacent body region) dystonias is localised injection of purified botulinum A toxin into the affected muscle groups. The dosage is highly individualised and needs to be repeated at intervals of 3 and 6 months. The injections have to be given with great caution, ideally by a registered injector.

Tics

Motor and vocal tics are a feature of Tourette disorder. If socially disabling, treat with:

- haloperidol 0.25 mg (o) nocte, very gradually increasing to 2 g (max.) daily[7]

  or
- clonidine 25 mcg (o) bd for 2 weeks, then 50–75 mcg bd

Facial nerve (Bell) palsy[15]

Idiopathic facial (7th nerve) palsy, which is an acute unilateral lower motor neurone paresis or paralysis, is the commonest cranial neuropathy. The classic type is Bell palsy, which is usually

idiopathic although attributed to an inflammatory swelling involving the facial nerve in the bony facial canal. In Ramsay–Hunt syndrome, which is due to infection with herpes zoster causing facial nerve palsy, vesicles may be seen on the ipsilateral ear.

Associations:

- herpes simplex virus (postulated)
- diabetes mellitus
- hypertension
- thyroid disorder, e.g. hyperthyroidism

Clinical features

- Abrupt onset (can worsen over 2–5 days)
- Weakness in the face (complete or incomplete)
- Preceding pain in or behind the ear
- Impaired blinking
- Bell phenomenon—when closing the eye it turns up under the half-closed lid

Less common:

- difficulty eating
- loss of taste—anterior two-thirds of tongue
- hyperacusis

Management[21]

- prednisolone 1 mg/kg (o) up to 75 mg (usually 60 mg) daily in the morning for 5 days (start within 48 hours of onset)

Note: This is controversial, but recent randomised trials and a Cochrane review support the use of prednis(ol) one. No good evidence for antiviral drugs, but low-grade evidence for benefit if combining with a corticosteroid.

- Patient education and reassurance
- Adhesive patch or tape over eye if corneal exposure (e.g. windy or dusty conditions, during sleep)
- Artificial tears if eye is dry and at bedtime

- Massage and facial exercises during recovery

Note:

- At least 70–80% achieve full spontaneous recovery; higher if mild. Remission should begin within 1 week of onset.
- Electromyography and nerve excitability or conduction studies are a prognostic guide only.
- No evidence that nucleoside analogue, for example, aciclovir, is useful but should be used for Ramsay–Hunt syndrome.
- No evidence that surgical procedures to decompress the nerve are beneficial.[15]

Patient education resources

Hand-out sheets from *Murtagh's Patient Education* 8th edition:

- Bell palsy
- Tremor: essential tremor
- Parkinson disease

Resources

Parkinson disease: www.parkinsons.org.au

Multiple sclerosis: www.msaustralia.org.au

Amyotrophic lateral sclerosis: www.mndaust.asn.au

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Diagnostic triads of neurological dilemmas

All triads show a chronic onset unless indicated by an asterisk (acute onset).

If you see this combination of signs:	**Consider:**
Charcot triad:	
• dysarthria + intention tremor + nystagmus	→ cerebellar disease (typical of MS)
• visual disturbance (blurred or transient loss) + weakness in limbs ± paraesthesia in limbs	→ multiple sclerosis
Note: There are many combinations of MS (Charcot has historical interest).	
• rigidity + bradykinesia + resting tremor	→ Parkinson disease
• tremor (postural or action) + head tremor + absence of Parkinsonian features	→ essential tremor
• fatiguable and weakness of eyelids and eye movements + limbs + bulbar muscles (speech and swallowing)	→ myasthenia gravis
• ascending weakness of limbs + of face + areflexia*	→ Guillain–Barré syndrome (GBS)
• (episodic) vertigo + tinnitus + hearing loss*	→ Ménière syndrome
• dementia + myoclonus + ataxia	→ Creutzfeldt–Jakob disease
• drowsiness + vomiting + headache (waking)	→ ↑ intracerebral pressure
• enophthalmos + meiosis + ptosis ± anhydrosis	→ Horner syndrome
• blank spell + lip-smacking (or similar automation) + olfactory/gustatory hallucination	→ complex partial seizure
• gradual spread (Jacksonian march) of focal jerking (mouth, arm or leg) or sensory disturbance or (rarely) visual field disturbance	→ simple partial seizure
• ↑ intracranial pressure +/or focal signs +/or epilepsy	→ cerebral tumour
• dysphagia + dysphonia/dysarthria + spastic tongue	→ pseudobulbar palsy
• recurrent: headache (often unilateral) + nausea (± vomiting) + visual aura*	→ migraine with aura (formerly ‘classical

	migraine')
• recurrent: severe retro-orbital headache + rhinorrhoea + lacrimation*	→ cluster headache
• instantaneous: headache ± vomiting ± neck stiffness	→ subarachnoid haemorrhage until disproven
• headache + visual obscurations + papilloedema (often in obese young female)	→ benign intracranial hypertension
• acute and transient: amaurosis fugax or dysphasia or hemiplegia*	→ TIA (carotid)
• typical facies (temporalis atropy and frontal balding) + muscle weakness esp. hands (± myotonia) + cataracts	→ dystrophia myotonica (myotonic dystrophy)
• ataxias + ophthalmoplegia + areflexia*	→ Miller–Fisher variant of GBS
• vertigo + provoked by movement (especially rolling in bed) + Hallpike test +ve	→ BPPV
• UMN signs + LMN signs + fasciculations	→ motor neurone disease
• leg weakness + ataxic gait + clumsiness (appears about 12 years)	→ Friedreich ataxia
• limb weakness + flaccid paralysis (day after exercise in a young person)	→ familial periodic paralysis

23 Genetic conditions

People love to oversimplify genetics, saying we have a 'gene for cancer' or a 'gene for diabetes'. But the fact is, genes determine only so much. Identical twins have identical genomes, yet one may develop juvenile diabetes and the other typically doesn't. Understanding the role of genes should help pinpoint environmental factors ... The genome is a history book showing the entire 6 billion-member human species traces back 7000 generations to a tiny founding population of some 60 000 people. Our species has only a modest amount of genetic variation—the DNA of any two humans is 99.9% identical.

