

15-25 Neurology

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1062 • NEUROLOGY Clinical examination of the nervous system Insets (winging of scapula, 12th nerve palsy, wasting of thenar eminence) Courtesy of Dr R.E. Cull, Western General Hospital, Edinburgh. Higher cerebral function Orientation Memory Speech and language Localised cortical functions Cranial nerves Optic fundi Papilloedema Optic atrophy Cupping of disc (glaucoma) Hypertensive changes Signs of diabetes Observation/general Back Scoliosis Operative scars Evidence of spina bifida occulta Winging of scapula Neck and skull Skull size and shape Neck stiffness and Kernig's test Carotid bruit • General appearance • Mood (e.g. anxious, depressed) •

Facial expression (or lack thereof) • Handedness • Nutritional status • Blood pressure Stance and gait Posture Romberg's test Arm swing Pattern of gait Tandem (heel-toe) gait Sensory Pin-prick, temperature Joint position, vibration Two-point discrimination Motor Wasting, fasciculation Abnormal posture Abnormal movements Tone (including clonus) Strength Coordination Tendon reflexes Abdominal reflexes Plantar reflexes Winging of right scapula (muscular dystrophy) Right 12th nerve palsy: wasting of right side of tongue 7th nerve palsy: drooping mouth and flattening of nasolabial skin fold Wasting of right thenar eminence due to cervical rib Pes cavus Haemorrhagic papilloedema

3rd nerve palsy: one eye points 'down and out'

Clinical examination of the nervous system • 1063

1 Examination of gait and posture Procedure Abnormality Disease Rising from chair Difficulty rising Proximal muscle weakness or joint disorders Gait initiation Difficulty starting to walk, frozen Cerebrovascular disease or parkinsonism Posture Stooped Parkinsonism Retropulsion/ anteropulsion Postural instability Parkinsonism Arms during walking Reduced arm swing Parkinsonism or upper motor neuron lesion Enhanced tremor Parkinsonism Dystonic posturing Dystonia Gait pattern Circumduction (stiff leg moves outwards in 'circular' manner) Hemiparesis, typically after stroke 'Slapping', high-stepping due to foot drop L5 radiculopathy or common peroneal nerve lesion Narrow-based, short strides, freezing in doorways Parkinsonism Stiff-legged, scissors gait Spastic paraparesis (multiple sclerosis, vascular disease, spinal cord lesions) Wide-based, unsteady, unable to perform tandem gait Cerebellar lesion Waddling gait Myopathies with proximal weakness 4 Examination of cranial nerves Nerve Name Tests I Olfactory Ask patient about sense of smell (examine only if change is reported) II Optic Visual acuity and colour vision Visual fields Pupillary responses Ophthalmoscopy III Oculomotor Eyelids (ptosis) Pupil size, symmetry, reactions Eye movements IV Trochlear Eye movements (superior oblique muscle) V Trigeminal Facial sensation Corneal reflex Muscles of mastication VI Abducens Eye movements (lateral rectus muscle) VII Facial Facial symmetry and movements VIII Vestibulocochlear Otoscopy Hearing Tuning fork tests (Rinne and Weber) IX Glossopharyngeal Swallowing X Vagus Palatal elevation (uvula deviates to side opposite lesion) Swallowing Cough (bovine) Speech XI Accessory Look for wasting of trapezius/sternocleidomastoid Elevation of shoulders Turning head to right and left XII Hypoglossal Look for wasting/fasciculation Tongue protrusion (deviates to side of lesion) 6 Root values of tendon reflexes Reflex Root value Arm Biceps jerk C5 Supinator jerk C6 Triceps jerk C7 Finger jerk C8 Leg Knee jerk L3/L4 Ankle jerk S1 Motor and sensory homunculi. The motor and sensory homunculi illustrate the cortical areas serving each anatomical area within the pre-central (motor) and post-central (sensory) gyri. Motor Sensory Toes Motor cortex (pre-central gyrus) Knee Trunk Arm Neck Face Tongue Teeth Somatic cortex (post-central gyrus) Leg Arm Face Tongue

