Neuromedicine summary

Amal Awwad

Epilepsy: occasional, sudden, excessive, rapid and local discharges of grey matter.
Clinically, epilepsy is a paroxysmal disorder in which cerebral cortical neuronal discharges result in intermittent, stereotyped attacks of altered consciousness, motor or sensory function, behavior or emotion.
Classification broadly into focal (partial) or generalized.
Partial seizures are further subclassified as:

- Simple partial seizures: consciousness is retained throughout the attack;
- Complex partial seizures: consciousness is impaired at any stage.

secondarily generalized, the patient losing consciousness with clinical evidence of spread across the cerebral cortex, e.g. bilateral convulsive movements.
** subdivided according to whether it is idiopathic (most) or symptomatic (cause)

Epidemiology

strong inherited predisposition.

Up to 1% of the general population suffer from active epilepsy, with 20–50 new patients being diagnosed/ 100,000/ year.
The approximate annual death rate for epilepsy is 2/ 100,000.
relate directly to seizures: uncontrolled series of seizures, failing to regain consciousness between attacks (status epilepticus), accidental injury.
sudden unexplained death usually assumed to be related to seizure activity and possibly to associated cardiorespiratory dysfunction.

Adulthood epilepsy:

Primary generalized epilepsy

often beginning in childhood, presents a common management problem and the most typical seizure type (tonic-clonic or grand mal) is so distinctive as to warrant separate description.
Before an attack: vague symptoms of dizziness or irritability.
The convulsion itself may begin with an epileptic cry.
The patient loses consciousness and falls to the ground.
1)tonic phase, generalized muscle spasms, lasting only few S.
2)Clonic phase, sharp repetitive muscular jerks.
Tongue biting, incontinence of urine and salivation may occur.
When jerking stops, patients usually remain unconscious for approximately 30 min and confused, drowsy for several h.
On recovery, there is usually a headache and stiffness or injury from the fall. Back pain is common; muscular spasms may be of sufficient violence to result in vertebral fractures.
usually controllable with one drug.

Neonates
Birth trauma
Intracranial haemorrhage
Hypoxia
Hypoglycaemia
Hypocalcaemia
Children
Congenital anomalies
Tuberous sclerosis
Metabolic storage diseases
Young adults
Head injuries
Drugs and alcohol
Middle-aged adults
Cerebral tumor
Elderly
Cerebrovascular disease
Degenerative disorders (Alzheimer's, prion diseases)
Not all are strictly age specific; e.g. tumors , Infection, e.g. meningitis, encephalitis, abscess, cysticercosis
Inflammation – MS (rarely), vasculitis
Metabolic encephalopathy

Differential diagnosis of epilepsy.
Syncope, Cardiac dysrhythmia, Pseudoseizures
Hyperventilation/panic attacks TIA, Migraine
Narcolepsy, Hypoglycaemia, Vestibular disorders

Partial epilepsy

Temporal lobe epilepsy

aura or warning of the attack: psychic symptoms (fear or a sensation of d´ej`a vu), hallucinations (olfactory, gustatory or formed visual images) or simply a rising sensation in epigastrium.
Patients may become confused and anxious, and exhibit organized, stereotyped movements (automatism).

chewing and lip smacking, or more complex aggressive and violent.

Jacksonian epilepsy

focal motor attacks typically begin in mouth corner, thumb and index finger or great toe. Movements rapidly spread across the face or ascend the limb (Jacksonian march).
** generally associated with underlying organic brain disease, e.g. tumor in motor cortex region.
After such an attack, the affected limb(s) may remain temporarily weak (Todd's paralysis).
Epilepsia partialis continua is a rare form , where the attack persists for days, weeks or even months.

epileptic syndromes in childhood and adolescence may have consequences in adulthood.

Febrile convulsions

Seizures associated with fever:

- in 3% of otherwise normal children aged 3 m- 5 y.
- usually brief (< 15 min) generalized, some have focal, prolonged attacks, sometimes with residual neurological signs.
- in 70% its isolated attack, 2–5% risk of subsequent epilepsy
- generally do not need prophylactic anti-epilepsy drugs.

Infantile spasms (West's syndrome) a triad of:

- brief spasms beginning within the first few months of life, characteristically shock-like flexion of arms, head and neck with drawing up of the knees (salaam attack).
- progressive learning difficulties.
- characteristic EEG abnormality (hypsarrhythmia).

In a minority it's idiopathic but usually due to(perinatal asphyxia, encephalitis, metabolic disorders and cerebral malformations).

Most conventional anticonvulsant drugs are ineffective (sodium valproate and vigabatrin may be beneficial). treatment of choice is often with corticosteroids.

Absence epilepsy ('petit mal')

- starts in childhood (peak age of onset 4–8 years, F), though there is also a juvenile form.
- The attacks (typical absences) occur without warning. The child stares blankly into space and stops talking. The eyes may flutter or roll up under the lids. Recovery within S and may be many attacks daily.
- characteristic EEG abnormalities: 3-Hz generalized, symmetrical spike–wave complexes .
- Treatment: sodium valproate, ethosuximide or both.
- Patients may subsequently develop other seizure types – risk of seizures as an adult is 10%.

Partial Carbamazepine, Sodium valproate Phenytoin, Lamotrigine
Absence Ethosuximide, Sodium valproate Lamotrigine
Myoclonic Sodium valproate, Clonazepam Lamotrigine
Generalized tonic-clonic Sodium valproate Phenytoin, Carbamazepine, Lamotrigine

Juvenile myoclonic epilepsy (Janz syndrome)

a common form of primary generalized epilepsy; onset in teens.

Patients have the clinical triad of:

- infrequent generalized seizures, often on waking.
- daytime absences.
- sudden, shock-like, involuntary jerking movements (myoclonus), usually in morning.

.inexplicably spill their breakfast or throw it across the room ('Kellogg's epilepsy').

The EEG shows polyspike–wave discharges and photosensitivity.

Treatment: sodium valproate is often successful, but recurrence is likely if medication is stopped.

Alternatives: clonazepam, levetiracetam and lamotrigine.

must be distinguished from progressive myoclonic epilepsies.

** if treated incorrectly with carbamazepine may worsen.

childhood conditions where severe myoclonus and epilepsy are associated with underlying brain degenerative disease

Investigation and diagnosis

diagnosis primarily clinical, based on a description from a witness .

Pseudo-seizures: simulated attacks, unconsciously – 'hysterical', or consciously – malingering).

Investigation aims: confirming or supporting the clinical diagnosis, classifying the epileptic syndrome, establishing a cause.

The EEG has a role in the first two aims, particularly in children.

In adults there are frequent FP and FN recordings.

minor non-specific EEG abnormalities in the normal population, some epileptic patients show no abnormalities on repeated recordings between attacks (interictal EEG).

* EEG yield increased by prolonged recordings, and sleep deprivation.

some patients may need ambulatory EEG or telemetry with simultaneous video recording of symptomatic events.

- Routine blood tests, serum glu and Ca+, achieving third aim.
- brain imaging, by CT or MR scanning. particularly in epilepsy of later onset, presenting as partial attacks, +- focal neurological signs and EEG abnormalities. adult patients presenting with an isolated seizure will expect a brain scan, despite the low yield and limited influence on management of scan findings in such an unselected population.

Drug treatment

Most neurologists will not prescribe prophylactic anti-epilepsy drugs after a single isolated seizure, but after a second attack.

The choice of drug is determined by the type of epileptic syndrome.

careful outpatient follow-up is required to establish the minimum effective dosage and monitor for side effects.

Measurement of blood levels of anti-epilepsy drugs may be helpful.

(70%) will be adequately controlled with a single drug (monotherapy).

When patients are on 3 or > drugs, the likelihood of completely successful medical treatment is low.

Reasons for refractory epilepsy include:

- non-concordance with medication,
- pseudo-seizures or non-epileptic attacks (alone or + genuine seizures),
- associated structural brain disease, e.g. developmental anomalies, which may or may not be amenable to surgery.
- alcohol and lifestyle.

long-term prognosis is good, most patients attaining a 5-year remission and many successfully stopping treatment, which will be determined by:

- duration of remission, type of epilepsy, treatment side effects.
- effect of seizure recurrence on driving and employment.

Surgical treatment

intractable epilepsy, refractory to optimal doses of anti-epilepsy drugs, are increasingly being considered for neurosurgical procedures.

**patients who have a definable site of seizure onset.

Small temporal lobe lesions, sclerotic or developmental (hamartomata's) in origin, previously missed on CT scan, are now detectable by more sophisticated MR imaging techniques. If no lesion is found on imaging, an epileptogenic focus may be localized electrophysiologically.

may undergo selective removal of the epileptogenic tissue.

In less specific symptomatic surgical procedures may be indicated, including hemispherectomy and disconnection procedures, e.g. section of the corpus callosum.

Other aspects Specific triggers are only infrequently recognized, but patients should avoid alcohol and some may have attacks provoked by flickering lights, e.g. television and computer screens.

Other forms of treatment: dietary (ketogenic diet) unproven benefit.

psychological consequences of a diagnosis of epilepsy are still often underestimated but may include depression and personality disorder.

Social aspects

1)Epilepsy and driving

in the UK, people with a history of epilepsy may drive only after a seizure-free interval of at least 6 months, and should inform the Driver and Vehicle Licensing Agency. More stringent restrictions apply to drivers of heavy goods and passenger-carrying vehicles. Sleep-related epilepsy Patients may drive if they have an established pattern of seizures occurring only in relation to sleep during the previous 3 years.

2)Employment

There are statutory barriers in armed services and emergency services, and as aircraft pilots and train drivers.

3)Leisure activities

Swimming and rock and tree climbing should be restricted to situations where there is adequate supervision.

Coronal MRI of the brain showing a developmental abnormality of temporal lobe

transient ischemic attack: rapid loss of focal CNS (including retinal) function < 24. presumed caused by embolic, thrombotic or hemodynamic vascular mechanisms. Some > 24 hours, yet patients recover completely – reversible neurological deficits.

Stroke: a syndrome consisting of rapidly developing (S-min) symptoms +- signs of loss of focal (sometimes global) CNS function. symptoms > 24 h or lead to death. Vascular mechanisms causing stroke may be **classified as:**

- infarction (embolic or thrombotic).
- haemorrhage.

risk factors: Age, HTN, DM
Family history of vascular disease
Hypercholesterolemia,
Plasma fibrinogen, Alcohol.
Smoking, Oral contraceptives

heart disease and cancer.

3rd most common cause of death in developed countries. annual incidence 2/ 1000, majority are cerebral infarcts.

etiology and pathogenesis: Thrombosis of A/ V in CNS may be attributable to 1/> of **Virchow's triad:**

- vessel wall abnormalities: degenerative or inflammation (vasculitis) or trauma (dissection).
- blood abnormalities , e.g. polycythemia.
- blood flow disturbances.

The most common cause:
1-atherosclerosis in larger vessels (consequent thromboembolism)
2-small vessel disease (lipohyalinosis).

**Embolism may complicate A degenerative disease or arise from the heart: valvular disease, atrial fibrillation, recent MI.

Pathophysiology: When an A is occluded by thrombus or embolus, the area of the CNS supplied by it will undergo infarction if there is no adequate collateral blood supply. Surrounding a central necrotic zone, an 'ischemic penumbra' remains viable for a time (may recover function if blood flow is restored).

may be accompanied by swelling for two reasons:

- cytotoxic oedema – accumulation of water in damaged glial cells and neurons.
- vasogenic oedema – EC fluid accumulation as a result of breakdown of BBB.

** may produce clinical deterioration in the day Following a major stroke.

Clinical features and classification

- **Total A** (carotid) circulation infarct
  hemiplegia (damage to upper part of corticospinal tract).
  hemianopia (damage to the optic radiation).
  cortical deficits, e.g. dysphasia (dominant hemisphere).
  visuo-spatial loss (non-dominant hemisphere).
- **Partial A** circulation infarct: 2 of the above, or cortical deficit alone.
- **Lacunar** infarct: intrinsic disease (lipohyalinosis) in a small deep (perforating) A producing a characteristic syndrome, e.g. pure motor or sensory stroke, or ataxic hemiparesis.

**Multiple may produce cumulative neurological deficits, including cognitive impairment (multi-infarct dementia) and a gait disorder= small steps (marche `a petits pas) and difficulty starting walking (ignition failure) – 'gait apraxia'.