ERIC LANDER, HUMAN GENOME PROJECT, 2000[1]

The family doctor has an important role to play in the exciting and rapidly expanding world of medical genetics. The role includes routine diagnosis, early detection, and community and ethical guidance. Virtually all of the three billion nucleotides of the human genome have been sequenced and the knowledge of their organisation into the known 30 000–35 000 functional units or genes continues to become more sophisticated.[2]

The genome project has commenced mapping out 'single nucleotide polymorphisms' (SNPs) as signposts throughout the genome to assist in locating disease-associated genes and studying variations between individuals.[3] Any two unrelated individuals differ by one base per every thousand or so—these as SNPs—and it is believed that SNPs contribute to the risk of common disease rather than directly cause disease. If we carry the wrong set of SNPs, we can be predisposed to various diseases.

Genetic testing is now available for many common hereditary disorders, such as the *HFE* genes for haemochromatosis, presymptomatic DNA tests are available for the hereditary neurological disorders, such as Huntington disease, and predictive DNA testing is available for some forms of hereditary cancer, such as breast and colon cancer, and in the future for cardiovascular disease and diabetes.[4] Also in the future, pharmacogenetics, which predicts genetically determined responses to pharmaceuticals, will greatly assist rational prescribing and minimise drug toxicity and adverse effects. Gene therapy is a futuristic treatment modality.[5]

An important development in gene expression has been advances in DNA technology, with the detection of fetal DNA in maternal plasma, thus allowing an excellent screening test for Down syndrome.[6]

Epigenetics

Epigenetics, meaning ‘on top of’ traditional genetic inheritance, is a study of changes in genetic expression or cellular phenotype caused by mechanisms other than changes in the DNA sequence. These factors, which include environment, lifestyle, nutrition and psychosocial influences, can influence the outcomes of chronic illness such as cancer, diabetes, autoimmune disorders and ageing. The incurred changes are heritable. This is an expanding development.

Prevalence of genetic disease[7,8]

The global prevalence of single gene (monogenetic) disorders is estimated to be 10 per 1000 population. Autosomal dominant conditions account for about 2% while recessive conditions 1.5 per 1000. Estimates of other conditions are X-linked recessive 6% and congenital malformations 20%. Genetic disorders may also be multifactorial or polygenic (e.g. hypertension, diabetes, asthma), whereby inheritance does not adhere to the simpler patterns of Mendelian disease. Chromosomal disorders occur in about 1% of the general population, in 8% of stillbirths and in close to 50% of spontaneously aborted fetuses.

Key facts and checkpoints

- All people carry a small number of recessive genes, which are carried asymptomatically.
- The background risk that any couple will bear a child with a birth defect is about 4%. This risk is doubled for a first-cousin (consanguineous) couple.[9]
- Although the majority of cancers are not inherited, some people carry inherited genetic mutations for certain cancers, notably breast and ovarian (linked), colorectal and others on a lesser scale, such as prostate cancer and melanoma.
- GPs should look out for a family history of cancer, including the number of people with cancer on both sides of the family, the type of cancer and the age and onset of primary cancers.
- A GP caring for 1000 patients would expect to have 15–17 patients with a hereditary cancer predisposition.
- As genetic testing becomes more accessible it is prudent to be aware of the psychological consequences to patients of predictive or presymptomatic testing. Specialised genetic counselling is advisable.
- Carrier screening is now widely used for thalassaemia, Tay–Sachs disorder and cystic fibrosis.

- Prenatal screening and testing for genetic disorders is also a reality, especially for Down syndrome, fetal abnormalities and the haemoglobinopathies. Once again, careful selection, screening and counselling is important.
- Genetic services and familial cancer clinics provide an excellent service for referral, especially for genetic counselling expertise and advice about appropriate services and genetic testing.
- Pharmacogenetics and gene therapy are the future hope for targeted treatments based on a person's genetic profile.

The spectrum of genetic disorders

The list of inherited disorders continues to grow as evidence supports intuition that certain conditions are hereditary. It is important for the family doctor to be aware of this potential. We are familiar with the more common classic disorders, such as cystic fibrosis, thalassaemia, Down syndrome and haemochromatosis, but it is incumbent on us to be conversant with the genetic basis of diseases such as cancer, particularly breast, ovarian and bowel cancer, in addition to the childhood chromosomal/microdeletion syndromes, various inborn errors of metabolism and the ever-emerging rare mutations, such as the mitochondrial disorders.

Genetic inheritance can be broadly grouped as four types:

- single gene inheritance, e.g. cystic fibrosis
- multifactoral, e.g. diabetes, CAD
- chromosomal abnormalities, e.g. Down syndrome
- mitochondrial, e.g. MELAS syndrome

Inheritance can also be considered as autosomal dominant (AD), autosomal recessive (AR) or sex linked (XL), e.g. haemophilia, red-green colour blindness.

A general classification of inherited genetic disorders is outlined in TABLE 23.1 . However, many other disorders are not included.

Table 23.1 An overview (classification) of significant genetic disorders

Specific important genetic disorders
Haemochromatosis

Cystic fibrosis

Neurological disorders (see CHAPTER 22)

Inherited childhood-onset neurological disorders

Duchenne muscular dystrophy

Familial periodic paralysis

Myotonic dystrophy

Neurofibromatosis

Spinal muscular atrophy

Tay–Sachs disease

Phenylketonuria

Tourette syndrome

Inherited adult-onset neurological disorders

Creutzfeldt–Jakob and other prion disorders

Familial Alzheimer disease

Familial epilepsy

Familial motor neurone disease

Friedreich ataxia

Hereditary peripheral neuropathies (Charcot–Marie–Tooth disease)

Hereditary spastic paralysis

Huntington disease

Mitochondrial disorders

Muscular dystrophies (various)

Parkinson disease of early onset (complex)

Retinitis pigmentosa

Spinocerebellar ataxias

Wilson disease

Mental health

Schizophrenia, bipolar disorder, major depression

Childhood: ADHD, autism spectrum disorder, Tourette syndrome

Hereditary haemoglobinopathies and haemolytic disorders

Thalassaemia α and β

Sickle-cell disorder

Hereditary spherocytosis

G6PD deficiency (favism)

Galactosaemia

Bleeding disorders(see CHAPTER 29)