1064 • NEUROLOGY 25.1 Neurological emergencies • Status epilepticus (p. 1080) • Stroke (if thrombolysis available) (p. 1158) • Guillain-Barré syndrome (p. 1140) • Myasthenia gravis (if bulbar and/or respiratory) (p. 1141) • Spinal cord compression (p. 1136) • Subarachnoid haemorrhage (p. 1160) • Neuroleptic malignant syndrome (p. 1197) The complexity of the brain differentiates us from other species, and its interactions with the spinal cord and peripheral nerves combine to allow us to perceive and react to the external world while maintaining a stable internal environment. The cerebral cortex provides a platform for processing information and forming a

response, and in doing so, both forms and is affected by our personality and mental state. Neurology has for too long been misperceived as a specialty in which intricate clinical examination and numerous investigations are required to diagnose obscure and untreatable conditions. In fact, nervous system disorders are common, accounting for around 10% of the UK's general practice consultations, 20% of acute medical admissions, and most chronic physical disability. The development of specific, effective treatments has made accurate diagnosis essential. Neurological management requires knowledge of a range of common conditions, which can then be applied to individual patients after careful history-taking, with lesser contributions arising from targeted examination and considered investigation. Pathological and anatomical localisation of symptoms and signs is important, but skill can be required to identify those not associated with neurological disease, differentiating patients requiring investigation and treatment from those who need reassurance. Initially, it is important to exclude conditions that constitute neurological emergencies (Box 25.1). If the presentation is not an emergency, time can be taken to reach a diagnosis. The history should provide a hypothesis for the site and nature of the potential pathology, which a focused examination may refine, and direct appropriate further investigations. An informed discussion with the patient and family regarding diagnosis, management and prognosis may then take place. As stroke has become a specific subspecialty in many centres, it is described in a separate chapter, although it is clearly a neurological condition. This chapter should be read with it, to help clarify how the presentation, diagnosis and management of stroke present their own challenges.

Functional anatomy and physiology

Cells of the nervous system

The nervous system comprises billions of specialised cells, forming a spectacular network of connections, each human brain having almost as many connections as there are grains of sand in the whole world. In addition to neurons, there are three types of glial cells. Astrocytes form the structural framework for neurons Fig. 25.1 Cells of the nervous system. (CSF = cerebrospinal fluid) Astrocyte foot processes surround the brain capillary (site of blood-brain barrier) Capillary Red blood cell in capillary Tight junction Capillary endothelial cell Astrocyte Synapse Neuron Oligodendrocyte Axon CSF Ependymal cell Sensory cell body in dorsal root ganglion Motor neuron cell body in anterior horn Spinal cord grey matter Node of Ranvier Vas nervorum Sensory axon Motor axon Schwann cell

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and control their biochemical environment, their foot processes adjoining small blood vessels and forming the blood-brain barrier (Fig. 25.1). Oligodendrocytes are responsible for the formation and maintenance of the myelin sheath, which surrounds axons and is essential for maintaining the speed and consistency of action potential propagation along axons. Peripheral nerves have axons invested in myelin made by oligodendrocytes (Schwann cells). Microglial cells derive from monocytes/macrophages and play a role in fighting infection and removing damaged cells. Ependymal cells line the cerebral ventricles. Generation and transmission of the nervous impulse

The role of the central nervous system (CNS) is to generate outputs in response to external stimuli and changes in internal Fig. 25.2 Neurotransmission and neurotransmitters. (1) An action potential arriving at the nerve terminal depolarises the membrane and this opens voltage-gated calcium channels. (2) Entry of calcium causes the fusion of synaptic vesicles containing neurotransmitters with the pre-synaptic membrane and release of the neurotransmitter across the synaptic cleft. (3) The neurotransmitter binds to receptors on the post-synaptic membrane either (A) to open ligand-gated ion channels that, by allowing ion entry, depolarise the membrane and initiate an action potential (4), or (B) to bind to metabotropic receptors that activate an effector enzyme (e.g.