- **P** (vertebrobasilar) circulation infarct
  evidence of brainstem lesion (vertigo, diplopia, altered consciousness),
  homonymous hemianopia.
  Spinal cord infarction.

Investigations and diagnosis *clinical.
Investigations directed towards:

- establishing the cause.
- preventing recurrence.
- in severely affected patients, identifying factors that may lead to further deterioration in CNS function.

Common investigations:

- CBC, ESR, urea, electrolytes, glu, lipids.
- chest radiograph, ECG, CT cranial scan .

distinguishing between infarction and haemorrhage.
eliminates IC tumor, subdural hematoma).

Complications and course
immobilized with dense hemiplegia.
complications that may lead to early death:

- pneumonia (50% dysphagic= risk of aspiration recovers spontaneously in most patients), septicemia (via P sores or UTI),
- DVT and PE, MI, arrhythmias and HF, fluid imbalance.

Approximately 10% die in the first 30 days. Up to 50% of survivors remain dependent. Factors contributing to long-term **disability include:**

- pressure sores, epilepsy, recurrent falls and fractures, spasticity, with pain, contractures and frozen shoulder, depression.

Treatment

acute management

- Admission to a stroke unit, surgery is rarely needed.
- Aspirin 300mg/D, modest benefit in 48 h of onset, 75mg after 4 weeks.
- Thrombolysis: 15% eligible with IV tissue plasminogen activator (alteplase).

Must be started within 3 h. (time window may be 4.5 h) ineligible if the exact time of stroke onset is unkown and if they have risk factors for IC or systemic haemorrhage.
The key steps are rapid transfer to hospital and equally rapid clinical assessment including CT brain scan to exclude IC haemorrhage.

**newer techniques such as intra-arterial thrombolysis and clot retrieval, but these have not been the subjects of controlled clinical trials.

cerebellar infarction may require urgent P fossa decompression and ventricular drainage -> swelling cause brainstem compression and obstruction to CSF flow.

**malignant MCA occlusion syndrome: Young patients with total MCA infarction develop massive cerebral oedema with a high risk of raised ICP, skull vault temporary removal on infarct side (hemicraniectomy) may be life-saving.

Prevention (low animal fat, low salt, avoiding excess alcohol)

- modifying risk factors: smoking, diet and cholesterol-lowering agents (statins), In long term BP control .
- For the first 2 weeks should not receive antihypertensive therapy beyond their pre-existing treatment unless there is evidence of malignant HTN.

** too rapid lowering may worsen ischemia in a region where the cerebral circulation is already compromised.

- Lifelong antiplatelet commencing as soon as possible after an infarct.
- Anticoagulation (warfarin) is effective prophylaxis in Afib and cardiac emboli.

Rehabilitation

environment is best suited to the meticulous control of important variables which can affect outcome, e.g. hydration, T and blood glu, along with appropriate management for swallowing difficulties and venous thromboembolism. Subsequent continued physiotherapy, occupational and speech therapy, and the involvement of social services may help survivors regain independence.

Hypotension and HTN Cerebral blood flow is relatively constant(80–180mm Hg systolic) by autoregulation: intracerebral arteries alter their calibre in response to changes in cerebral perfusion P (BP -ICP), fall in P producing a widening of vessel lumen and hence constant flow.

hypovolemic shock: BP falls below autoregulatory range blood vessels are unable to dilate further infarction may occur.

**regions most likely affected: border zones or watersheds between vascular territories, as perfusion P here is usually at its lowest.

**the patient may develop visual field defects or visual agnosia as a result of infarction at the border zone between P and MCA territories.

**IN malignant HTN, the autoregulatory range may be exceeded and cerebral blood flow rises, with damage to vessel walls (fibrinoid necrosis) and consequent cerebral oedema = features of raised ICP – headache, V, drowsiness and papilledema – along with seizures and focal neurological signs.

Treatment of hypertensive encephalopathy

lowering of BP, diastolic 100–110 mm Hg initially (more drastic lowering may result in cerebral infarction if long-standing HTN has shifted autoregulatory curve to R).

IC venous sinuses Thrombosis clinical syndromes distinct from A infarction.

1)S sagittal sinus: headache, papilledema and other features resembling Benign ICP, early seizures, bilateral signs of neurological deficit, progressive, with impairment of consciousness.

causes: puerperium, dehydration, cachexia, coagulopathies, O contraceptives.

2) cavernous sinus (producing a red swollen eyelid and conjunctiva, III-Vab VI, CN palsies and papilledema) infection from the face and orbit

3)L sinus (raised ICP, seizures and drowsiness)infection from the ear.

Treatment is aimed at the underlying cause Formal IV heparinization in non-infective cases, but there may be concern about the use of anticoagulants in the presence of hemorrhagic venous infarction of the brain.

TIAs: most commonly caused by thromboembolism from atheromatous neck vessels, lipohyalinosis of IC small vessels and cardiogenic embolism. More rarely, may be due to vasculitis or hematological disease.

Clinical features

The hallmark: sudden loss of focal CNS function.

symptoms syncope, confusion and dizziness insufficient for diagnosis.

**typically last min, not h.

A territory of the attack determines the symptoms:

- Carotid (most common), hemiparesis, hemisensory loss, dysphasia, monocular visual loss (amaurosis fugax) caused by retinal ischemia;
- Vertebrobasilar: bilateral or alternating paresis or sensory loss, bilateral sudden visual loss (in older patients), diplopia, ataxia, vertigo, dysphagia – at least two simultaneously.

Prognosis and treatment

increased risk of MI, risk of stroke and MI or vascular death is 9%/ annum.

The risk of stroke in the first 5 years after a TIA is 7%/ annum, the greatest risk being in the first year, indeed the first hours, days and weeks. Up to 15% of patients presenting with their first stroke will have had preceding TIAs. risk of stroke after TIA can be stratified, depending on whether they are older, diabetic or hypertensive, and on the description and duration of the event.

**Some symptoms do not localize accurately to a specific A territory, e.g. hemianopia or dysarthria alone, usually taken to be vertebrobasilar.

**Neurological signs are usually absent by the time the patient is seen by a doctor, but cholesterol emboli may be visible on ophthalmoscopy in patients with amaurosis fugax.

**A carotid bruit may be audible if on appropriate side of a carotid TIA.

**Cardiac arrhythmias and murmurs may point to a cardiac source of embolism.

**A rare cause of vertebrobasilar TIAs is the subclavian steal syndrome.

stenosis of the proximal subclavian (sometimes with a bruit low in the neck and reduction in BP and pulse volume in the ipsilateral arm) may lead to retrograde flow down vertebral A when the arm is exercised.

Investigations and diagnosis - recognition depends on history.

Investigations are directed towards identifying the cause preventing recurrence.

- CBC, ESR, blood glu and cholesterol, syphilis serology, ECG.
- chest radiograph, echocardiogram, 24-h ECG – when cardiogenic embolism is suspected,
- CT cranial scan – detect pre-existing cerebrovascular disease, exclude remote possibility of a structural lesion (tumor, presenting with TIA symptoms)
- carotid US or angiography – detect carotid stenosis in carotid territory TIAs.
- blood cultures – when infective endocarditis is suspected.

High-risk patients assessed within 24h, low-risk within a week, to apply preventive measures:

1) modifying risk factors (HTN, smoking, serum cholesterol by diet and drugs)

2) surgical to clear atheroma from the origin of the internal carotid A is warranted for symptomatic severe carotid stenosis (>70% stenosis), TIAs or minor stroke, in less severe or asymptomatic stenoses is not so well established.

3)Carotid angioplasty and stenting is a viable alternative to surgery.

**no surgical option for most vertebrobasilar TIAs (only subclavian steal syndrome have), though selected patients have been treated by vertebral angioplasty and stenting.

- antiplatelet (low-dose aspirin):+ dipyridamole is more effective than either alone.
- contraindicated in active peptic ulcer, clopidogrel is an alternative
- anticoagulants (warfarin) with cardiogenic, non-rheumatic Afb, carotid endarterectomy

Intracranial haemorrhage

Subarachnoid haemorrhage

Etiology Bleeding into subarachnoid space is most commonly from:

- aneurysm rupture – congenital weakenings at junctions in Willis circle.
- arteriovenous malformations (angiomas) – anomalous malformed vessels, also congenital, enlarge and present in adult life.

Rarer causes: trauma, vessels weakened by infection- septic emboli from infective endocarditis (mycotic aneurysms), coagulopathies.

Clinical features

blood irritates the meninges, sudden S very severe headache with photophobia, N, V and signs of meningism (neck stiffness and Kernig's sign).

**more severe hemorrhages, ICP may rise and LOC deteriorate.

Papilledema and retinal hemorrhages may be detectable on fundoscopy.

Focal neurological signs may develop as a result of:

- false localizing effect of raised ICP,
- coexistent intracerebral haemorrhage,
- spasm of vessels, as a result of the irritant effect of blood, with concomitant ischemia.

Systemic features: bradycardia and HTN, with rising ICP, and fever possibly caused by hypothalamic damage.

pulmonary oedema and cardiac arrhythmias, chest radiograph and electrocardiogram

Investigation

- CT cranial scan will reveal subarachnoid blood in most cases.
- Small bleeds may not be detectable on CT scan.

LP may be required to confirm (no contraindication once mass lesions have been excluded by imaging and no bleeding diathesis.

** shows frank blood that fails to clear, i.e. all three bottles uniformly bloodstained. The CSF supernatant is straw or yellow colored (xanthochromia), within 3 h of the haemorrhage, because of the presence of Hb breakdown products.

- Bleeding disorders should be excluded.
- Glycosuria is sometimes present.

Prognosis and management

-Aneurysmal have very high mortality, 30–40% die in first few days.

-significant risk of rebleeding, particularly in first 6 weeks, may be more severe.

management is directed towards immediate resuscitation of the patient and prevention of rebleeding, Bed rest and analgesia are initially instituted.

calcium antagonist nimodipine reduce ischemia early morbidity.

Early complications: hydrocephalus due to CSF pathways obstruction by blood clot. may also occur later (communicating hydrocephalus). If the patient is alert or only mildly drowsy, investigation for the source of bleeding, by cerebral angiography. Identification of an aneurysm may then permit early intervention.

Operative techniques, aneurysmal neck clipping or wrapping the aneurysm, largely superseded by endovascular interventional neuroradiological approaches – occlusion of the aneurysm using detachable coils introduced by selective catheterization.

** timing and advisability of angiography and intervention in patients with more severe and impairment of consciousness is a matter of specialist judgement, as they have a worse prognosis and tolerate treatment poorly.

Bleeding arteriovenous malformations have a lower mortality than aneurysms. Investigation by angiography and treatment may be by surgery, radiotherapy or interventional neuroradiology. Arteriovenous malformations presenting without bleeding, e.g. with epilepsy, should not usually be treated surgically.

Spontaneous intracerebral haemorrhage 10% of all strokes. into the substance of the brain may be caused by:

- HTN, with microaneurysm formation (Charcot–Bouchard aneurysms),
- bleeding into tumors, trauma, blood disorders, blood vessel disorders – arteriovenous malformations, vasculitis, amyloid.

***present with** focal neurological signs depending on the site of the bleed, seizures and features of raised ICP.

diagnosis is usually evident on CT scan.

Complications: hydrocephalus and coning. (>50% mortality)

as brainstem hemorrhages, Large hematomas have a poor prognosis.

Treatment is initially medical with antihypertensive drugs, anti-epilepsy drugs for seizures, correction of coagulopathies and mannitol for raised ICP.

Surgical intervention: ventricular drainage – for acute hydrocephalus

- evacuation of hematoma – for cerebellar or cerebral lobar hemorrhages with progressive deterioration.

Parkinson's disease: a degenerative condition primarily affecting extrapyramidal pathways where dopamine is the neurotransmitter, characterized by clinical triad of:

- akinesia – poverty of movement, rigidity, tremor – shaking back and forth, of upper limbs.

Etiology and pathogenesis

MPTP, a synthetic heroin by-product, could produce acute Parkinsonism. The fact that an unusual exogenous toxin may lead to selective CNS damage and Parkinsonism has reinforced the view that idiopathic Parkinson's disease itself may be caused by exposure to a more widely prevalent environmental factor perhaps acting by a similar mechanism . Further support for environmental factors includes the following:

- The disease is increasingly common with age (mean age of onset 60 y).
- Genetic causative factors have been identified but family history is relatively unusual in idiopathic Parkinson's disease.
- a weak association with various environmental factors, exposure to wood pulp and pesticides.