Haemophilia A and B

von Willebrand disease

Inherited thrombocytopenia

Hereditary haemorrhagic telangiectasia

Thrombophilia (see CHAPTER 123)

Factor V Leiden gene mutation

Prothrombin gene mutation

Protein C deficiency

Protein S deficiency

Antithrombin deficiency

Chromosomal microdeletion syndromes (childhood expression)

Down syndrome (Trisomy 21)

Edward syndrome (Trisomy 18)

Patau syndrome (Trisomy 13)

Fragile X syndrome

Prader–Willi syndrome

Williams syndrome

Marfan syndrome

Noonan syndrome

Angelman syndrome (complex)

Progeria

CHARGE syndrome (mutation)

Achondroplasia

Sex chromosome abnormalities

Klinefelter syndrome

Jacob syndrome

Turner syndrome

Intersex states

Mixed gonadal dysgenesis

Ovotesticular disorder DSD

46 XX DSD (androgenised females)

46 XY DSD (underandrogenised males)

Congenital adrenal hyperplasia

Developmental delay and intellectual disability

Chromosomal microdeletion syndromes (majority above)

Autism spectrum disorder (uncertain)

Fetal alcohol spectrum disorder

Cardiovascular conditions

Sudden arrhythmic/cardiac death syndrome

Familial hypertrophic cardiomyopathies

Familial hyperlipoproteinaemia/hypercholesterolaemia

Familial cancer

Features of breast–ovarian cancer syndrome

Colorectal cancer

Other cancers where family history is important

Other inherited conditions—unclassified

Diabetes (mixed)

Gaucher disease

Glycogen storage disease (liver glycogenosis)

Polycystic kidney disease

Skin disorders (e.g. psoriasis, atopic dermatitis, hyperhidrosis)

The porphyrias

Tuberous sclerosis

Pharmacogenomics—drug response with inherited genes

The genogram

The genogram is a valuable pedigree chart that usually covers at least three generations of a family tree. It is a simple and disciplined means of gathering data about an individual couple or family to determine inheritance patterns. The data have to be gathered with tact and care. A useful strategy is to encourage patients to develop their own family genogram using charts as templates.

An example including the use of symbols is shown in FIGURE 23.1 .

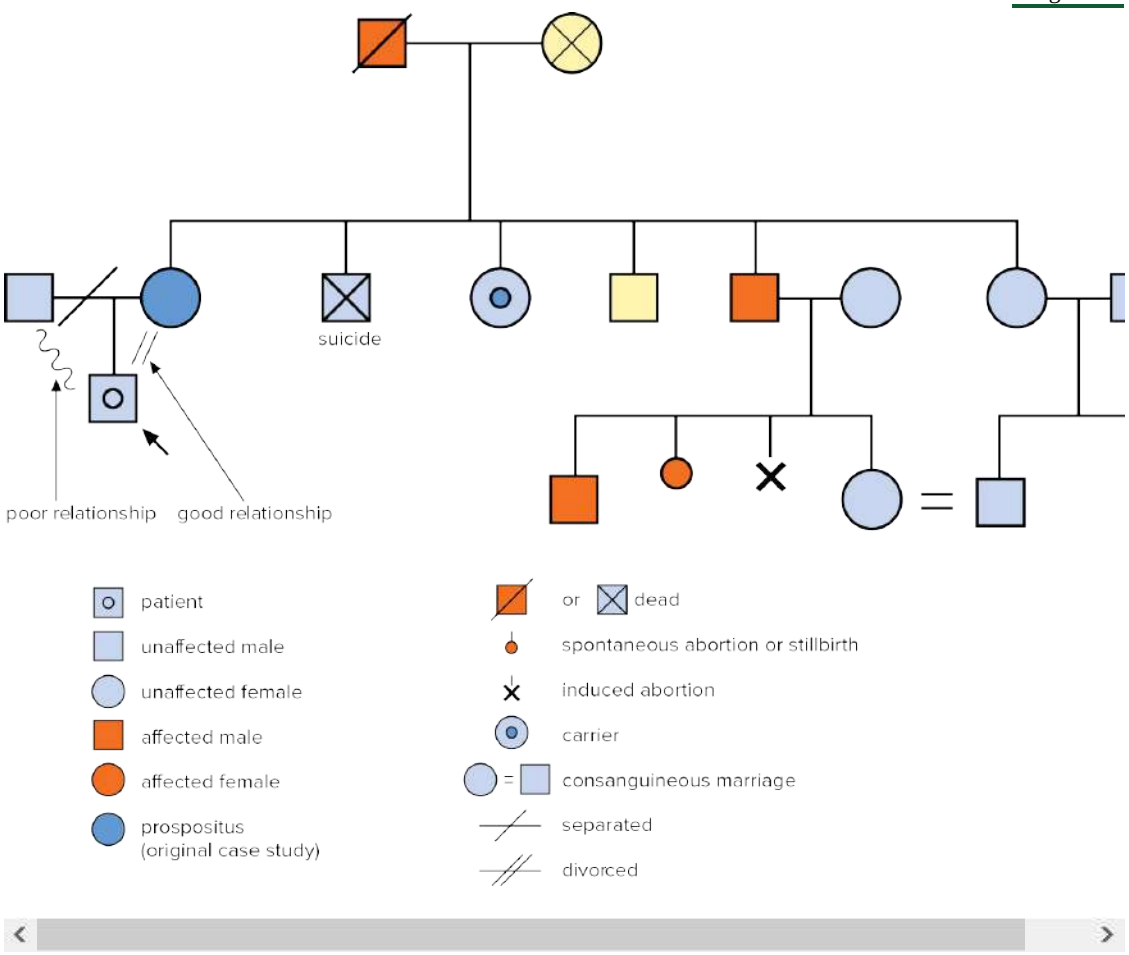

FIGURE 23.1 Genogram: illustration of a family tree for an inherited disorder

Specific important genetic disorders

Haemochromatosis

Hereditary haemochromatosis (HHC), which is a disorder of iron overload, is the most common serious single gene genetic disorder in our population.

It is a common condition in which the total body iron concentration is increased to 20–60 g (normal 4 g). The excess iron is deposited in and can damage several organs:

- liver—cirrhosis (10% develop cancer)
- pancreas—‘bronze’ diabetes

- skin—bronze or leaden grey colour
- heart—restrictive cardiomyopathy
- pituitary—hypogonadism, impotence
- joints—arthralgia (especially hands), chondrocalcinosis

It is usually hereditary (autosomal recessive = AR) or may be secondary to chronic haemolysis and multiple transfusions.