adenylyl cyclase) and thus modulate gene transcription via the intracellular second messenger system, leading to changes in synthesis of ion channels or modulating enzymes. (5)
Neurotransmitters are taken up at the pre-synaptic membrane and/or metabolised. (cAMP = cyclic adenosine monophosphate; DNA = deoxyribonucleic acid; mRNA = messenger ribonucleic acid)
Transcription factor Microtubules in axon down which neurotransmitters and/or precursors are transported

Ca²⁺ Voltage-gated calcium channels Action potential

Ions Ions G-protein mRNA DNA Cell nucleus Translation New ion channel or modulating enzyme
Second messengers e.g. cAMP A B Fig. 25.3 The major anatomical components of the nervous system. Posterior Anterior Cerebral hemispheres Sensation and perception Cerebellum Brainstem Spinal cord Autonomic Autonomic Behaviour and motor Gastrointestinal tract Sensory receptor Heart and circulation Muscle Neuromuscular junction Bladder Reproductive organs conditions. The CNS has to maintain a delicate balance between responsivity to external stimuli and remaining stoic enough to remain stable in a rapidly changing environment. Each neuron receives input by synaptic transmission from dendrites (branched projections of other neurons), which sum to produce output in the form of an action potential that is then conducted along the axon, resulting in synaptic transmission to other neurons or, in the motor system, to muscle cells. Summation of the inputs causes net changes in the target neuron's electrochemical gradient, which, if large enough, will trigger an action potential. Communication between cells is by synaptic transmission that involves the release of neurotransmitters to interact with structures on the target cell's surface, including ion channels and other cell surface receptors (Fig. 25.2). At least 20 different neurotransmitters are known to act at different sites in the nervous system, most of which are potentially amenable to pharmacological manipulation. Each neuronal cell body may receive synaptic input from thousands of other neurons. The synapsing neuron terminals are also subject to feedback regulation via receptor sites on the pre-synaptic membrane, modifying the release of transmitter across the synaptic cleft. In addition to such acute effects, some neurotransmitters produce long-term modulation of metabolic function or gene expression. This effect probably underlies more complex processes such as long-term memory. Functional anatomy of the nervous system Major components of the nervous system and their interrelationships are depicted in Figure 25.3.

1066 • NEUROLOGY are regions dealing with numerical function. The non-dominant parietal lobe is concerned with spatial awareness and orientation. The temporal lobes contain the primary auditory cortex and primary vestibular cortex. On the inner medial sides lie the olfactory and parahippocampal cortices, which are involved in memory function. The temporal lobes also link intimately to the limbic system, including the hippocampus and the amygdala, which are involved in memory and emotional processing. The dominant temporal lobe also participates in language functions, particularly verbal comprehension (Wernicke's area). Musical processing occurs across both temporal lobes, rhythm on the dominant side and melody/pitch on the non-dominant. The occipital lobes are responsible for visual interpretation. The contralateral visual hemifield is represented in each primary visual cortex, with surrounding areas processing specific visual submodalities such as colour, movement or depth, and the analysis of more complex visual patterns such as faces. Deep to the grey matter in the cortices, and the white matter (composed of neuronal axons), are collections of cells known as the basal ganglia that are concerned with motor

control; the thalamus, which is responsible for the level of attention to sensory perception; the limbic system, concerned with emotion and memory; and the hypothalamus, responsible for homeostasis, such as temperature.