Epidemiology

common, affecting about 1–2% > 60 y, no significant gender bias.

It has a worldwide distribution, though it appears more common in Europe and North America.

Pathology

The dopaminergic neurons primarily affected are those projecting from the substantia nigra of the midbrain to the striatum of basal ganglia (caudate nucleus and putamen). Macroscopically, atrophy of the substantia nigra in advanced Parkinson's disease is recognizable by loss of the characteristic melanin pigmentation.

Microscopically, severe neuronal loss is demonstrable in substantia nigra, remaining neurons often containing a distinctive IC inclusion, the Lewy body.

Symptoms: when about 60–80% of nigrostriate dopaminergic neurons have been lost. damage to dopaminergic pathways leads to an imbalance in extrapyramidal system in favor of cholinergic and other neurotransmitter mechanisms

Rigidity

increase in muscle tone differs from spasticity by being relatively constant throughout the range of movement of the joint being tested – lead pipe rigidity.

Cogwheel rigidity may be regarded as a consequence of the tremor being superimposed on background lead pipe rigidity, detected with repeated flexion and extension, or rotation, at the wrist. Rigidity in one arm can be accentuated by asking the patient simultaneously to lift and lower the opposite arm repeatedly.

Clinical features

Akinesia

'slowed down' physically (bradykinesia), difficulty with complex motor tasks, e.g. dressing, shaving, handwriting (which often becomes smaller – micrographia).

Lack of spontaneous movement may manifest itself by:

- poverty of facial expression mask-like face.
- difficulty changing position, e.g. turning in bed.
- quiet and monotonous speech.
- abnormal gait and stance, as a consequence of akinesia and loss of normal postural control.

Gait flexed, or stooped, posture (simian or apelike).

may be unable to maintain a normal stance in response to P from behind, the patient falling forward (propulsion), or from in front, falling backwards (retropulsion).

- Initiation of walking may be difficult ('freezing'), as may turning.
- 'tricks': deliberately stepping over a walking stick to change direction or get through doorways, small shuffling steps.
- festinant, as if the patient is hurrying to keep up with his or her own center of gravity. Normal arm swing on walking is lost.
- Advanced: severe postural instability, increasing risk of falls.

Tremor: involuntary, repetitive, rhythmic sinusoidal movement usually affecting one or more limbs, but occasionally involving the head (titubation), face, jaw or trunk.

- primarily affects the hands but may involve upper and LL, less frequently jaw and lips, but not the head or neck,
- in the hands is often described as 'pill rolling',
- has a characteristic frequency of 3–6 Hz,
- ipresent at rest and exacerbated by anxiety or stress,
- improves and may disappear on action.

Early are typically markedly asymmetrical, even unilateral. A substantial minority of patients display only akinesia and rigidity, without tremor. Other patients may have a postural tremor rather than a classical resting tremor.

Other motor symptoms and signs

• CN: eye movements- a mild impairment of up-gaze.
eyelids may be tremulous (blepharoclonus).
'glabellar tap sign' repeated taps to the forehead, a blink response each time the forehead is touched, without fatigue.
normally, re-flex blinking rapidly fatigues.
the sign is far from specific for Parkinson's. tendency to drool
• Difficulty swallowing, including saliva, (sialorrhoea).
• Limbs: power, reflexes and sensation are normal; plantar responses are down, Pain or aching in muscles is common – a 'frozen shoulder' is common.

Non-motor symptoms

• Depression is common and may arise independently of motor dysfunction degree .
• visual hallucinations: Vivid, particularly at night, not necessarily indicate cognitive impairment or psychosis.
• Psychosis: Worsening hallucinations and may escalate to full-blown psychosis, particularly with cognitive impairment.
• Dementia: Cognitive impairment common accompaniment.
• Sleep disorder: Insomnia is common and may relate to immobility, mood disturbance, hallucinations and various sleep-related behavioral and movement disorders.

Autonomic symptoms:

• skin may have a greasy seborrhoeic texture, Constipation.
• bladder disturbance and erectile dysfunction.
• Postural hypotension, milder than in multiple system atrophy but still common in advanced Parkinson's.
• Anosmia may antedate the onset of motor dysfunction by many years.

Course and prognosis progressive, three stages:
early, symptom control is good.
mid, motor fluctuations and dyskinesias develop.
late, treatment-resistant features, dementia and falls.
*Untreated reach a severely disabling degree of immobility, with threat to life from the risk of bronchopneumonia, septicaemia or PE, after 7–10 Y.

Diagnosis

• based on the triad of clinical features.
Asymmetry of signs at onset is important.
• Brain imaging by standard CT or MR is unhelpful.
• PET scanning is purely a research tool.
Dopamine transporter (DaT) SPECT scans can reveal a nigrostriate dopaminergic lesion, but the changes aren't specific to idiopathic Parkinson's disease and may be found in other akinetic–rigid syndromes.
• doubt, response to drug treatment is informative.
**some patients with multiple system atrophy will respond to this treatment, at least initially.

Other movement disorders –

dyskinesias opposite pole of the spectrum of movement disorders to akinetic–rigid syndromes. Excessive involuntary movements may be encountered as a consequence of drug treatment of Parkinson's disease, but there is other causes.

Chorea: irregular, random and variable movements with flowing or 'dancing' quality of any part of the body, may appear semipurposeful (normal movement being interrupted by chorea).

acquired

-chronic L-DOPA therapy in Parkinson's.
-postinfectious (Sydenham's chorea in association with rheumatic fever, now rarely seen),
-polycythaemia rubra vera, SLE, thyrotoxicosis.
-pregnancy and oral contraceptive,
-phenytoin, alcohol, neuroleptics.

Hereditary Huntington's in association with dementia, other rare inherited disorders.

Treatment:

1)monoaminedepleting (tetrabenazine), may produce severe depression.
2)neuroleptics, e.g. sulpiride or haloperidol.

hemiballismus: more violent and jerky movements, restricted to one side of the body, as a result of damage to the contralateral subthalamic nucleus.

Athetosis: movements are slower and more 'writhing' in quality than chorea.

* transition from one dystonic posture to another, typically associated with congenital brain damage (cerebral palsy), particularly that which used to occur with neonatal hyperbilirubinemia (kernicterus).

Tremor

Essential tremor: a common condition typically characterized by:

• positive family history,
• postural tremor of both hands difficulty holding cups, writing. other body parts: the head (titubation) may be affected;
tremor absent at rest,
-no extrapyramidal or cerebellar features,
-may be relieved by alcohol.
-may respond to propranolol or primidone.

Primary orthostatic tremor

unsteadiness or tremor in the legs, brought on by prolonged standing. Clonazepam can be helpful.

Dystonia:

Involuntary sustained muscle contractions resulting in abnormal postures may be subclassified as:

1) Focal:

- blepharospasm – involuntary eye closure,
- oculogyric crisis – eyes rolled upwards, in postencephalitic Parkinsonism,
- spasmodic torticollis – 'wry neck', painful contraction of sternomastoid, which may hypertrophy (and other neck muscles), resulting in head being turned involuntarily to one side, sometimes forwards (antecollis) backwards (retrocollis),
- laryngospasm – with stridor,
- trismus – jaw spasm,
- writer's cramp – painful, abnormal posture of the hand, task-specific.

2)Generalized:

- inherited primary torsion dystonia (dystonia musculorum deformans)
- drug reactions
- symptom of many causes of cerebral damage, e.g. anoxia.

Treatment: drugs is generally unsatisfactory, generalized may respond to increasing doses of anticholinergic agents, e.g. trihexyphenidyl.

* One rare form of inherited dystonia, typically presenting in the LL in childhood, is strikingly responsive to modest doses of L-DOPA.

Focal may be successfully treated by injection of affected muscles with botulinum toxin, in specialist centers.

Rare paroxysmal dystonia may respond to antiepilepsy drugs.

Myoclonus: rapid, abrupt, jerky, 'shock-like' movements of part or the whole body, which may occur in the context of abnormal electrical discharges of cerebral cortex, association with epilepsy.

myoclonic jerks can also arise from spinal cord, and may feature in degenerative and metabolic brain disorders.

* Sodium valproate and clonazepam are first-line for myoclonic epilepsies.

Tics: rapid, compulsive, repetitive, stereotyped movements = habit spasms.

can be voluntarily resisted for a limited period, but often is more violent immediately after resistance has been abandoned.

**Gilles de la Tourette syndrome, complex tics associated with involuntary utterances, which are often repetitive (echolalia) and obscene (coprolalia).

Treatment: difficult but may respond to neuroleptics.

Drug-induced movement disorders

Neuroleptic drugs: through their dopamine receptor antagonist action, are associated with many motor side effects, including:

- acute dystonic reactions.
- akathisia – restlessness, patient typically seeming 'jittery' and unable to sit.
- drug-induced Parkinsonism,
- tardive dyskinesia – patients develop involuntary movements, especially of face and mouth, may persist after the drug has been discontinued.

neuroleptic malignant syndrome: The most severe movement disorder seen with neuroleptics, potentially life-threatening , where patients have generalized muscular rigidity and fever in association with tremor, incontinence, altered consciousness and cardiovascular changes.

The rigidity is sufficient to produce muscle damage with elevation of serum creatine kinase activity and sometimes myoglobinuria.

Treatment: resuscitative measures and withdrawal of the offending drug, includes attempting to redress the neurochemical balance with a dopamine receptor agonist – bromocriptine – and use of a muscle relaxant – dantrolene.

Miscellaneous movement disorders

- **Restless legs syndrome**: (Ekbom's syndrome), a common disorder in which patients have a distressing, irresistible desire to move the legs (akathisia), associated with an uncomfortable deep-seated sensation in the legs, worse in the evening or at night, Early-onset often familial, usual presentation is an old F with no family history, who may have signs of an underlying peripheral NP. symptoms are brought on by rest and relieved by movement.

Other associations: lumbar root disease, iron deficiency and renal failure.

If severe enough first-line treatment is dopaminergic agents, either dopamine receptor agonists or L-DOPA,, opiates, clonazepam, gabapentin and iron.

- **painful legs and moving toes syndrome:** is rarer and harder to treat. severe pain in the legs associated with involuntary continuous writhing toes movements. may be underlying disease of lumbar roots or peripheral N.
- **Stiff person syndrome** is a very rare condition of slowly progressive rigidity of the trunk and proximal limbs, with superimposed painful muscle spasms. *association with diabetes and epilepsy, diagnosis supported by characteristic EMG findings, specific auto-antibodies and CSF oligoclonal bands.

In keeping with its presumed autoimmune basis, some patients respond to immunomodulatory measures: steroids, IVIG or plasma exchange.

Others benefit from symptomatic treatment: with benzodiazepines.

symptomatic but probably have also improved avg life expectancy.

Treatment

Drug therapy: symptomatic and aimed at restoring neurochemical balance either by anticholinergic agents or drugs that enhance the dopaminergic pathway.

Treatment is best delayed until symptoms warrant it.

L-DOPA mainstay drug for Parkinson's severe enough to cause significant functional disability.

It is the natural substrate for dopamine synthesis.

able to cross BBB and reach site of action following oral administration, most of an oral dose is metabolized to dopamine by peripheral DOPA decarboxylase before reaching the brain. It is therefore generally given in combination with a peripheral DOPA decarboxylase inhibitor (benserazide or carbidopa).

**additional benefit of reducing peripheral side effects of L-DOPA (N, V), also be limited by gradual escalation of the dose of L-DOPA in accordance with symptoms.

Co-careldopa (L-DOPA plus carbidopa) and cobeneldopa (L-DOPA plus benserazide) may have central side effects (postural hypotension, confusion, hallucinations, delusions).

Complications of long-term L-DOPA: 2–5 y, the efficacy of L-DOPA is limited by motor fluctuations and dyskinesias.

complications of Motor fluctuations:

- 'wearing-off': individual doses produceonly short-lived effects,
- 'on–off', switch from symptomatic benefit from medication ('on') to akinetic–rigid state ('off'), often without any predictable relationship to drug doses timing.

Dyskinesias: involuntary movements in association with drug treatment, e.g. twisting, turning movements when dopamine levels are high ('peak-dose dyskinesias'), or painful sustained muscle contractions, typically of the feet, when dopamine levels are low ('wearing-off dystonias').