Note: Hereditary haemochromatosis is the genetic condition; haemosiderosis is the secondary condition.

Genetic profile[9]

Being an autosomal recessive disorder, the patient must inherit two altered (mutated) copies of the gene. It is a problem mainly affecting Caucasians, usually from middle age onwards. About 1 in 10 people are silent carriers of one mutated gene, while 1 in 200 are homozygous and are at risk of developing haemochromatosis. These people can have it to a variable extent (the penetrance factor), and some are asymptomatic while others have a serious problem. It is rare for symptoms to manifest before the third decade.[10]

The two common identified specific mutations in the *HFE* gene are C282Y and H63D (another is S65C):

- homozygous C282Y—high risk for HHC
- homozygous H63D—unlikely to develop clinical HHC
- heterozygous C282Y and H63D—milder form of HHC

The key diagnostic sensitive markers are serum transferrin saturation and the serum ferritin level. The serum iron level is not a good indicator. An elevated ferritin level is not diagnostic of HHC but is the best serum marker of iron overload.

Clinical features

Most patients are asymptomatic but may have extreme lethargy, abdominal discomfort, signs of chronic liver disease, polyuria and polydipsia, arthralgia, erectile dysfunction, loss of libido and joint signs.

Signs: look for hepatomegaly, very tanned skin, cardiac arrhythmias, joint swelling, testicular atrophy.

Diagnosis

- Increased serum transferrin saturation: >50% (F); >60% (M)

- Increased serum ferritin level: >200 mcg/L (F); >300 mcg/L (M) (see CHAPTER 13)
- CT, MRI or FerriScan—increased iron deposition in liver
- Liver biopsy (if liver function test enzymes are abnormal or ferritin >1000 mcg/L or hepatomegaly)—FerriScan now preferred
- Genetic studies: *HFE* gene—a C282Y and/or H63D mutation
- Screen first-degree relatives (serum ferritin levels and serum transferrin saturation in older relatives and genetic testing in younger ones). No need to screen before adulthood. HbEPG gene for pregnant patient and partner.
- Routine screening not recommended

Note: Full blood count (FBE) and erythrocyte sedimentation rate are normal.

Management

- Refer for specialist care
- Weekly venesection 500 mL (250 mg iron) until serum iron stores are normal (may take at least 2 years), then every 3–4 months to keep serum ferritin level <100 mcg/L (usually 40–80 mcg/L), serum transferrin saturation <50% and iron levels normal
- Desferrioxamine can be used but not as effective as venesection
- Normal, healthy low-iron diet
- Avoid or limit alcohol
- Avoid iron tablets and vitamin C
- Life expectancy is normal if treated before cirrhosis or diabetes develops

Cystic fibrosis[10]

Cystic fibrosis is the result of a defect in an ion channel protein, the cystic fibrosis transmembrane receptor, which is found in the membranes of cells lining the exocrine ducts. The defect affects the normal transport of chloride ions, leading to a decreased sodium and water transfer, thus causing viscid secretions that affect the lungs, pancreas and gut.

Genetic profile[7,11]

- The most common AR paediatric illness
- About 1 in 2500 Caucasians affected

- About 1 in 20–25 are carriers
- A mutation (δ-F508) of chromosome 7 is the most common of some 500 possible mutations of the gene. This deletes a single phenylalanine residue from a 1480-amino acid chain.

Clinical features

- General: malaise, failure to thrive, exercise intolerance
- Chronic respiratory problems: cough, recurrent pneumonia, bronchiectasis, sinus tenderness, nasal polyps
- Gastrointestinal: malabsorption, pale loose bulky stools, jaundice (pancreatic effect), meconium ileus (10% of newborn babies)
- Infertility in males (atrophy of vas deferens)
- Pancreatic insufficiency
- Early mortality but improving survival rates (mean age now 31 years)

DxT failure to thrive + chronic cough + loose bowel actions → cystic fibrosis

Diagnosis

- Screening for immunoreactive trypsin/trypsinogen in newborns detects 75%
- Sweat test for elevated chloride and sodium levels
- DNA testing for carriers identifies only the most common mutations (70–75%)

Treatment

- Early diagnosis and multidisciplinary team care are important
- Physiotherapy for drainage of airway secretions
- Hypertonic saline solution (by nebuliser) preceded by a bronchodilator
- Treatment of infections: therapeutic and prophylactic antibiotics
- Oral pancreatic enzyme replacement
- Dietary manipulation
- Lung and liver transplantation are considerations

There is currently no cure for cystic fibrosis; treatment is based on correcting the nutritional deficiencies and minimising chest infections.

Inherited childhood-onset neurological disorders

Neurofibromatosis

- NF1—peripheral neurofibromatosis (von Recklinghausen disorder)
- NF2—central type, bilateral acoustic neuromas (schwannomas) (rare)

The gene for NF1 is carried on chromosome 17 and NF2 on chromosome 22. Diagnostic genetic testing is not routinely available. Diagnosis is by clinical examination.

DxT light-brown skin patches + skin tumours + axillary freckles → NF1

Clinical features of NF1[9]

- Six or more café-au-lait spots (increasing with age)
- Freckling in the axillary or inguinal regions
- Flesh-coloured cutaneous tumours (appear at puberty)
- Hypertension
- Eye features (iris hamartomas)
- Learning difficulty
- Musculoskeletal problems (e.g. scoliosis, fibrous dysplasia, pseudoarthrosis)
- Optic nerve gliomas

General rule

- One-third asymptomatic, only have skin stigmata
- One-third minor problems, mainly cosmetic
- One-third significant problems (e.g. neurological tumours)

Management

- No special treatment available
- Surgical excisions of neurofibromas as appropriate
- Refer to a special clinic, including neurofibroma clinic
- Careful surveillance—report new symptoms
- Yearly examination for children and adults, including blood pressure, neurological, skeletal and ophthalmological examination

Duchenne muscular dystrophy (DMD)

DMD is a progressive proximal muscle weakness disorder with replacement of muscle by connective tissue. Becker muscular dystrophy is a less severe variant. Early diagnosis is important. First signs are delayed motor development, speech and language.