Cerebral hemispheres The cerebral hemispheres coordinate the highest level of nervous function, the anterior half dealing with executive ('doing') functions and the posterior half constructing a perception of the environment. Each cerebral hemisphere has four functionally specialised lobes (Box 25.2 and Fig. 25.4), with some functions being distributed asymmetrically ('lateralised'), to produce cerebral dominance for functions such as motor control, speech or memory. Cerebral dominance aligns limb dominance with language function: in right-handed individuals the left hemisphere is almost always dominant, while around half of left-handers have a dominant right hemisphere. Frontal lobes are concerned with executive function, movement, behaviour and planning. As well as the primary and supplementary motor cortex, there are specialised areas for control of eye movements, speech (Broca's area) and micturition. The parietal lobes integrate sensory perception. The primary sensory cortex lies in the post-central gyrus of the parietal lobe. Much of the remainder is devoted to 'association' cortex, which processes and interprets input from the various sensory modalities. The supramarginal and angular gyri of the dominant parietal lobe form part of the language area (p. 1088).

25.2 Cortical lobar functions

Lobe	Function	Effects of damage	Cognitive/behavioural	Associated physical signs
Frontal	Personality, Emotional control, Social behaviour	Contralateral motor control	Language, Micturition	Disinhibition, Lack of initiation, Antisocial behaviour, Impaired memory, Expressive dysphasia, Incontinence, Impaired smell
Contralateral	hemiparesis	Frontal release signs	1 Seizures – often nocturnal with motor activity	Versive head movements
Parietal: dominant	Language, Calculation	Dysphasia, Acalculia, Dyslexia, Apraxia	3 Agnosia	5 Contralateral hemisensory loss, Astereognosis
2 Agraphesthesia	4 Contralateral homonymous lower quadrantanopia	Asymmetry of optokinetic nystagmus (OKN)	Focal sensory seizures	Parietal: non-dominant
Spatial orientation, Constructional skills	Neglect of contralateral side	Spatial disorientation	Constructional apraxia, Dressing apraxia	Contralateral hemisensory loss, Astereognosis
2 Agraphesthesia	4 Contralateral homonymous lower quadrantanopia	Asymmetry of OKN	Focal sensory seizures	Temporal: dominant
Auditory perception, Language, Verbal memory, Smell, Balance	Receptive aphasia, Dyslexia, Impaired verbal memory	Contralateral homonymous upper quadrantanopia	Complex hallucinations (smell, sound, vision, memory)	Temporal: non-dominant
Auditory perception, Melody/pitch perception, Non-verbal memory, Smell, Balance	Impaired non-verbal memory, Impaired musical skills (tonal perception)	Contralateral homonymous upper quadrantanopia	Complex hallucinations (smell, sound, vision, memory)	Occipital
Visual processing, Visual inattention, Visual loss, Visual agnosia	Homonymous hemianopia (macular sparing), Simple visual hallucinations (e.g. phosphenes, zigzag lines)	1 Grasp reflex, palmomentary response, pout response.	2 Inability to determine three-dimensional shape by touch.	3 Inability to perform complex movements in the presence of normal motor, sensory and cerebellar function.
4 Inability to 'read' numbers or letters drawn on hand, with the eyes shut.	5 Inability to recognise familiar objects, e.g. faces.			

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and appetite control. The cerebral ventricles contain cerebrospinal fluid (CSF), which cushions the brain during cranial movement. CSF is formed in the lateral ventricles and protects and nourishes the CNS. CSF flows from third to fourth ventricles and through foramina in the brainstem to dissipate over the surface of the CNS, eventually being reabsorbed into the cerebral venous system.

(see Fig. 25.44, p. 1132). The brainstem In addition to containing all the sensory and motor pathways entering and leaving the hemispheres, the brainstem houses the nuclei and projections of most cranial nerves, as well as other important collections of neurons in the reticular formation (Fig. 25.5). Cranial nerve nuclei provide motor control to muscles of the head (including face and eyes) and coordinate sensory input from the special sense organs and the face, nose, mouth, larynx and pharynx. They also relay autonomic messages, including pupillary, salivary and lacrimal functions. The reticular formation is mainly involved in control of conjugate eye movements, the maintenance of balance and arousal, and cardiorespiratory control. The spinal cord The spinal cord is the route for virtually all communication between the extracranial structures and the CNS. Afferent and efferent fibres are grouped in discrete bundles but collections of cells in the grey matter are responsible for lower-order motor reflexes and the primary processing of sensory information. Fig. 25.4 Anatomy of the cerebral cortex. Face Parahippocampal cortex Corpus callosum Foot Supplementary motor area Superior temporal gyrus