Some patients are prepared to tolerate moderate dyskinesias if they can remain mobile.

A small proportion seem to crave L-DOPA at doses well above that required for motor function, with resulting bizarre, repetitive, compulsive behavioral disturbances (dopamine dysregulation syndrome).

Motor fluctuations and dyskinesias can be partially alleviated in some patients by:

- frequent small doses of L-DOPA.
- controlled release preparations,
- L-DOPA+ selegiline, a monoamine oxidase type B (MAO-B) inhibitor (blocks dopamine metabolism), entacapone, a catechol-O-methyltransferase (COMT) inhibitor (which blocks L-DOPA metabolism), or direct dopamine R agonists .

Tolcapone:COMT inhibitor, restricted by the very rare occurrence of severe liver failure, which can be fatal.

- attempts to mimic physiological dopamine levels by continuous administration of L-DOPA or dopamine agonists, as opposed to intermittent nature of oral therapy.

**transdermal administration of rotigotine, a dopamine agonist, subcutaneous infusion of apomorphine, another agonist, and duodenal infusion of L-DOPA.

** other, more rapidly progressive, forms of spinal rigidity, some of which may be paraneoplastic.

- Hemifacial spasm.
- Psychogenic movement disorders should be diagnosed with caution. A psychogenic basis may be suspected if a patient's movements are unusually variable, disappear with distraction and are associated with other clinical features suggesting a 'non-organic' cause .

Bacterial (pyogenic) meningitis

Etiology

In the developed world, most cases:

- Neisseria meningitidis (meningococcus).
- Streptococcus pneumoniae (pneumococcus).
- Mycobacterium tuberculosis, in immunocompromised.

Haemophilus influenzae (type b) become rarer after vaccine.

incidence is 5–10 in 100,000/ annum in developed countries.

patterns of occurrence:

- Meningococcal meningitis may occur in epidemics.
- Pneumococcal infection is more common in older patients and is also associated with alcoholism and splenectomy.

It may spread to the meninges from adjacent structures (ears, nasopharynx) or from the lungs by the bloodstream.

Clinical features

Headache: severe rapid (minutes to hours) and may be associated with pain and stiffness in the neck and back, V and photophobia.

not usually as sudden as with subarachnoid haemorrhage.

Patients may present with an altered level of consciousness and seizures.

General examination: signs of infection (fever, tachycardia, shock and sometimes evidence of primary source of infection (pneumonia, endocarditis, sinusitis, otitis media).

A petechial or purpuric rash is present in most meningococcal meningitis.

Neurological signs:

- 'meningism' – evidence of meningeal irritation – neck stiffness on attempted flexion, high-pitched 'meningeal cry' in infants, Kernig's sign.
- deteriorating level of consciousness,
- raised ICP – papilledema, bulging fontanelle in infants,
- cranial nerve palsies and other focal signs.

Complications

Acute: seizures, abscess formation, hydrocephalus, inappropriate antidiuretic hormone secretion and septic shock with disseminated intravascular coagulation and adrenal hemorrhages is a complication of meningococcal meningitis (Waterhouse– Friderichsen syndrome).

*arthritis, either directly septic or immune-complex mediated.

Investigations and diagnosis

1) LP in untreated acute bacterial meningitis reveals

- turbid CSF, raised CSF P, polymorph leukocytosis (100-1000 of cells/ µL),
- raised [protein] (>l g/L), low [glucose] (<1/2 [blood], frequently undetectable).

*causative organism on gram stain or by culture or molecular techniques.

- Contraindications to LP: papilledema, deteriorating LOC and focal neurological signs, pre-LP cranial CT is needed to exclude a mass lesion, e.g. in the P fossa, which may mimic meningitis, antibiotic before scan, after blood has been taken for culture.

2)full blood count (neutrophilia).

3)coagulation studies (disseminated intravascular coagulation).

4) electrolytes (hyponatremia).

5) blood cultures (may be positive even if CSF is sterile)

- chest and skull (sinus) radiography (to identify primary source of infection).

Management

- may be fatal within h: early diagnosis and treatment with high doses of appropriate IV antibiotics are essential.
- Benzylpenicillin is the drug of choice for meningococcal and pneumococcal if the prevalence of penicillin-resistant organisms is low., initial dose 2.4 g followed by 1.2 g 2 h.

Within 48–72 h, with clinical improvement, the regimen can be relaxed to 4-6 hourly, though with the same total daily dose (14.4 g), continue for 7 days after the patient has become afebrile (14 days for pneumococcus).

- Empirical antibiotic treatment where the prevalence of penicillin-resistant organisms exceeds 5% is generally with cefotaxime or ceftriaxone.

Ampicillin added if the patient is immunosuppressed, pregnant or elderly (Listeria).

Vancomycin if risk of Staph aureus, e.g. shunt-associated meningitis.

- suspected meningococcal meningitis a single IV or IM injection of benzylpenicillin before urgent admission to hospital.
- increasing evidence that initial treatment with high-dose IV corticosteroids (dexamethasone 0.4 mg/kg body weight daily for 4 days) in parallel with antibiotics improves morbidity and mortality by reducing the inflammatory response.
- general: bed rest, analgesics, antipyretics, anti-epilepsy, supportive measures for coma, shock, raised ICP, electrolyte disturbances and bleeding disorders.

Prevention

- Chemoprophylaxis (rifampicin or ciprofloxacin) for meningococcal household.
- Immunization against H. influenzae infection (H. influenzae type b vaccine) is recommended routinely for children at the ages of 2, 3 and 4 months, and has greatly reduced the incidence of meningitis caused by this organism.

Prognosis

mortality from acute bacterial meningitis is 10% overall – > in S. pneumoniae. Pneumococcal disease is also more likely to result in long-term sequelae 30%: hydrocephalus, CN palsies, visual and motor deficits and epilepsy.
Children may be left with behavioral disturbances, learning difficulties, hearing loss and epilepsy.

Brain abscess < common but may complicate otitis media (giving rise particularly to temporal lobe and cerebellar abscess) and other local sites of infection (e.g., paranasal sinuses). It may also arise by distant spread from the lungs (bronchiectasis), pelvis or heart (bacterial endocarditis and congenital lesions).

Clinical features

predictable features of an expanding mass in the brain:

- raised ICP, focal signs (dysphasia, hemiparesis, ataxia), seizures.

Fever is common but does not always develop.
The progression of symptoms and signs, typically over days or even a few weeks, may closely resemble that of a brain neoplasm.

Investigation

- CT scan or MRI is mandatory.
- LP is contraindicated.
- full blood count (neutrophil leucocytosis).
- blood cultures

Management

- Neurosurgical intervention to decompress and drain the abscess may be necessary to treat the clinical features and achieve a bacteriological diagnosis.
- Broad-spectrum antibiotics (e.g., cefotaxime plus metronidazole) are required until an accurate bacteriological diagnosis has been reached.
- Corticosteroids (with antibiotic) may be required to treat cerebral oedema.

Parameningeal infections

Pus in epidural space, particularly spine.
The causative organism is usually S. aureus from a distant skin infection.
associated with osteomyelitis of vertebrae and infection of IV discs.
present with: severe back pain, fever (may not be marked) and a rapidly evolving paraparesis.
Investigation: spinal MRI and blood cultures.
Treatment: anti-staphylococcal antibiotics and early surgical intervention in neural compression.
Local infections of the face and scalp may spread to the intracranial subdural space (subdural empyema) and to the intracranial venous sinuses, resulting in septic venous sinus and cortical venous thrombosis .

Syphilis

Neurosyphilis is still seen, particularly among homosexual in the context of HIV, parenchymatous forms are now rare.
clinical entities:

- mild self-limiting meningitis of secondary syphilis,
- meningovascular syphilis: inflammation of meninges and cerebrospinal arteries in tertiary syphilis – presenting as subacute meningitis with focal signs, e.g. cranial nerve palsies, hemiparesis, paraparesis and wasting of the intrinsic hand muscles (syphilitic amyotrophy),
- gumma – focal meningovascular disease presenting as an intracranial mass lesion, e.g. with epilepsy, focal deficits, raised ICP.
- tabes dorsalis – parenchymatous disease primarily affecting dorsal root ganglion cells of spinal cord.
- 'general paralysis of the insane' – parenchymatous disease of the brain.
- congenital neurosyphilis.

diagnosis: serological tests for syphilis in blood and CSF.
The CSF may also show up to 100 lymphocytes/μL, raised protein and oligoclonal bands.
Treatment: intramuscular procaine penicillin, 1.8–2.4 g daily for 17 days, in combination with oral probenecid. Steroid cover is advisable during initial penicillin therapy to avoid the Jarisch–Herxheimer reaction – an inflammatory response to the rapid killing of Spirochaetes.

Tuberculosis

A. Tuberculous meningitis typically < purulent bacterial , clinical diagnosis can be difficult. Immunocompromised and those from ethnic minorities and immigrant are at risk.

Clinical features:

*persistent headache, fever, seizures and focal neurological signs, developed over weeks.
*CSF is at raised P may contain 100s cells/ microlitre (mixed polymorphs and lymphocytes),
*raised protein and low glucose.

Diagnosis:

1-auramine or Ziehl–Neelsen staining -frequently not found.
2-Multiple CSF specimens and culture.
3-Detection of mycobacterial nucleic acid by PCR.

Treatment: not be delayed in suspected cases, initially with isoniazid (with pyridoxine cover), rifampicin, pyrazinamide and a fourth drug, ethambutol or streptomycin.

* long term (9–12 months or >) and under the supervision of a tuberculosis specialist.
* pyrazinamide and fourth drug may be discontinued after 2 months.
* Corticosteroids are used initially, in combination with antituberculous drugs, to suppress the host's inflammatory response and hence reduce the risk of cerebral edema.

B. chronic caseating granulomas (tuberculomas), which act as intracranial mass lesions. may arise during the course of tuberculous meningitis or as isolated phenomena. Spinal tuberculosis may result in cord compression (Pott's disease of spine).

Other complications: hydrocephalus and stroke-like events.
*fatality and morbidity is high (both up to 30%) despite treatment.

Lyme disease

Infection with spirochaete Borrelia burgdorferi, transmitted by tick bite, may produce neurological manifestations in addition to the systemic features.

acute phase= first month: meningism may occur, along with fever, rash and joint pains.
Chronic disease=weeks or months after the bite: meningitis, encephalitis, cranial nerve palsies (especially facial N), spinal root and peripheral N lesions.
Diagnosis: Serological.
Treatment: usually sensitive to cefotaxime or ceftriaxone.

Leprosy Mycobacterium leprae: directly invade peripheral nerves.
'tuberculoid leprosy', more benign and less infectious, have a patchy sensory polyneuropathy with palpable thickened Ns and depigmented anaesthetic areas of skin.
*rare in Europe and North America, probably MCC of a multifocal neuropathy worldwide.

Bacterial toxins

- Tetanus toxin, Clostridium tetani in wound infections: jaw tonic spasms ('lockjaw' – trismus) and trunk (opisthotonos), then fever with painful paroxysmal spasms of whole body, with arched back, clenched teeth and extended limbs.

Treatment: intensive care unit involves muscle relaxants and ventilatory support, along
with human antitetanus immunoglobulin, penicillin and wound cleansing.
* eradicated if active immunization with tetanus toxoid was universally followed.

- **Botulism toxin:** production by Clostridium botulinum, a contaminant in inadequately sterilized canned foods, encountered in heroin addicts.

Clinical features: D, V, within 2 days weakness 'descending= first ptosis, diplopia and paralysis of accommodation, then severe weakness of bulbar and limb muscles'.
*Assisted ventilation is generally required and recovery is very slow – months or even years.

- Diphtheria toxin may cause a polyneuropathy; now very rare in developed countries with immunization.

Viral infections

Viral meningitis: mumps, enteroviruses produce a benign self-limiting illness without severe complications.
* CSF pressure may be raised and several hundred cells present per microlitre, though usually lymphocytes with
few polymorphs except in the early stages of infection.
* Protein modestly elevated, and glucose is normal.

Viral encephalitis

Viral invasion of the brain may produce a lymphocytic inflammatory reaction with necrosis of neurones and glia.

HSV 1 most common cause of sporadic encephalitis in developed world.

Other: herpes zoster, cytomegalovirus, EBV (all herpesviruses, particularly in immuno-compromised patients), adenovirus and mumps.