Genetic profile

DMD is an X-linked recessive condition. It is caused by a mutation in the gene coding for dystrophin, a protein found inside the muscle cell membrane.

Clinical features[9]

- Usually diagnosed from 2–5 years
- Weakness in hip and shoulder girdles
- Walking problems: delayed onset or starting in boys aged 3–7
- Waddling gait, falls, difficulty standing and climbing steps
- Pseudohypertrophy of muscles, especially calves
- Most in wheelchair by age 10–12
- ± Intellectual retardation/learning difficulties
- Most die of respiratory problems by age 25
- Gower sign: patient uses ‘trick’ method by using hands to climb up his or her legs when rising to an erect position from the floor

DxT male child + gait disorder + bulky calves → DMD

Diagnosis (initiate at first suspicion)

- Elevated serum creatinine kinase level
- Electromyography
- Direct dystrophin gene testing
- Muscle biopsy

Treatment

- Counselling, especially genetic counselling, education, screening (especially mother)
- No specific treatment available; support; corticosteroids delay progression

Spinal muscular atrophy (SMA)

Claimed to be the leading genetic cause of infant death, SMA includes several types, all manifesting as progressive muscle wasting and leading to early death in the more severe types.

Genetic profile

SMA is autosomal recessive and due to mutation in SMN1 gene on chromosome 5. Prevalence 1 in 6000–10 000; carriers 1 in 40.

Clinical features

- Muscle weakness, poor tone and floppiness
- Feeding difficulties and feeble cry in babies
- Weak swallowing, coughing and breathing
- Normal intelligence and sensory modalities

Diagnosis is by DNA screening at birth and EEG studies. There is no cure at present and treatment is mainly supportive. Zolgensma gene therapy is given as a single IV injection into children <2 years before symptoms appear. Intrathecal injections of nusinersen are available.

Myotonic dystrophy

Genetic profile: AD disorder.

Clinical features

- Typically presents 20–30 years as myotonia (tonic muscle spasm), occasionally in

childhood

- Muscle weakness, esp. hands, legs, face, neck
- Slow relaxation of hand grip
- ‘Hatchet face’—long haggard look with atrophy of facial muscles
- Frontal baldness in men
- Cataracts
- Mental impairment
- Cardiac disturbances, e.g. cardiomyopathy
- Endocrine abnormalities, e.g. diabetes

Investigation: electromyography.

Treatment (to date) has no effect on the course of this disorder.

Familial periodic paralysis

See CHAPTER 22 .

Tay–Sachs disease

About 1 in 25 Ashkenazi Jews is a carrier of Tay–Sachs disease (gangliosidosis), an AR disorder caused by a total deficiency of hexosaminidase A resulting in an accumulation of gangliosides in the brain.

The infantile form is fatal by age 3 or 4 with early progressive loss of motor skills, dementia, blindness, macrocephaly and cherry-red retinal spots. The juvenile-onset form presents with dementia and ataxia, with death at age 10–15. The adult form has progression of neurological symptoms following clumsiness in childhood and motor weakness in adolescence. Carrier testing is available and prenatal diagnosis is available.

Phenylketonuria (PKU)[10]

This autosomal recessive disorder of the catabolism of the amino acid, phenylalanine, is caused by a deficiency of phenylalanine hydroxylase activity, leading to an elevation of plasma phenylalanine, which if untreated can cause intellectual disability (often very severe) and other neurological symptoms, such as seizures. Neonatal screening for high blood phenylalanine levels (the Guthrie test) is performed routinely.

Treatment aims to limit phenylalanine intake so that essential amino acid needs are met but not

exceeded. Diet therapy must commence as soon as possible. Females who have been treated for PKU need pre-pregnancy counselling and dietary management during pregnancy to prevent damage to the fetus by high phenylalanine levels.

Tourette syndrome

See CHAPTER 87 .

Tourette syndrome appears to be a genetic condition since a child of a person with TS has a 50% chance of developing it (possibly AD with variable penetrance).

Inherited adult-onset neurological disorders[11,12]

These disorders have the following common features.

- They are serious and usually eventually fatal.
- Onset is in adulthood.
- They are currently incurable.
- They affect successive generations.
- Most are inherited from a parent in an autosomal dominant fashion.
- Specific genetic testing is usually available.

Examples of inherited adult-onset neurological conditions are:

- Huntington disease
- Creutzfeldt–Jakob disease and other prion diseases (see CHAPTER 22)
- familial Alzheimer disease
- familial epilepsy
- familial motor neurone disease
- Friedreich ataxia
- hereditary peripheral neuropathies (Charcot–Marie–Tooth disease)
- mitochondrial disorders
- hereditary spastic paraparesis
- muscular dystrophies

- myotonic dystrophy
- spinal muscular atrophy
- spinocerebellar ataxias

A minority of these conditions are due primarily to a dominantly inherited genetic alteration (mutation), e.g. Huntington disease, and are usually more accessible to genetic testing. Some gene alterations (polymorphism) may be associated with a higher risk of developing certain neurological conditions. Testing for polymorphisms is more complex. If concerned about a hereditary basis, GPs should refer their patients with these disorders to a neurologist or a neurogenetics clinic.

Huntington disease[10]

Genetic profile

- Inherited as an AD disorder.
- The responsible mutant gene has been located on the short arm of chromosome 4.
- One genetic mutation accounts for the vast majority of cases, which means that there is an accurate diagnostic test.
- Both sexes are equally affected.

DxT chorea + abnormal behaviour + dementia + family history → Huntington disease

Clinical features

- Insidious onset and progression of chorea
- Onset most often between 35 and 55 years
- Mental changes—change in behaviour (can be as early as childhood or in very late life), intellectual deterioration leading to dementia
- Family history present in the majority
- Motor symptoms: flicking movements of arms, lilting gait, facial grimacing, ataxia, dystonia
- Usually a fatal outcome 15–20 years from onset

Treatment

- There is no cure or specific treatment
- Supportive treatment with agents such as haloperidol

Genetic testing and counselling

This is available, sensitive and important because offspring have a 1 in 2 risk and the onset may be late—after child-bearing years. It is appropriate to refer to expert centres for those seeking it. Of interest is that only 20% have undergone testing since it became available, indicating that those at risk generally prefer the uncertainty of not knowing the reality.