Inferior frontal gyrus Primary motor cortex Leg Central sulcus Primary sensory cortex Supramarginal gyrus Angular gyrus Primary visual cortex 1 Frontal eye field 2 Broca's area 3 Primary vestibular cortex 4 Primary auditory cortex 5 Wernicke's area Frontal lobe Temporal lobe Parietal lobe Occipital lobe Key Fig. 25.5 Anatomy of the brainstem. Cranial nerves Cerebellum 10th 9th 8th 7th 6th 5th 3rd 4th Pontine nuclei Sensory tracts Motor tracts Pyramidal motor tract Reticular system 12th 11th

1068 • NEUROLOGY resulting in weakness and reduced muscle tone. Subsequently, denervated muscle fibres atrophy, causing muscle wasting, and depolarise spontaneously, causing 'fibrillations'. Except in the tongue, these are usually perceptible only on electromyography (EMG; p. 1076). With the passage of time, neighbouring intact neurons sprout to provide re-innervation, but the neuromuscular junctions of the enlarged motor units are unstable and depolarise spontaneously, causing fasciculations (large enough to be visible). Fasciculations therefore imply chronic denervation with partial re-innervation. Upper motor neurons Upper motor neurons have both inhibitory and excitatory influence on the function of lower motor neurons in the anterior horn. Lesions affecting the upper motor neuron result in increased tone, most evident in the strongest muscle groups (i.e. the extensors of the lower limbs and the flexors of the upper limbs). The weakness of upper motor neuron lesions is conversely more pronounced in the opposing muscle groups. Loss of inhibition will also lead to brisk reflexes and enhanced reflex patterns of movement, such as flexion withdrawal to noxious stimuli and spasms of extension. The increased tone is more apparent during rapid stretching ('spastic catch') but may quickly give way with sustained tension (the 'clasp-knife' phenomenon). More primitive reflexes are also released, manifest as extensor plantar Sensory peripheral nervous system The sensory cell bodies of peripheral nerves are situated just outside the spinal cord, in the dorsal root ganglia in the spinal exit foramina, while the distal ends of their neurons utilise various specialised endings for the conversion of external stimuli into action potentials. Sensory nerves consist of a combination of large, fast, myelinated axons (which carry information about joint position sense and commands to muscles) and smaller, slower, unmyelinated axons (which carry information about pain and temperature, as well as autonomic function). Motor peripheral nervous system The anterior horns of the spinal cord comprise cell bodies of the lower motor neurons. To increase conduction speed, peripheral motor nerve axons are wrapped in myelin produced by Schwann cells. Motor neurons release acetylcholine across the neuromuscular junction, which changes the muscle end-plate potential and initiates muscle

contraction. The autonomic system The autonomic system regulates the cardiovascular and respiratory systems, the smooth muscle of the gastrointestinal tract, and many exocrine and endocrine glands throughout the body. The autonomic system is controlled centrally by diffuse modulatory systems in the brainstem, limbic system, hypothalamus and frontal lobes, which are concerned with arousal and background behavioural responses to threat. Autonomic output divides functionally and pharmacologically into two divisions: the parasympathetic and sympathetic systems.