Encephalitis may occur in epidemics, as a result of arbovirus infection in parts of the world where mosquitoes act as vectors.

Clinical features

headache, fever and deteriorating level of consciousness over h-days. Seizures may occur, and focal neurological signs may point to cerebral hemispheric (dysphasia, hemiparesis) or brainstem dysfunction.

Investigations

- Brain CT/MRI may exclude mass lesions and show swelling.

asymmetrical low density in the temporal lobes.

may take several days to develop.

- CSF is under increased P, with a lymphocytosis.
- raised protein and normal glucose.

Diagnosing: viral antibody titres are helpful only in retrospect.

Early-> viral antigen immunoassay and PCR For DNA amplification.

- EEG is abnormal with evidence of diffuse brain dysfunction.

characteristic periodic complexes may be present over temporal region.

Management

Aciclovir (10 mg/kg IV every 8 h for 14 days). ON SUSPETION.

Death and serious disability (epilepsy, dysphasia and amnesic syndrome) result when diagnosis and treatment are delayed.

ganciclovir if cytomegalovirus infection is suspected.

- no specific treatment for other causes of encephalitis, Patients require supportive measures: anti-epilepsy drugs for seizures and dexamethasone or mannitol for worsening cerebral oedema.

Herpes zoster -Varicella zoster virus- dormant in dorsal root ganglion cells after an initial chickenpox infection, may reactivate as shingles.

Clinical features: localized pain and itching before appearance of characteristic unilateral vesicular rash, which affects a single dermatome or a few adjacent dermatomes, often on trunk. After the rash has healed, pain may persist and prove difficult to treat (post-herpetic Neuralgia).

Variants include:

- Zoster ophthalmicus – rash involves ophthalmic division of trigeminal N, risk of corneal damage, and of troublesome facial post-herpetic neuralgia
- Ramsay Hunt syndrome – unilateralLMN facial palsy and vesicles in external auditory meatus or on the fauces. There may be severe ear pain and occasionally associated vertigo, tinnitus and hearing loss (zoster oticus).
- Motor zoster – muscle weakness in myotomes at a similar level to dermatomes affected by the rash, e.g. unilateral diaphragmatic palsy in association with a rash on one side of the neck and one shoulder (C3, C4, C5 dermatomes).
- Some patients have selective involvement of the spinal cord (zoster myelitis) or of cerebral vessels, which may present as hemiplegia.

Management: usually self-limiting, but treatment with aciclovir, in higher oral doses than for superficial herpes simplex infections, to speed healing and reduce pain and risk of complications -particularly in immunocompromised individuals, including a generalized rash, and encephalitis.

- **Poliomyelitis**: now rare in developed countries following immunization.

Clinical features:

1-most only 'minor illness' headache, fever and V 7–14 days

-virus enter through gut or nasopharynx.

2-preparalytic -virus reached CNS-, with meningitis, spinal and limb pain.

3-Because of the virus' tropism for A horn cells and equivalent cells in brainstem, a further proportion developed the paralytic illness with progressive muscle weakness over several days.

exclusively those of LMN damage, with variable, often patchy and asymmetrical muscle involvement, fasciculation in early stages and later wasting and areflexia. Only a minority of patients develop bulbar and respiratory failure. Though some recovery occurs at the end of the paralytic stage, many patients are left with permanent weakness and a few require long-term ventilatory support. The post-polio syndrome is a controversial entity, late deterioration in poliomyelitis victims generally being due to the superadded effects of other illnesses.

complications have become less common in developed countries with the advent of highly active antiretroviral therapy (HAART).
Retroviruses other than HIV are also neurotropic.
Thus, the virus HTLV-1, prevalent in certain areas (Caribbean), is associated with tropical spastic paraparesis (HTLV-1- associated myelopathy, HAM).

Retroviral infections

HIV, may lead to neurological complications for two reasons.

1. virus itself has an affinity for neural tissue,- neurotropic and lymphotropic. meningitic illness may occur at seroconversion. Later, a slowly progressive dementia and involvement of other parts of the nervous system, particularly the spinal cord and peripheral nerves, may develop.

2. opportunistic infection and unusual neoplasms involving CNS in full-blown AIDS.

Cerebral toxoplasmosis: Presences of focal hemispheric (hemiparesis, dysphasia, extrapyramidal disorders), cerebellar (ataxia) or cranial N deficits in an AIDS patient, possibly with headache and seizures, CT or MRI evidence of focal or multifocal encephalitis warrants anti-toxoplasma treatment.
with pyrimethamine, folinic acid and either sulphadiazine or clindamycin.
Brain biopsy is generally reserved for non-responders to this treatment.

Cryptococcal meningitis: yeast Cryptococcus neoformans -may be identified on an Indian ink preparation or by detection of antigen in CSF or blood- most common cause of meningitis in AIDS patients.
clinical presentation: acute or subacute headache, fever and sometimes seizures and focal neurologicaldeficits.
CSF (after CT to exclude intracranial mass lesion) reveals a lymphocytosis, usually with raised protein and low glucose.
TXR: combined antifungal drugs (amphotericin B& flucytosine), though it may fail.
*may complicate other immunosuppressed states, e.g. post-organ transplantation.

Herpesviruses – cytomegalovirus infection is common in AIDS patients and may result in encephalitis or cord involvement.
herpes simplex and herpes zoster, may also produce focal or diffuse encephalitis.

Progressive multifocal leucoencephalopathy (PML): due to opportunistic infection by papovaviruses (JC and others), resulting in multiple white matter lesions in cerebral hemispheres, brainstem and cerebellum, presenting with progressive dementia and focal deficits (hemiparesis and dysphasia). Death is usual within months.

other immunodeficiency states, e.g. haematological malignancies, TB, sarcoidosis.

Cerebral lymphoma may present with focal or multifocal disease in cerebral hemispheres and P fossa, both clinically and on CT or MR imaging.
diagnosis on brain biopsy in non-responders to anti-toxoplasma therapy.

Rabies: eradicated from UK and other countries but endemic elsewhere.

- acquired by infected dog bite or other mammals.
- The virus migrates slowly (days- weeks) from bite site of to CNS -> excites an inflammatory reaction, with diagnostic intracytoplasmic inclusions (Negri bodies) seen in neurons post-mortem.
- If the brunt of the inflammatory change is in brainstem, 'furious' rabies develops after a prodrome of fever and psychiatric disorder.

Clinical features:
1- hydrophobia: laryngospasm and terror on attempting to drink.
2-'dumb' or 'paralytic' rabies: flaccid paralysis if inflammation predominantly involves spinal cord. Rabies is almost invariably fatal, once symptoms are established.
** Prophylactic immunization for those handling potentially infected animals, and active and passive immunization should be commenced immediately after a bite, along with thorough wound cleansing.

Postviral phenomena

- Subacute sclerosing panencephalitis: a late and virtually universally fatal complication of measles infection, now very rare due to immunization.
- Acute disseminated encephalomyelitis: a rare sequel of viral infection.
- Guillain–Barr´e syndrome: associated with antecedent infection, often viral, in most patients
- EBV postviral fatigue syndrome impaired concentration and memory.

Protozoa

- Malaria must be excluded on blood films, in febrile individuals from endemic areas. Plasmodium falciparum causes haemorrhagic encephalitis.
- Toxoplasmosis: cause of multifocal encephalitis in AIDS patients, but it may also be acquired in utero, leading to hydrocephalus, intracranial calcification and choroidoretinitis.
- Trypanosomiasis in tropical Africa presents as a low-grade encephalitis, with hypersomnolence and seizures ('sleeping sickness').

Metazoa: Encysted tapeworm larvae may present as cerebral lesions.

- In hydatid disease, cysts may act as intracranial masses, rupture-> chemical meningitis.
- In cysticercosis multiple cysts may cause epilepsy, high ICP, focal neurological signs, hydrocephalus.

Treatment: praziquantel and steroid cover.

Multiple sclerosis (MS): most typical form characterized by lesions separated both in space and time in the CNS.

- common chronic neurological conditions affecting young people.
- primarily affects white matter (brain, spinal cord), and optic N.
- Chronic inflammatory cells are present and myelin is damaged, with relative initial sparing of axons.

relatively normal-appearing regions of white matter interspersed with plaues foci of inflammation and demyelination often located near venules, which leads to a reduction in their conduction velocity with distortion and ultimately loss of information conveyed by impulse traffic along these pathways.

At an early stage there is local breakdown of BBB, then evidence of inflammation with edema, loss of myelin and eventually CNS equivalent of scar tissue, gliosis.

Final result: a shrunken area of sclerosis, may be associated with little clinical deficit compared with when plaque was pathologically most active. partly because of remyelination, for which CNS has some potential, and also signifies a return of function with resolution of the inflammation and edema.

**This pathological sequence corresponds to the clinical pattern of MS relapses, with symptoms being present for a period then resolving partially or completely.

Further inflammatory lesions, close to sites of preexisting damage, may contribute to the eventual accumulation of neurological deficit, but axonal loss, with consequent brain, cord and optic atrophy, is now recognized as a major pathological substrate for the progressive phase of the illness. Plaques need not invariably be associated with specific clinical events, e.g. if they are small or occur in relatively 'silent' areas of CNS.

Common modes of presentation of MS include:

1- Optic (retrobulbar) inflammatory demyelination of one or (less commonly) both optic Ns, may herald MS onset.

Symptoms of unilateral optic neuritis include:

- pain around one eye, particularly on eye movement.
- blurred vision, may proceed to complete monocular blindness in days or weeks, loss of color vision.

Examination:

- if inflammatory demyelination is immediately behind optic N head pink, swollen optic disc on fundoscopy
- visual field defect – typically a central scotomain.
- relative afferent pupillary defect.

A bout of optic neuritis will usually resolve over a period of weeks or months, may be left with some impairment of vision, and fundoscopy will generally reveal optic disc pallor caused by optic atrophy. does not= MS –may be a monophasic illness, particularly in children and if bilateral.

Optic disc swelling in acute phase, if bilateral, must be distinguished from papilledema

-visual acuity is relatively better preserved, only field defect in early papilledema is enlargement of physiological blind spot- caused by raised ICP, may look similar on ophthalmoscope.

2-diplopia, often associated with vertigo and N, hence indicative of a brainstem plaque.

Examination: may reveal internuclear ophthalmoplegia. May be associated cerebellar ataxia.

Sensorimotor disturbances: imply a lesion in spinal cord or cerebral hemispheres, asymmetrical spastic paraparesis +- paraesthesiae, thermal anaesthesia and limbs dysaesthesiae.

P column lesion may produce the near-pathognomonic symptom of rapid tingling sensations shooting down the arms or legs on neck flexion (Lhermitte phenomenon).

In some patients, motor, sensory or indeed visual symptoms are temporarily much worse after a hot bath (Uhthoff phenomenon).

Epidemiology

more common in areas of temperate than tropical climate, may suggest a role for environmental factors in the Faroe Islands and Iceland.

Ethnic differences in incidence used as an argument in favor of genetic susceptibility.

There is also evidence that individuals born in an area of high risk for MS will carry that risk if they emigrate to an area of lower risk and vice versa, but only if migration occurs after mid-teens. This implies that the hypothetical virus is acting in the first decade or two of life.

F:M 3:1, may develop at any age, first onset is rare in children and old, usual 20-40.

pathogenesis

a working hypothesis is that an environmental agent (virus) triggers the condition in a genetically susceptible individual. The role of immune mechanisms is supported by several findings, including the presence of chronic inflammatory cells in active plaques and linkage of the condition to specific genes in major histocompatibility complex (MHC), evidence for a genetic component as is the occurrence of familial cases, and the finding of increased concordance for the condition in identical (monozygous) as opposed to non-identical (dizygous) twins, no single gene shown to be necessary.

Other presentations

1- Pain -less common-:typical trigeminal neuralgia as a result of a brainstem plaque and others may have pain in limbs.
2- Epilepsy has increased incidence.
3- bladder disturbance (urgency and urine retention) impotence.

Course

temporal pattern of symptom evolution in a patient presenting in one of the above ways is that clinical features worsen over days or weeks, reach a plateau and then gradually resolve, partially or completely, over weeks or months, recurrences at unpredictable intervals, affecting the same or different parts of CNS.
with initial episodes complete or near-complete symptomatic resolution (relapsing–remitting in 70–80% of patients).
The role of: physical injury, intercurrent infection, pregnancy and emotional stress in precipitating a relapse is controversial.

subsequent episodes of demyelination may leave some residual disability, entering a secondary phase of steady progression without resolution (secondary progressive disease).
10–20% particularly presenting in middle life with a spastic paraparesis, will have no clear-cut relapses and remissions (primary progressive disease) may accumulate disability slowly without the benefit of remissions; long-term prognosis is relatively poor.