Familial Alzheimer disease (FAD)

Early-onset familial Alzheimer disease (EoFAD), which accounts for less than 1% of all Alzheimer disease, is defined as the presence of two or more affected people with onset age <65 years in more than one generation of a family, with postmortem pathologically proven Alzheimer disease in at least one person. There are two forms of FAD: early onset (EoFAD <65 years) and late onset (LoFAD). Mutations in any one of three different forms (alleles) of the susceptible *APOE* gene are known to cause FAD.[10,13]

Parkinson disease

Most cases are sporadic, and the majority of cases with a family history do not have a clear inheritance pattern and could be the result of several factors including a genetic predisposition or simply a chance aggregation. Consider referral to a neurogenetics clinic for families with unusual features, such as familial aggregation and/or early-onset Parkinson disease.

Motor neurone disease (MND) (amyotrophic lateral sclerosis)

Five to 10% of motor neurone disease is inherited, with an autosomal dominant inheritance pattern. Inherited MND shows familial aggregation and an earlier age of onset than average (40s or younger); otherwise clinical features are essentially the same as the sporadic form (see CHAPTER 22). If more than one family member presents with MND consider referral to a neurogenetic clinic.

Mitochondrial disorders

Mitochondrial disease is usually caused by mutations of the genes or DNA. Since mitochondria are the ‘power plants of the cells’, disorders cannot convert food into energy so high energy tissues such as muscle and the brain are particularly at risk. The variety of disorders include neuromuscular diseases (referred to as mitochondrial myopathies), Leber hereditary optic neuropathy, varieties of Parkinson disease, myoclonic epilepsy, chronic progressive external ophthalmoplegia and the deadly MELAS syndrome (myopathy, encephalopathy, lactic acidosis and stroke-like episodes). Suspected cases should be referred for diagnosis which includes

muscle testing. Treatment is supportive.

The epilepsies

The epilepsies comprise a group of disorders with differing genetic components and the inheritance or genetic contribution relates to each specific disorder. Further studies on this subject are in progress. If there are two or more individuals in a family with epilepsy, referral for advice about the nature and inheritance about their form of epilepsy may be appropriate.

Mental health

According to Nature Genetics Consortium, there are five significant inherited psychiatric disorders:[14]

- schizophrenia
- bipolar disorder
- major depressive disorder
- attention deficit hyperactivity disorder (ADHD)
- autism spectrum disorder

Serious psychotic and mood disorders can run in families, especially schizophrenia and bipolar disorder, which have a clear genetic component that appears to be complex and poorly understood (see TABLE 23.2). To date, no genes causing schizophrenia have been identified, but large regions on some chromosomes have been associated with schizophrenia. Individuals with a first-degree relative with bipolar disorder or purely depressive (unipolar) disorder have an increased risk of a mood disorder, but the genetics are not understood. Tourette syndrome is another psychological disorder that has a hereditary basis through an autosomal dominant gene with variable expression (penetrance).

Table 23.2 Genetic risks (approximate) in schizophrenia and bipolar disorder

Affected relative	Schizophrenia (% risk)	Bipolar (% risk)
Nil (general population)	1	2–3
Parent	13	15
Both parents	45	50
Sibling	9	13
Sibling and one parent	15	20

Monozygotic twin	40	70
Dizygotic twin	10	20

Source: Reproduced with permission from Harper PS. *Practical Genetic Counselling*. 3rd ed. Butterworth-Heinemann; 1988.

Hereditary haemoglobinopathies, haemolytic disorders, and bleeding and clotting disorders[10,15]

The commonest haemoglobinopathies are the thalassaemias, which are caused by a deficiency in the quality of globin chains, whereas other haemoglobinopathies are caused by structural variations in the globin chain. These conditions include HbS (sickle cell), HbC, HbD, HbE, HbO and HbLepore.

Other inherited conditions that can cause haemolytic anaemia are those with a red cell membrane defect and include hereditary spherocytosis, hereditary elliptocytosis and hereditary stomatocytosis.

Thalassaemia

The thalassaemias, the most common human single-gene disorders in the world, are a group of hereditary disorders characterised by a defect in the synthesis of one or more of the globin chains (α or β)—there are two of each (α2, β2). This causes defective haemoglobin synthesis leading to hypochromic microcytic anaemia. α-thalassaemia is usually seen in people of Asian origin while β-thalassaemia is seen in certain ethnic groups from the Mediterranean, the Middle East, South-East Asia and the Indian subcontinent. However, in our multicultural communities one cannot assume a person's origins. It is recommended that all women of child-bearing age be screened for thalassaemia. The thalassaemias are described as 'trait' when there are laboratory features without clinical expression.

Genetic profile[9]

α-thalassaemia is usually due to the deletion of one or more of the four genes for α-globin, the severity depending on the number of genes deleted: deletion of all four genes—α-thalassaemia (hydrops fetalis); of three genes—haemoglobin H disease, which results in lifelong anaemia of mild-to-moderate degree; of one or two genes—a symptomless carrier.

In β-thalassaemia, the β-chains are produced in decreased quantity rather than having large deletions. People who have two mutations (one in each β-globin gene) have β-thalassaemia major.

- β-thalassaemia minor—a single mutation (heterozygous)—the carrier or trait state
- β-thalassaemia major—two mutations (homozygous)—the person who has the disorder

If both parents are carriers, there is a 1 in 4 chance that their child will have the disorder.

Clinical features

Carriers are clinically asymptomatic and do not need treatment apart from counselling. Patients with thalassaemia major present with symptoms of severe anaemia (haemolytic anaemia). Without treatment, children with thalassaemia major are lethargic and inactive, show a failure to thrive or to grow normally, and delayed puberty, hepatosplenomegaly and jaundice. Signs usually appear after 6 months and death from cardiac failure used to be common but with regular blood transfusions and iron-chelating treatment people can now live in good health.