The motor system A programme of movement formulated by the pre-motor cortex is converted into a series of excitatory and inhibitory signals in the motor cortex that are transmitted to the spinal cord in the pyramidal tract (Fig. 25.6). This passes through the internal capsule and the ventral brainstem before crossing (decussating) in the medulla to enter the lateral columns of the spinal cord. The pyramidal tract 'upper motor neurons' synapse with the anterior horn cells of the spinal cord grey matter, which form the lower motor neurons. Any movement necessitates changes in posture and muscle tone, sometimes in quite separate muscle groups to those involved in the actual movement. The motor system consists of a hierarchy of controls that maintain body posture and muscle tone, on which any movement is superimposed. In the grey matter of the spinal cord, the lowest order of the motor hierarchy controls reflex responses to stretch. Muscle spindles sense lengthening of the muscle; they provide the afferent side of the stretch reflex and initiate a monosynaptic reflex leading to protective or reactive muscle contraction. Inputs from the brainstem are largely inhibitory. Polysynaptic connections in the spinal cord grey matter control more complex reflex actions of flexion and extension of the limbs that form the basic building blocks of coordinated actions, but complete control requires input from the extrapyramidal system and the cerebellum.

Lower motor neurons Lower motor neurons in the anterior horn of the spinal cord innervate a group of muscle fibres termed a 'motor unit'. Loss of lower motor neurons causes loss of contraction within this unit, Fig. 25.6

The motor system. Neurons from the motor cortex descend as the pyramidal tract in the internal capsule and cerebral peduncle to the ventral brainstem, where most cross low in the medulla (A). In the spinal cord the upper motor neurons form the corticospinal tract in the lateral column before synapsing with the lower motor neurons in the anterior horns. The activity in the motor cortex is modulated by influences from the basal ganglia and cerebellum. Pathways descending from these structures control posture and balance (B). Neuromuscular junction

A B Skeletal muscle Anterior horn cells Lateral corticospinal tract Spinal cord Foot Hand Mouth Cortical pyramidal cells Motor cortex Basal ganglia Cerebellum Descending control of posture and balance Pyramidal tract Internal capsule

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Vision The neurological organisation of visual pathways is shown in Figure 25.7. Fibres from ganglion cells in the retina pass to the optic disc and then backwards through the lamina cribrosa to the optic nerve. Nasal optic nerve fibres (subserving the temporal visual field) cross at the chiasm but temporal fibres do not. Hence, fibres in each optic tract and further posteriorly carry representation of contralateral visual space. From the lateral geniculate nucleus, lower fibres pass through the temporal lobes on their way to the primary visual area in the occipital cortex, while the upper fibres pass through the parietal lobe. Normally, the eyes move conjugately (in the same direction at the same speed), though horizontal convergence allows fusion of images at different distances. The control of eye movements begins in the cerebral hemispheres, particularly within the frontal eye fields, and the pathway then descends to the brainstem with input from the visual cortex, superior colliculus and cerebellum. Horizontal and vertical gaze centres in the pons and

mid-brain, respectively, coordinate output to the ocular motor nerve nuclei (3, 4 and 6), which are connected to each other by the medial longitudinal fasciculus (MLF) (Fig. 25.8). The MLF is particularly important in coordinating horizontal movements of the eyes. The resulting signals to extraocular muscles are supplied by the oculomotor (3rd), trochlear (4th) and abducens (6th) cranial nerves. The pupillary size is determined by a combination of parasympathetic and sympathetic activity. Parasympathetic fibres originate in the Edinger-Westphal subnucleus of the 3rd nerve, and pass with the 3rd nerve to synapse in the ciliary ganglion before supplying the constrictor pupillae of the iris. Sympathetic fibres originate in the hypothalamus, pass down the brainstem and cervical spinal cord to emerge at T1, return up to the eye in association with the internal carotid artery, and supply the dilator pupillae. responses. Spasticity may not be present until some weeks after the onset of an upper motor neuron lesion. The extrapyramidal system

Circuits between the basal ganglia and the motor cortex constitute the extrapyramidal system, which controls muscle tone, body posture and the initiation of movement (see Fig. 25.6). Lesions of the extrapyramidal system produce an increase in tone that, unlike spasticity, is continuous throughout the range of movement at any speed of stretch ('lead pipe' rigidity). Involuntary movements are also a feature of extrapyramidal lesions (p. 1084), and tremor in combination with rigidity produces typical 'cogwheel' rigidity. Extrapyramidal lesions also cause slowed and clumsy movements (bradykinesia), which characteristically reduce in size with repetition, as well as postural instability, which can precipitate falls. The cerebellum