The natural history of MS in individual patients is very variable.

- one or more initial episodes then no symptoms for years (10%)
- accumulate disability, though remain able to work for years.
- 1/3 are more severely affected.
- not possible to predict these individuals at onset, though motor and cerebellar involvement carry a poor prognosis.

* young patient with advanced MS is very distressing for family , hyperacute with death occurring within months -average life expectancy exceeds 25 years from onset-.

Diagnosis

clinical, based on the occurrence of at least two lesions in CNS with appropriate clinical characteristics, separated in time and space.
Some specialist investigations are now available may provide lab support.

- anatomical evidence of CNS separate lesions.
- evidence of disturbed CNS immunology.
- excluding other diagnoses.

<u>Salient investigations include:</u>

- brain and spinal MRI , may reveal lesions corresponding to plaques of demyelination.

Not specific (cerebral small vessel disease similar).
criteria to diagnose MS after a first clinical attack ('clinically isolated syndrome') on MRI:

- Visual evoked potentials, may show delayed central conduction in visual pathways, result of previous subclinical optic neuritis.
- CSF examination, nonspecific changes:
  - lymphocytosis with active disease.
  - raised protein (Ig).
  - 'oligoclonal bands' by electrophoresis= local synthesis of Ig within the CNS.
  - imperfect, other immunological and infective disorders FP and rare MS patients FN.

* in minor sensory symptoms, investigations best delayed. In the absence of definite physical signs, patients may experience such symptoms and become concerned about the possibility of MS, yet have no significant underlying neurological disease, Even if symptoms seem likely to be due to MS, investigation is not necessarily indicated in the absence of limitation of function, not least because there is currently no curative treatment.

In primary progressive disease - classical clinical diagnostic criteria are not applicable- present with progressive spastic paraparesis.
The salient investigation is spinal MRI to exclude a compressive lesion of spinal cord (tumor), the main differential diagnosis potentially treatable.
Other differentials:
1- relapsing and remitting:

- sarcoidosis, SLE, TIA.

2- for progressive disease

- motor neuron disease, spinal and cerebellar degenerations.

Management

Patients should be informed of diagnosis when it is definite, a full discussion is the best policy if not, possibility of MS should not be denied after one episode, such individuals should be made aware that they may have experienced a 'one-off' illness.
physician has a educative role, in guiding with potentially expensive treatments of unproven benefit, e.g. dietary manipulation and use of hyperbaric O2.

* important aspects of treatment:

- management of an acute relapse.
- disease course modification.
- control of symptoms.

Peripheral nerve disorders

Mononeuropathies: affected individually by trauma, P or damage to blood supply (vasa nervorum).

1) Carpal tunnel syndrome: often bilateral

Compression of median N at the wrist, as it passes through the carpal tunnel, may occur:

- in isolation: manual occupations,
- when the carpal tunnel is 'crowded' with excessive or abnormal soft tissue : Pregnancy, DM, Rheumatoid arthritis, Myxoedema, Acromegaly, Amyloidosis, Local deformity: (osteoarthritis, fracture)

***if unkown cause: glucose, ESR and TFT.

clinical features:

- pain in hand or arm, > at night, or on exertion.
- wasting and weakness of thenar eminence muscles.
- sensory loss in median N distribution.
- tingling paranesthesia in median N distribution:

- percussion of carpal tunnel region (Tinel's sign)
- max passive wrist flexion for 60 s (Phalen's test).

Diagnosis: electrodiagnostically or US.

Treatment depending on severity:

- splinting the hand, especially at night, in a position of partial wrist extension.
- local injection with corticosteroids.
- surgical decompression of median N at wrist.

2) Radial palsy

P on radial N in the upper arm may lead to an acute wrist drop and sometimes sensory loss in superficial radial N distribution. e.g. draped awkwardly over an armchair due to alcohol intoxication ('Saturday night palsy').

3) Meralgia paraesthetica

sensory loss due to compression of thigh L cutaneous N as it passes under inguinal ligament. Onset is associated with a change in weight.

4) Ulnar neuropathy

damage from P at several sites along its course, but particularly at elbow.

Clinical features include:

- pain +- tingling paraesthesia radiating from elbow down the forearm to hand ulnar border.
- wasting and weakness of the intrinsic muscles of the hand (sparing the thenar eminence).
- sensory loss in the hand in ulnar N distribution.
- claw hand deformity in chronic lesions.

Diagnosis: N conduction studies may localize lesion.

Treatment:

- Mild lesions may respond to splinting of arm at night, with the elbow extended to reduce P.
- more severe lesions, good results of surgical decompression, or transposition, not guaranteed.
- Op justified in continuing ulnar N damage, persisting pain+- progressive motor impairment.

5) Brachial plexus lesions

acute trauma (traction as a result of birth injury or road accidents, usually involving motorcyclists (upper roots – Erb's paralysis)

(lower roots – Klumpke's paralysis)

A. cervical rib or band of fibrous tissue may compress at thoracic outlet

was over diagnosed and overtreated by operations.

- Surgical exploration of plexus in progressive wasting and weakness of intrinsic hand muscles, appropriate sensory loss (usually along hand ulnar border) electrodiagnostic studies support.
- Imaging of brachial plexus is not usually of value.
- X ray may reveal a cervical rib, but compression may result from a fibrous band invisible .

Pancoast tumor:

Bronchogenic carcinoma at lung apex may invade brachial plexus lower roots causing progressive pain in ipsilateral arm, distal wasting and weakness, and sensory loss, particularly in C7, C8 and T1 dermatomes.

**associated Horner's syndrome as a result of involvement of pre-ganglionic sympathetic fibres.

A similar pattern may develop in other tumors.

Particular diagnostic difficulties in breast carcinoma with previous local radiotherapy – involvement of the brachial plexus may be due to invasion by tumor or radiation plexopathy.

Acute brachial neuritis (neuralgic amyotrophy or idiopathic brachial plexopathy):

characterized by severe pain at onset in arm and shoulder, usually no obvious cause but it may follow immunization or operation.

- When pain subsides (days or weeks) patchy wasting and weakness of periscapular and more distal upper limb muscles is apparent.
- Some muscles are particularly prone to being affected: serratus A -> scapula winging.
- more often unilateral
- sensory involvement may be minimal.
- CSF is normal.

Diagnosis: Electrodiagnostic studies generally unhelpful, may be evidence of denervation in affected muscles.

Treatment: nothing specific, spontaneous recovery of upper limb function may take 18 months - 2 years, but not guaranteed.

Lateral popliteal palsy

common peroneal N is liable to damage from P as it winds round fibular neck, leading to a foot drop.

There is weakness of ankle dorsiflexion and eversion, and of extensor hallucis longus, with variable sensory loss.

- commonly in immobile and DM.
- A foot drop may also result from L5 lesion, inversion of foot -tibialis P supplied by tibial not peroneal N-.
- Electrodiagnostic studies are generally required to localize the lesion to the knee.
- often reversible, being caused by conduction block (neurapraxia), may benefit from a foot drop splint.

Polyneuropathy: multifocal = mononeuritis multi systemic:
1- render Ns excessively sensitive to P, e.g. DM.
2- widespread compromise of vasculature (vasculitis)
3- inflammatory, metabolic or toxic processes -> diffuse, distal, symmetrical damage usually lower limbs first.

Vasculitis: pain, weakness and sensory loss in distribution of multiple peripheral Ns, LL > commonly affected.
Individual N lesions accumulate acutely or subacutely-> patchy and asymmetrical clinically.

Diffuse peripheral Ns disease, subclassified to whether sensory or motor involvement or both, or demyelinating and axonal neuropathies (N conduction studies).

Clinical features:
1- distal numbness and/ or paraesthesiae or pain.
2- distal weakness, wasting and tendon areflexia.
3- Longstanding -> foot and hand deformity (claw hand)
4- neuropathic ulcers and joint deformity in severe sensory loss
5- may be co-existent autonomic symptoms.
6- sensory ataxia if distal position sense loss.
7- 'glove-and-stocking' impairment of pain, T and touch.
8- Peripheral nerves may be thickened.

Treatment depends on the cause:

Guillain–Barr´e syndrome: Acute inflammatory demyelinating a potentially a neurological emergency.

Chronic inflammatory demyelinating polyneuropathy (CIDP) and vasculitis neuropathies: corticosteroid +- immunomodulatory measures -immunosuppressants (azathioprine, cyclophosphamide or cyclosporin), IV Ig or plasma exchange-.

Symptomatic treatment may alleviate neuropathic complications, including autonomic features and pain.

Neuromuscular junction

Myasthenia gravis

AID in which patients -all ages- have circulating Abs to Ach receptors at the neuromuscular junction. may be associated with thymus pathology (hyperplasia, atrophy or thymoma). rare, annual incidence 0.4 in 100,000, most surviving long term, prevalence is almost 1 in 10,000.

Clinical features:
- fatigable ptosis; diplopia, eye movements limitation
- facial weakness, weakness of eye closure
- 'myasthenic snarl',
- dysphagia (nasal regurgitation of liquids),
- dysarthria (nasal quality);
- involvement of respiratory muscles (acute bulbar and respiratory symptoms are a neurological emergency.
- neck and limb muscle weakness, worse after fatigability.

Diagnosis:
- Serum Ach receptor Ab analysis (15% – but, other + auto-Ab).
- 'Tensilon' test: transient and rapid improvement after IV edrophonium (short-acting anticholinesterase temporarily preserves Ach by blocking its metabolism).

* best performed 'double-blind', with atropine and resuscitation equipment in view of muscarinic effects of excess Ach.

- EMG, including single-fibre studies.
- TFT for associated thyrotoxicosis.
- Striated muscle Ab analysis, + in most thymoma.
- mediastinum CT, thymic enlargement.

Treatment:
- symptoms relief by anticholinesterase, e.g. pyridostigmine, increasing doses may develop muscarinic cholinergic side effects: salivation, V, D, abdominal pain, in extreme weakness may worsen
- Corticosteroids (prednisolone), +- Immunosuppression (azathioprine) for moderately severe disease unresponsive to other treatment in alternate-day regime. gradually increased as symptoms may worsen. Hospital admission for starting steroids if not purely ocular.
- Thymectomy for thymoma, and for younger patients early in the disease or reduce requirements for medical therapy and, in a minority, achieve complete remission.
- Plasma exchange or IV Ig in preparation for thymectomy and in severe disease.

Certain antibiotics, such as aminoglycosides, should be avoided because of their blocking effect at the neuromuscular junction.

**The neuromuscular junction may rarely be the site of congenital disease, or of a paraneoplastic disorder (Lambert–Eaton myasthenic syndrome).

Myopathy

present with weakness of trunk and proximal limb muscles. dysphagia, weakness of neck flexion and/or extension, and facial expression muscles, waddling gait.

In acquired disorders, muscle wasting relatively mild at least in early stages sporing tendon reflexes.

Investigation of primary muscle disease:

- blood tests, ESR, auto-Ab (in acquired),
- creatine kinase – from damaged muscle cells;
- EMG, muscle biopsy.

Acquired disorders

Inflammatory myopathies

Polymyositis: in isolation or in association with autoimmune CT disorders: SS, fibrosing alveolitis and Sj¨ogren's syndrome.

Dermatomyositis: association of an inflammatory myopathy with a characteristic lilac (heliotrope) rash affecting the face.

- A purple-red rash may also involve the knuckles, A chest wall and other sites, particularly extensor surfaces.
- a minority -M < 45 years- an underlying malignancy: bronchus or stomach carcinoma
- Clinical features: as proximal myopathy, dysphagia, and muscle pain and tenderness.
- Arthralgia and Raynaud's phenomenon.

Treatment, after histological confirmation, with corticosteroids and immunosuppressant (azathioprine) patients requiring monitoring for several years and most being left with some muscle weakness.

inclusion body myositis: histological variant, relatively common typically affects older M unresponsive to treatment - Secondary to an underlying degenerative process in the muscles- characteristic selective involvement of finger flexors and quadriceps muscles.