DxT pallor + jaundice + hepatosplenomegaly → thalassaemia major

Diagnosis[10]

- FBE: in most carriers the mean corpuscular haemoglobin/mean corpuscular volume is low but can be normal. There is usually mild hypochromic microcytic anaemia but this is severe with the homozygous type.
- Haemoglobin electrophoresis: measures relative amounts of normal adult haemoglobin (HbA) and other variants (e.g. HbA_2, HbF). This will detect most carriers.
- Serum ferritin level: helps distinguish from iron deficiency, which has a similar blood film.
- DNA analysis: for mutation detection (mainly used to detect or confirm carriers).

Treatment for thalassaemia major

Treatment is based on a regular blood transfusion schedule for anaemia. Avoid iron supplements. Folate supplementation and a low-iron diet are advisable. Excess iron is removed by iron chelation (e.g. desferrioxamine). Allogeneic bone marrow transplantation has been used with success.[16] Splenectomy may be appropriate.

Sickle-cell disorders

The most important abnormality in the haemoglobin (Hb) chain is sickle-cell haemoglobin (HbS), which results from a single base mutation of adenine to thymine, leading to a substitution of valine for glutamine at position 6 on the β-globin chain. The defective Hb causes the red cells to become deformed in shape—'sickled'. The sickled cells tend to flow poorly and clog the microcirculation, resulting in hypoxia, which compounds the sickling. Such attacks, which result in tissue infarction, are called 'crises'. Sickling is precipitated by infection, hypoxia, dehydration, cold and acidosis, and may complicate operations. The autosomal recessive disorder occurs mainly in Africans (25% carry the gene), but it is also found in India, South-East Asia, the Middle East and southern Europe.

- Heterozygous state for HbS = sickle-cell trait
- Homozygous state = sickle-cell anaemia/disease

Sickle-cell anaemia

This varies from being mild or asymptomatic to a severe haemolytic anaemia and recurrent painful crises. It may present in children with anaemia and mild jaundice. Children may develop digits of varying lengths from the hand-and-foot syndrome due to infarcts of small bones.

Features of infarctive sickle crises include:

- bone pain (usually limb bones)
- abdominal pain
- chest—pleuritic pain
- kidney—haematuria
- spleen—painful infarcts
- precipitated by cold, hypoxia, dehydration or infection

Hb electrophoresis is needed to confirm the diagnosis.

Long-term problems include chronic leg ulcers, susceptibility to infection, aseptic necrosis of bone (especially head of femur), blindness and chronic kidney disease. The prognosis is variable. Children in Africa often die within the first year of life. Infection is the commonest cause of death.

Sickle-cell trait

People with this usually have no symptoms unless they are exposed to prolonged hypoxia, such as anaesthesia and flying in non-pressurised aircraft. The disorder is protective against malaria.

Hereditary spherocytosis

This is the commonest cause of inherited haemolytic anaemia in northern Europeans. It is an autosomal dominant disorder of variable severity, although in 25% of patients neither parent is affected, suggesting spontaneous mutation in some instances. Jaundice may present at birth or be delayed or occur not at all. Splenomegaly is a feature and splenectomy is considered to be the treatment of choice in severe cases. Maintenance of folic acid levels is important.

Glucose-6-phosphate dehydrogenase deficiency

G6PD deficiency is a common disorder affecting over 400 million people worldwide. It is the

most common red cell enzyme defect that causes episodic haemolytic anaemia because of the decreased ability of red blood cells to cope with oxidative stresses. It is an X-linked recessive inherited disorder with a high prevalence among people of African, Mediterranean or Asian ancestry. In some countries such as Malaysia there is a national screening program.

The important clinical features are:

- asymptomatic in many
- neonatal jaundice—infants at risk should be observed after delivery (at least 5 days)
- episodic acute haemolytic anaemia—triggered by antioxidants and infections, and drugs, especially antimalarials, sulfonamides, nitrofurantoin, quinolones, traditional medicines, vitamins C and K, high dose aspirin, fava (broad) beans and naphthalene (e.g. moth balls)

There is no specific treatment. Known precipitants should be avoided. Avoid penicillin and probenecid.

Diagnosis is by G6PD assay and a blood film during an attack.

Galactosaemia[10]

Galactosaemia is an inborn error of metabolism in which the body is unable to metabolise galactose to glucose. There are three clinical syndromes caused by differing enzyme deficiencies, one of which is galactose-1-phosphate uridyl transferase, which causes the classic syndrome. It is an autosomal recessive disorder with an incidence of about 1 in 60 000 births. As lactose is the major source of galactose, the infant becomes anorexic and jaundiced within a few days or weeks of taking breast milk or lactose-containing formula. It can be rapidly fatal. Management is with a galactose (mainly lactose)-free formula such as soy with added calcium and vitamins.

Bleeding disorders

In inherited bleeding deficiency disorders, there are deficiencies of vital factors (see CHAPTER 29). The common significant disorders are:

- haemophilia A (factor VIII deficiency)—X-linked recessive
- haemophilia B (factor IX deficiency)—X-linked recessive
- von Willebrand disease (deficiency of factor VIII:C + defective platelet factor)—autosomal dominant

Others to consider are:

- hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu disease)
- inherited thrombocytopenia

Hereditary haemorrhagic telangiectasia

This is an autosomal dominant disorder of the development of vasculature. A strong family history aids diagnosis.

Key features:

- mucocutaneous telangiectasia (Osler–Weber–Rendu syndrome)
- recurrent epistaxis in children and adolescents
- visceral arteriovenous malformations, e.g. GIT, lips
- diagnosis is clinical, aided by imaging to detect AVMs

Thrombophilia

This should be considered in patients with a past and/or family history of DVT or other thrombotic episodes (see CHAPTER 122). There are several causes, including important inherited factors, which are:

- factor V Leiden gene mutation (activated protein C resistance)
- prothrombin gene mutation
- protein C deficiency
- protein S deficiency
- antithrombin deficiency

It is important to be aware of these factors, especially in people with a past history of unexplained thrombotic episodes. Prescribing the oral contraceptive pill (OCP) is an issue but preliminary screening for thrombophilias is not recommended. In factor V Leiden, the most common factor in this group, there is a 35-fold increased risk of thrombosis for those taking the OCP.

Chromosomal/microdeletion syndromes (childhood expression)[10]

The following disorders, whose clinical features manifest in children, present with developmental and intellectual disability.

Down syndrome[17]

Down syndrome (trisomy 21) is based on typical facial features (flat facies, slanting eyes, prominent epicanthic folds, small ears), hypotonia, intellectual disability and a single palmar crease.