The cerebellum fine-tunes and coordinates movement initiated by the motor cortex, including articulation of speech. It also participates in the planning and learning of skilled movements through reciprocal connections with the thalamus and cortex. A lesion in a cerebellar hemisphere causes lack of coordination on the same side of the body. Cerebellar dysfunction impairs the smoothness of eye movements, causing nystagmus, and renders speech dysarthric. In the limbs, the initial movement is normal, but as the target is approached, the accuracy of the movement deteriorates, producing an 'intention tremor'. The distances of targets are misjudged (dysmetria), resulting in 'past-pointing'. The ability to produce rapid, accurate, regularly alternating movements is also impaired (dysdiadochokinesis). The central vermis of the cerebellum is concerned with the coordination of gait and posture. Disorders of this area therefore produce a characteristic ataxic gait (see below). Fig. 25.7

Visual pathways and visual field defects. Schematic representation of eyes and brain in transverse section. Retina Optic nerve Optic chiasm Optic tract Lateral geniculate body Optic radiation Lower fibres in temporal lobe Upper fibres in anterior parietal lobe Occipital cortex Visual fields L R Visual field defects Monocular blindness Bitemporal hemianopia Right homonymous hemianopia Right superior homonymous quadrantanopia Right inferior homonymous quadrantanopia Right homonymous hemianopia with macular sparing R

L

1070 • NEUROLOGY sensation (including vibration) enter the spinal cord at the posterior horn and pass without synapsing into the ipsilateral posterior columns. In contrast, fibres conveying pain and temperature sensory information (nociceptive neurons) synapse with secondorder neurons that cross the midline in the spinal cord before ascending in the contralateral anterolateral spinothalamic tract to the brainstem. The second-order neurons of the dorsal column sensory system cross the midline in the upper medulla to ascend through the brainstem. Here they lie just medial to the (already crossed) spinothalamic pathway. Brainstem lesions can therefore cause sensory loss affecting all modalities on the contralateral side of the body. Distribution of facial

sensory loss due to brainstem lesions arises from the anatomy of the trigeminal fibres within the brainstem. Fibres from the back of the face (near the ears) descend within the brainstem to the upper part of the spinal cord before synapsing, the second-order neurons crossing the midline and then ascending with the spinothalamic fibres. Fibres conveying sensation from more anterior areas of the face descend a shorter distance in the brainstem. Thus, sensory loss in the face from low brainstem lesions is in a 'balaclava helmet' distribution, as the longer descending trigeminal fibres are affected. Both dorsal column and spinothalamic tracts end in the thalamus, relaying from there to the parietal cortex. Pain is a complex perception that is only partly related to activity in nociceptor neurons (p. 1338 and Fig. 34.2). Higher up, chronic and severe pain interacts extensively with mood and can exacerbate or be exacerbated by mood disorder, including depression and anxiety. Modification of psychological and psychiatric sequelae is a vital part of pain management (p. 1343).

Sphincter control The sympathetic supply to the bladder arises from roots T11-L2 to synapse in the inferior hypogastric plexus, while the parasympathetic supply leaves from S2-4. In addition, a somatic supply to the external (voluntary) sphincter arises from S2-4, travelling via the pudendal nerves.

Fig. 25.8 Control of conjugate eye movements. Downward projections pass from the cortex to the pontine lateral gaze centre (A). The pontine gaze centre projects to the 6th cranial nerve nucleus (B), which innervates the ipsilateral lateral rectus and projects to the contralateral 3rd nerve nucleus (and hence medial rectus) via the medial longitudinal fasciculus (MLF). Tonic inputs from the vestibular apparatus (C) project to the contralateral 6th nerve nucleus via the vestibular nuclei.