Muscular dystrophies

Dystrophinopathies

mutations of X-linked gene for muscle protein dystrophin may present in childhood, or in adolescence or adult life.

Duchenne muscular dystrophy:

- severe proximal weakness in early childhood.
- difficulty rising from a squatting position, using their hands to 'climb' up their legs (Gowers' sign).
- Calf muscles pseudohypertrophy replacement of muscle fibres with fatty CT.
- usually confined to a wheelchair before teens.
- progresses relentlessly, with death from cardiac and respiratory complications before 20, now surviving into early adult life.

Becker muscular dystrophy:

- Less severe present in adolescence or adult life
- normal lifespan, with progressive disability.
- Distinction by molecular analysis of dystrophin gene.

Facioscapulohumeral muscular dystrophy: AD

- bilateral facial weakness and winging of both scapulae.
- weakness and wasting of proximal upper limb muscles
- weakness of the spinal and pelvic muscles.
- waddling gait and pronounced lumbar lordosis.

Myotonic dystrophy: AD with abnormally sustained muscle contraction or myotonia.

** inability to release the grip.

striking a muscle with a hammer may elicit percussion myotonia, electromyography is used for diagnosis.

There are other typical features:

- bilateral ptosis, cataracts, facial weakness.
- wasting and weakness of sternomastoids.
- endocrine: DM, frontal balding and testicular atrophy.
- little muscle wasting or weakness in myotonia congenita.

treated with phenytoin or mexiletine.

Other inherited disorders

Metabolic defects, e.g. glycogen storage diseases, may produce muscle weakness, often with pain and cramps.

familial periodic paralysis: profound muscle weakness, provoked by exercise, a high carbohydrate or exposure to cold, may be associated with hypo/ hyperkalaemia.

Huntington's disease: AD disorder characterized most typically by progressive chorea- partially alleviated by Drugs–and dementia.
age of onset 35–40 years, relentless, death ensuing within 15 years
juvenile form: rigidity predominates over chorea (Westphal variant).
Pathologically: atrophy of caudate nucleus, along with more generalized cerebral atrophy.
Mutation can now be detected directly by DNA analysis.
This development has posed enormous ethical issues, because of devastating implications of a positive diagnosis.

Wilson's disease: rare AR defect of copper metabolism treatable and is fatal without therapeutic intervention.
Levels of serum copper and ceruloplasmin, copper transport protein, are low and copper is deposited in tissues -liver and basal ganglia, cornea, as Kayser–Fleischer rings, detectable on slit-lamp exam -.
Present: in childhood with cirrhosis.
in adolescence neurological features - akinetic–rigid syndrome, dystonia, cerebellar signs or sometimes neuropsychiatric- dominate.
** diagnosis: serum copper and caeruloplasmin, Kayser–Fleischer rings, increased urine copper excretion, if necessary, liver biopsy.
Treatment: penicillamine, a copper-chelating drug.

Cerebellum
Friedreich's ataxia: rare AR disorder presents in childhood with progressive ataxia, tendon areflexia and upgoing plantar responses.
Skeletal deformities: kyphoscoliosis and pes cavus are generally found, ECG abnormalities, indicative of underlying cardiomyopathy, usual cause of early death.
DNA diagnosis is now available.
Late-onset ataxia: A number of conditions, AD and preserved tendon reflexes (distinct from Friedreich's), present in adult life with a progressive cerebellar syndrome. DNA testing is possible for several
Dementia: significant impairment (interfere with life) of two or more domains of cognition, one must be memory, no evidence of delirium.
Most patients have degenerative disease of the brain.

Alzheimer's disease: Neurodegenerative disorder characterized by IC neurofibrillary tangles composed of 'paired helical filaments', and EC neuritic plaques containing an amyloid core,along with neuronal loss.
**mcc of dementia in all age groups, markedly increased frequency in the elderly.
pathogenesis:
Chemical analysis of neuritic plaques contents revealed that their core is largely composed of a peptide, amyloid beta-protein -fragment of amyloid precursor protein (APP)-, encoded by a gene on chromosome 21.
Amyloid role established from rare instances of familial AD caused by a mutation in the APP gene.
Observations on patients with Down's syndrome as they develop premature features of AD and may be at risk of excess amyloid formation from APP gene extra copy.
majority of cases are non-familial, and in some familial examples, mutations in genes other than that coding for APP.
An isoform of lipid transport protein apolipoprotein E is an independent risk factor for familial and sporadic cases.
death of neurones in specific areas of cerebral cortex concerned with cognition, hippocampus and adjacent structures, and temporal neocortex. deeper structures involved -nucleus basalis of Meynert in frontal lobe.
Cholinergic neurones are particularly affected, we can use cholinergic-enhancing drugs to improve memory.
Clinical features: history is obtained from near relatives.

1) Early memory loss, particularly recent events, difficulty learning and retaining new information.
2) Later + attention deficits -> disorientation in time.
3) word-finding difficulties and general knowledge loss.
4) Perceptual deficits +- hallucinations and delusions.
5) severe global loss of cognitive function – amnesia, dysphasia, dyspraxia and agnosia.
6) Personality disintegrates with behavioural disturbances, incontinence, increasing dependence.
7) death within 5–10 years.

Diagnosis: no specific test. However, application of clinical diagnostic criteria is accurate in > 80% of cases.

Management

- Systemic illness can exacerbate dementia.
- No sedative drugs (unless indicated), alcohol and fatigue.
- Simple memory aids in early disease (labels, diaries).
- Medic Alert bracelets.
- driver licensing authority should be notified.
- cholinergic-enhancing drugs improve memory early in disease, albeit for only a few months, most notably cholinesterase inhibitors donepezil, rivastigmine
- galantamine (agonist nicotinic R).
- Memantine affects glutamate transmission in moderate- severe AD in UK.
- No drugs are yet known to affect progression.
- symptomatic e.g. donepezil, continued if patient or carer is aware of clear benefit to quality of life.
- non-cognitive features: antidepressants, neuroleptics , anxiolytics.
- external support services, e.g. psychiatric care in the community, day hospitals, opportunities for respite care and information from specialist organizations, e.g. Alzheimer's Society in UK.

Other causes of dementia

Degenerative diseases

Prion diseases: group of rare neurodegenerative disorders in animals and man, previously classified together largely on the basis of shared histological characteristics ('spongiform encephalopathies').

archetypal human disorder, Creutzfeldt–Jakob disease (CJD), remarkable characteristics common to these conditions in that it is potentially both inherited and transmissible.

The molecular basis resides in the infectious pathogen of spongiform encephalopathies= 'prion' composed entirely of prion protein [PrP], with no evidence for a nucleic acid component, and is highly resistant to heat and formaldehyde.

- a normal isoform of PrP, present in uninfected cells, and encoded by a normal human gene, difference unclear.

Most CJD are sporadic= somatic mutation of PrP gene.

Familial (10–15%) AD, due to a point mutation of PrP gene.

Infectious CJD following accidental inoculation of patients with prions at surgery, or from corneal grafts, or the use of GH made from human pituitary extract.

incubation period is very long – several years.

Intense research and media interest despite their rarity, stimulated by a variant of CJD, attributed to human consumption of prion-contaminated beef (bovine spongiform encephalopathy).

Clinical:

1) rapidly progressive dementia, death in 1–2 years or less.
2) cortical visual problems and motor features, e.g. myoclonus, muscle wasting and fasciculation.
3) Variant in younger patients initially presents with psychiatric features, sensory disturbance and ataxia before onset of dementia.
4) EEG may show a 'periodic complexes'.
5) Neuroimaging is relatively normal, a characteristic appearance of thalamus on MR has been described in many patients with variant CJD.
6) CSF may contain elevated levels of neuronal proteins

diagnosis: biopsy (brain or LN – tonsil) or at autopsy.

no proven treatment for spongiform encephalopathies.

Other degenerative dementias distinguished from AD by different histological appearances of brain at autopsy.

neurodegeneration in some of these conditions tends to be confined, at least initially, frontotemporal dementias.

-frontal type – changes in personality, social behaviour and higher executive function, often associated with a progressive non-fluent dysphasia (focal frontal lobe atrophy).

-semantic dementia- word-finding difficulties and loss of general knowledge (focal temporal lobe atrophy). progressive dysphasia remains fluent.

-Frontotemporal dementia- in younger patients.

-Subcortical dementia- associated with movement disorders, e.g. Huntington's disease and progressive supranuclear palsy, with prominent slowing of cognitive function (bradyphrenia), personality and mood changes and relative absence, at least initially, of the focal cortical deficits (e.g., dysphasia, dyspraxia and agnosia) so typical of AD.

dementia with Lewy bodies (DLB) is recognized as a relatively common neurodegenerative cause of dementia of cortical and subcortical features, second only to AD.

Lewy bodies are the major histological features of Parkinson's disease when confined to nigrostriate neurons but here its more widely distributed.

Distinguishing features of DLB include:

- fluctuating cognition with nocturnal confusion,
- visual hallucinations,
- evidence of Parkinsonism,
- worsening of clinical features with neuroleptic and antiparkinsonian drugs, even in small doses.

Patients with straightforward idiopathic Parkinson's not uncommonly develop dementia some years after the onset of the movement disorder (Parkinson's disease with dementia [PDD]). You don't know if its AD superimposed on Parkinson's disease or more widespread Lewy body changes.

DLB if movement disorder and dementia present within a year of each other.

PDD if dementia onset is delayed by more than a year after the emergence of Parkinsonism.

Corticospinal tract

Hereditary spastic paraplegia:

Progressive spastic paraparesis, apparent in childhood, with a typical 'scissoring' gait, and associated skeletal Deformities (pes cavus).

'pure' form: AD, little or no clinical sensory involvement, sphincter dysfunction occurs late, if at all.

AR and sex-linked modes of inheritance are seen.

Leber's hereditary optic neuropathy

Due to mutation of mitochondrial DNA, presents in adolescence or early adult with subacute unilateral then bilateral visual failure. > M.

Patients have severe visual deficits.

A horn cell: Hereditary spinal muscular atrophies

LMN signs of wasting and weakness in affected muscle groups. There are numerous variants, from a fatal infantile form (Werdnig–Hoffman disease) to milder generalized disease presenting later in childhood or in adolescence (Kugelberg–Welander disease).

Even milder forms may be confined to a single limb or show other focal distributions and a normal life expectancy. AR or sex-linked.

Peripheral N: Charcot–Marie–Tooth disease (CMT)

clinically and genetically heterogeneous group of disorders, (hereditary motor and sensory neuropathy).

The most common variant in Western Europe (CMT1A)AD, diagnosed by DNA analysis. slowly progressive distal wasting and weakness, particularly affecting AL muscle compartment of the leg + pes cavus, a characteristic appearance of LL.

Tendon reflexes usually absent; sensory loss relatively mild. Ns may be palpably thickened (hypertrophy).

Electrodiagnostic studies show marked slowing of conduction velocities. Histo: segmental demyelination.

CMT2 resembles type 1, but the age of onset may be later, N conduction velocity is relatively preserved, reflecting underlying axonal rather than demyelinating pathology.

Prognosis: extremely variable, even within families. Some patients are wheelchair-bound by the time they reach middle age, whereas others are asymptomatic throughout a normal lifespan.

Other genetic causes of a peripheral neuropathy may be associated with specific metabolic defects, e.g. familial amyloidosis, porphyria and the leucodystrophies

Muscular dystrophies: AD,AR, sex-linked.

Other myopathies

Mutations of mitochondrial DNA may be detectable in blood or muscle. Point mutations in the mitochondrial genome show a maternal pattern of inheritance. may be seen with specialized staining of muscle biopsies ('ragged red fibers').

Patients present with chronic progressive external ophthalmoplegia (superficially resembling ocular myasthenia) or combinations of multiple other neurological and systemic features, e.g. ataxia, dementia, neuropathy, epilepsy, retinitis pigmentosa, generalized myopathy, cardiomyopathy and lactic acidosis.

Neurogenetic tumor syndromes AD

Mutations in genes with presumed 'tumor suppressor' function lead to disorders characterized by tumors, hamartomas, cysts and other abnormalities in multiple organs, but with a predilection for nervous system.

primary headache syndromes: uncertain pathogenesis. more benign but still a significant source of morbidity.