DxT typical facies + hypotonia + single palmar crease → Down syndrome

Facts

- 95% have extra chromosome of maternal origin (trisomy 21)
- Remainder due to either unbalances, translocations or mosaicism
- Prenatal screening tests include early ultrasound (nuchal translucency) and maternal serum screening in first trimester (serum maternal and fetal DNA). Karyotyping of chorionic villus sampling on amniocytes for pregnancies at risk is available.
- Prevalence 1 in 650 live births

Associated disorders

- Seizures (usually later onset)
- Impaired hearing
- Leukaemia
- Hypothyroidism
- Congenital anomalies (e.g. heart, duodenal atresia, Hirschsprung, TOF)
- Alzheimer-like dementia (fourth–fifth decade)
- Atlantoaxial instability
- Coeliac disease
- Diabetes

Management

- Assess child’s capabilities
- Refer to agencies for assessment (e.g. hearing, vision, developmental disability unit)
- Advise on sexuality, especially for females (i.e. menstrual management, contraception) as fertility must be presumed

- Genetic counselling for parents

CHARGE syndrome

- Coloboma, heart abnormalities, choanal atresia, development retardation, GU anomalies, ear abnormalities
- Caused by a gene mutation on chromosome 8

Edward syndrome[10]

Trisomy 18

Clinical features

These include:

- incidence 1 in 2000 live births (approx.)
- microcephaly
- facial abnormalities, e.g. cleft lip/palate
- malformations of major organs, e.g. heart
- malformations of hands and feet—clenched hand posture
- neural tube defect

Prognosis is poor—about one-third die in first month, <10% live beyond 12 months.

Prenatal diagnosis is available.

Patau syndrome[10]

Trisomy 13

Clinical features

These include:

- incidence 1 in 7000 (approx.)
- microcephaly
- brain and heart malformation

- cleft lip/palate
- polydactyly
- neural tube defect

Prognosis is poor—50% die within first month.

Fragile X syndrome (FXS)[17]

FXS presents as a classic physical phenotype with large prominent ears, long narrow face, macro-orchidism and intellectual disability. It is the most common inherited cause known of developmental disability and should always be considered. The cause is the result of an increase in the size of a trinucleotide repeat in the *FMR-I* gene on the X chromosome (the number of sequences determines carrier or full mutant status). Any individual with significant development delay should be tested for FXS.

DxT characteristic facies + intellectual disability + large testes → FXS

Facts

- M:F ratio 2:1
- Prevalence of full mutation 1 in 4000
- Variable spectrum of characteristic features, making detection difficult in some cases
- 1 in 250 are pre-mutation carriers
- Family history of intellectual disability
- Affects all ethnic groups
- Females may appear normal but may be affected

Diagnosis

- Cytogenetic testing (karyotyping)
- DNA test (specific for full mutation as well as carriers)

Associated disorders[18]

- Intellectual disability (IQ <70)

- Autism or autistic-like behaviour
- Attention deficit in 10% (with or without hyperactivity)
- Seizures (20%)
- Connective tissue abnormalities
- Learning disability and speech delay
- Coordination difficulty
- Primary ovarian insufficiency
- Late-onset tremor/ataxia syndrome

Management

- Careful genetic appraisal and counselling
- Assessment of child's capabilities
- Multidisciplinary assessment, including developmental disability unit
- Referral for integration of speech and language therapy, special education, behaviour management
- Pharmacological treatment of any epilepsy, or attention or mood behaviour disorders
- Medications may determine whether the child remains in the community or not

Prader–Willi syndrome

This uncommon disorder (1 in 10 000–15 000) has classic features, especially a bizarre appetite and eating habits, of which the GP should be aware. It is probable that there are many undiagnosed cases in the community. The most common cause is a deletion of the short arm of chromosome 15.

DxT neonatal hypotonia + failure to thrive + obesity (later) → Prader–Willi syndrome

Clinical features

- Hypotonic infants with weak suction and failure to thrive, then voracious appetite causing morbid obesity
- Usually manifests at 3 years

- Intellectual disability
- Narrow forehead and turned-down mouth
- Small hands and feet
- Hypogonadism

Management

- Early diagnosis and referral
- Multidisciplinary approach
- Expert dietetic control

With proper care and support, longevity into the eighth decade is a reality.[17]

Williams syndrome

Williams syndrome (idiopathic hypercalcaemia or elfin face syndrome) is due to a microdeletion on chromosome 7, a deletion in the elastin gene.

Children have a distinctive elfin facial appearance, mild pre- and postnatal growth retardation, mild microcephaly and mild-to-moderate developmental delay. In the first 2 years of life, feeding problems, vomiting, irritability, hyperacusis, constipation and failure to thrive may lead to presentation, but children are rarely diagnosed at this stage.

DxT 'elfin' face + intellectual disability + aortic stenosis → Williams syndrome

Marfan syndrome[10]

This is a systemic connective tissue disorder characterised by abnormalities of the skeletal, cardiovascular and ocular systems. It has variable expressions and is a potentially lethal disorder. If untreated, death in the 30s and 40s is common.

DxT tall stature + dislocated lens and myopia + aortic root dilatation → Marfan syndrome

Genetic profile

- Mutations in the fibrillin gene on chromosome 15
- Autosomal dominant

- Prevalence about 5 per 100 000
- No specific laboratory test to date

Clinical features

- Disproportionally tall and thin
- Long digits—arachnodactyly
- Kyphoscoliosis
- Joint laxity (e.g. genu recurvatum)
- Myopia and ectopic ocular lens
- High arched palate
- Aortic dilatation and dissection
- Mitral valve prolapse

Management

- Needs surveillance of eyes, heart and thoracic aorta
- Echocardiography, possibly aortic root dilatation
- Long-term beta blockade therapy reduces rate of dilatation
- Consider prophylactic cardiovascular surgery
- Genetic counselling for the family

Noonan syndrome[17]

This is an AD disorder with mutation of chromosome 11. It has been described as a male Turner syndrome but affects both sexes.

DxT facies + short stature + pulmonary stenosis → Noonan syndrome

Clinical features[17]

- Characteristic facies—down-slanting palpebral fissures, widespread eyes, low-set ears ± ptosis
- Short stature