1. **Migraine:** a periodic unilateral or sometimes bilateral headache, +- V and visual disturbance.
   - >10% of general population experiencing at least one migraine attack in their lifetime, IT develops at any age, but onset in teens or twenties, > in F.
   - A family history is present in majority of patients.
   - Many individuals with travel sickness and cyclical V in childhood subsequently develop migraine.
   - a relationship to HTN and head injury.

Pathophysiology:

-initial neurological symptoms – aura (visual, sensory and other phenomena) – have attributed to a phase of intracerebral vasoconstriction (a spreading wave of depolarization across cerebral cortex).

-vasodilatation of extracerebral vessels in the scalp and dura, may be responsible for the headache.

- pharmacological evidence shows serotoninergic (5-HT) pathways involvement with vasoactive neuropeptides.

- Genetic studies of families with hemiplegic migraine have recently indicated a role for Ca++ channels.

Diagnosis: almost exclusively on history, periodicity. Continuous headache week after week is unlikely to be due to straightforward migraine, though rarely a status migrainosus may develop.

Neurological examination is normal (except during an attack of hemiplegic or ophthalmoplegic, or migrainous cerebral infarction has occurred).

-cranial bruit:: migraine being with a vascular malformation of the brain.

DD of transient focal neurological symptoms is:

- TIA, epilepsy, migraine -slow rate of spread of symptoms (min), always recurring on the same side (brain imaging to exclude an underlying lesions)-

Clinical features

1. Migraine with aura (classical migraine): vague prodromal symptoms -drowsiness, mood changes, hunger or anorexia- hs before attack.

Visual symptoms:

expanding scotomata, may scintillate (teichopsia). Crenated/castellated pattern (fortification spectra). A homonymous hemianopia or blindness.

Sensory symptoms less common:

unilateral numbness parasthesia of face, arm, leg. Dysphasia and limb weakness are rare.

The aura resolves after 15–20 min (it may last for an hour), headache supervenes, though headache and focal neurological symptoms may coexist.

The headache Unilateral and periorbital, often contralateral hemianopia with throbbing pain that is exacerbated by coughing, straining or bending (jolt phenomenon). It lasts 4 -72 h.

Associated symptoms: N, V, diuresis, photophobia - lie in a dark room and may gain relief from sleep-

1. Migraine without aura (common migraine): may have vague prodromal symptoms, +- headache on waking but is otherwise similar classical.
2. Basilar migraine (Bickerstaff variant): teen F with prominent features suggestive of vertebrobasilar ischemia during aura -vertigo, diplopia, dysarthria, ataxia and syncope.
3. Hemiplegic & ophthalmoplegic migraine: (rare) headaches accompanied by hemiplegia or ophthalmoplegia, with focal neurological signs persisting for days or weeks.

**Exclude structural causes, e.g. aneurysm.

Management

Acute attack: soluble analgesics (aspirin paracetamol), with an antiemetic.

Episodes unresponsive: ergotamine -a potent vasoconstrictor (used rarely nowadays)-

triptans -sumatriptan, a selective 5-HT1 receptor agonist, given subcutaneously, intranasally or orally, interacts with ergotamine, lithium, monoamine oxidase inhibitors, selective 5-HT reuptake inhibitors.

Ergot alkaloids -may cause acute poisoning (ergotism), V, muscle pain and weakness, paraesthesia in extremities, chest pain, pruritus, dysrhythmias, Chronic excessive use may lead to gangrene= contraindicated in PVD.

Combined use is contraindicated, as is the use of sumatriptan or ergotamine in IHD.

Prophylaxis

-dietary triggers should be avoided.

-estrogen-containing preparations, e.g. oral contraceptives and hormone replacement therapy, should be used with caution.

-Prophylactic in frequent attacks >1/month: first-line: propranolol -or other BB, contraindicated in uncontrolled HF, obstructive airways disease, severe PVD and cardiac bradyarrhythmias-, and pizotifen - 5-HT2 receptor antagonist, SE: drowsiness and weight gain; anticholinergic effects also limit its use in patients with glaucoma and urinary retention- Either of them for 3–6 months may be sufficient to reduce the frequency of attacks, without recurrence on drug withdrawal.

- sodium valproate, verapamil, topiramate and methysergide- 5-HT receptor antagonist restricted to severe and frequent migraines, unresponsive to other agents, in hospital due to risk of development retroperitoneal fibrosis-.

- Tricylic antidepressants (amitriptyline) and related drugs (dosulepin), in coexistent tension- headache

2. **Cluster headache:** unilateral in M 20-60s, Severe attacks of pain around one eye (same side) for 20–120 min and may recur several times a day, waking the patient more than once at night, continues for days, weeks or months then symptom-free for many weeks, months or even years. Alcohol may precipitate an attack.
   - Patients often restless during an attack and may appear red rather than pale.
   - Autonomic accompaniments of pain: conjunctival injection, lacrimation and nasal discharge/ congestion, due to histaminergic and humoral mechanisms.
   - Horner's may develop and persist after attack.

Treatment:

1) high-flow 100% oxygen,
2) ergotamine (best in suppository form at bedtime in combination with caffeine)
3) sumatriptan or corticosteroids (2-week reducing course of prednisolone or dexamethasone).
4) Long-term to prevent recurrence of a cluster: methysergide, verapamil or pizotifen.
5) Lithium in more chronic clusters -monitor blood level.

Other rare 'trigeminal–autonomic' syndromes are strikingly responsive to indometacin.

4. **Chronic daily headache:** => 15 days / month.

Causes: medication overuse, secondary headache syndromes, chronic tension-type headache and 'transformed' migraine- normal periodicity is lost, but other migrainous features may persist-.

Withdrawal overused medication by transitional strategies to cover the period of withdrawal headache, e.g. with NSAIDs (or steroids), antiemetics and dihydroergotamine. Preventive measures, notably tricyclic and related drugs, should be introduced early.

1. **Tension-type headache:** very common, unknown cause - abnormal contraction of muscles -triggered by psychogenic factors, i.e. anxiety or depression, or by local disease e.g. cervical spondylosis or dental malocclusion- of head and neck .

Clinical feature:

- RANGE :dull pain at various sites, to a global P sensation, to feeling a tight band around the head.
- No associated symptoms.
- neurological examination is normal.

Treatment

1) reassurance that no sinister underlying cause.
2) if frequent or persistent 3–6-month tricyclic or related compound, e.g. amitriptyline or dosul also in analgesic withdrawal.
3) Physiotherapist: relaxation exercises, psychotherapy (stress management).

Facial pain: giant cell arteritis, cluster and migraine.

Trigeminal neuralgia: attributable to compression of trigeminal sensory root adjacent to brainstem, previously subdivided into idiopathic -now has cause such as aberrant arterial loop- and symptomatic -cerebellopontine angle tumors and, in younger patients, MM (demyelination has affected trigeminal sensory fibers within brainstem).

lancinating unilateral brief, severe, sharp, electric shock-like jolts pain within distribution of 1or > of N divisions (mandibular and maxillary most commonly).

- a continuous background pain may also be present.
- 'trigger' areas, gentle P -speaking, cold breeze, Chewing food may be difficult, resultant WL- may produce pain.

Anxiety about it -> involuntary facial spasms – 'tic douloureux'.

- normal N function on examination -abnormal neurological signs may = underlying lesion, e.g. tumor at cerebellopontine angle, do MRI-

Treatment:

- Simple analgesics are of no use .
- Most respond to carbamazepine, adequate pain control.

If not tolerated or fails: (less likely to help) baclofen, phenytoin, sodium valproate, gabapentin, clonazepam or tricyclic antidepressants.

- Surgical treatment may be needed
- glycerol injection into ganglion or radiofrequency thermocoagulation.
- definitive P fossa exploration and root decompression.

- Previous operations, where trigeminal ganglion was sectioned, often led to Persisted pain despite facial numbness – 'anaesthesia dolorosa'.

Glossopharyngeal neuralgia: is a similar (rarer) disorder with pain in the throat or deep inside the ear.

Post-herpetic neuralgia: persistent facial pain after the rash has healed after shingles in one of trigeminal N branches (1st –zoster ophthalmicus). may be very severe and intractable, lasting 2–3 years after the eruption, but sometimes responds to tricyclic antidepressants, carbamazepine or topical application of capsaicin.

Atypical facial pain: constant in a non-anatomical distribution, no local cause. Treatment is unsatisfactory, coexistent anxiety and/or depression may indicate potential benefit from tricyclic and related drugs, e.g. dosulepin.

Headaches may be subdivided into:

- **secondary:** has defined pathophysiological basis.

A. Disorders of ICP:

1) **headache of raised ICP** (cerebral tumor -Rarely present with headache alone-): Occipital 'bursting' pain, present on waking or wake him may improve later in the day. exacerbated by: sneezing, straining, bending, lifting, lying. short history – days, weeks at most months. in a crescendo quality, the pain becoming increasingly severe, persistent, and ultimately occurring daily, without fail.
Associated with: N, V -Effortless V= P fossa mass close to 4th ventricle, irritating V center-.
On CT a small minority will prove to have a brain tumor.

2) **Headaches of low ICP.** The hallmark is relation to posture -relieved by lying down-.
consequence of lumbar puncture, spontaneous low P headache is an increasingly recognized.

3) **Idiopathic ('benign') IC HTN:** raised ICP symptoms but no mass lesion is identified in young, obese F . Pathophysiology not fully understood but may involve impaired CSF absorption.

* morning headache, V and sometimes visual disturbance – typically diplopia and visual obscurations (sudden, transient bilateral visual loss with changes in posture),Tinnitus.
Examination: bilateral papilloedema, Uni/bilateral 6th N palsies 'false localizing sign', no other focal neurological signs.
CT: no mass and normal or small ventricles (unlike hydrocephalus).
CSF exam -after mass excluded- >40cm with normal content.
may be self-limiting with WL and after one or a few LP. If threat to vision from secondary optic atrophy give diuretics carbonic anhydrase inhibitor acetazolamide, chlortalidone, or corticosteroids.
surgery: drain CSF via a lumboperitoneal shunt or to protect optic N via fenestration procedures (optic N sheath incision).
similar syndrome may be symptomatic of: IC venous sinus thrombosis, SLE, hypervitaminosis A, tetracyclines and corticosteroids, disturbances of Ca++ metabolism.

A. Giant cell arteritis (cranial/ temporal arteritis): Granulomatous inflammatory changes -Lumen narrowing, may be occluded with thrombus- (with giant cells) in branches of external carotid A -superficial temporal vessels- IC vessels and optic N head blood supply.
* etiology is uncertain, viral infection and AID
Symptoms: non-specific headache may localize to temples, Scalp tenderness may become apparent when comb their hair, Pain on chewing due to impairment of blood supply to mastication muscles (intermittent jaw claudication), Temporal As may become swollen and non-pulsatile; rarely skin ulceration occurs.
Transient loss of vision in one eye (amaurosis fugax), risk of permanent monocular or blindness. Diplopia: 3rd or 6th N involvement. Constitutional symptoms. more generalized arteritis: disturbance of liver function, rarely a peripheral neuropathy, and IC vessels involvement -stroke in vertebrobasilar territory-.
Salient investigations are:

- ESR >100 mm/h, CRP also high.
- normochromic, normocytic anaemia and abnormal LFT, particularly raised alkaline phosphatase;
- temporal A biopsy: - does not exclude 'skip lesions'.

Once suspected, treat urgently with IV hydrocortisone highly sensitive, 40–60 mg daily of prednisolone, A rapid 24-48h response helps in diagnosis, gradually tapered down after 18 months- 2 years.

polymyalgia rheumatica: characterized by girdle pains and morning stiffness with some constitutional upset without cranial manifestations also dramatically responsive to corticosteroids, often in lower dosage (7.5–15 mg daily of prednisolone).

C. Meningeal irritation - inflammatory processes or blood (subarachnoid hemorrhage)- :
severe global or occipital headache with V, photophobia and neck stiffness (nuchal rigidity: resistance to passive neck flexion). in children may be due to P fossa mass with negative Kernig's sign: (pain and resistance to passive knee extension with the hip flexed)
In subarachnoid hemorrhage: very sudden S severe pain, patient may lose consciousness.
In bacterial meningitis: acute worsening over min-hs.

Other causes

D. accompanies stroke caused by hemorrhage, IC venous sinus thrombosis or arterial dissection.
E. Metabolic disturbances, e.g. hypoxia, hypercapnia and hypoglycemia.
F. vasoactive drugs and other substances (alcohol, monosodium glutamate, nitrites and nitrates).