Fig. 25.9 Areas of the cerebral cortex involved in the generation of spoken language. Arcuate fasciculus Posterior language comprehension area (Wernicke's) Broca's area Auditory cortex Bulbar muscles Corticobulbar tract Verbal memory Speech

Much of the cerebral cortex is involved in the process of forming and interpreting communicating sounds, especially in the dominant hemisphere (see Box 25.2). Decoding of speech sounds (phonemes) is carried out in the upper part of the posterior temporal lobe. The attribution of meaning, as well as the formulation of the language required for the expression of ideas and concepts, occurs predominantly in the lower parts of the anterior parietal lobe (the angular and supramarginal gyri). The temporal speech comprehension region is called Wernicke's area (Fig. 25.9). Other parts of the temporal lobe contribute to verbal memory, where lexicons of meaningful words are 'stored'. Parts of the non-dominant parietal lobe appear to contribute to non-verbal aspects of language in recognising meaningful intonation patterns (prosody). The frontal language area is in the posterior end of the dominant inferior frontal gyrus known as Broca's area. This receives input from the temporal and parietal lobes via the arcuate fasciculus. The motor commands generated in Broca's area pass to the cranial nerve nuclei in the pons and medulla, as well as to the anterior horn cells in the spinal cord. Nerve impulses to the lips, tongue, palate, pharynx, larynx and respiratory muscles result in the series of ordered sounds comprising speech. The cerebellum also plays an important role in coordinating speech, and lesions of the cerebellum lead to dysarthria, where the problem lies in motor articulation of speech.

The somatosensory system The body surface can be described by dermatomes, each dermatome being an area of skin in which sensory nerves derive from a single spinal nerve root (Fig. 25.10). Sensory information ascends in two anatomically discrete systems (Fig. 25.11). Fibres from proprioceptive organs and those mediating specific

disappears and activity becomes dominated by deepening slow-wave activity. As sleep deepens and dreaming begins, the limbs become flaccid, movements are 'blocked' and EEG signs of rapid eye movements (REM) are superimposed on the slow wave. REM sleep persists for a short spell before another slowwave spell starts, the cycle repeating several times throughout the night. REM phases lengthen as sleep progresses. REM sleep seems to be the most important part of the sleep cycle for refreshing cognitive processes, and REM sleep deprivation causes tiredness, irritability and impaired judgement.

Localising lesions in the central nervous system After taking a history and examining the patient, the clinician should have an idea of the nature and site of any pathology (see Box 25.10). Given the intricate anatomy of the brainstem, this section will dwell on the possible localisation in more detail (see Fig. 25.5). Brainstem lesions typically present with symptoms due to cranial nerve, cerebellar and upper motor neuron dysfunction and are most commonly caused by vascular disease. Since the anatomy of the brainstem is very precisely organised, it is usually possible to localise the site of a lesion on the basis of careful history and examination in order to determine exactly

Storage of urine is maintained by inhibiting parasympathetic activity and thus relaxing the detrusor muscle of the bladder wall. Continence is also helped by simultaneous sympathetic- and somatic-mediated tonic contraction of the urethral sphincters. Voiding in adults is usually carried out under conscious control, which triggers relaxation of tonic inhibition on the pontine micturition centre from higher centres, leading to relaxation of the pelvic floor muscles and external and internal urethral sphincters, along with parasympathetic-mediated detrusor contraction.

Personality and mood The physiology and pathology of mood disorders are discussed elsewhere (Ch. 28) but it is important to remember that any process affecting brain function may influence mood and affect. Conversely, mood disorder may have a significant effect on perception and function. It can be difficult to disentangle whether psychological and psychiatric changes are the cause or the effect of any neurological symptoms.

Sleep The function of sleep is unknown but it is required for health. Sleep is controlled by the reticular activating system in the upper brainstem and diencephalon. It is composed of different stages that can be visualised on electroencephalography (EEG). As drowsiness occurs, normal EEG background alpha rhythm

Fig. 25.10 The areas supplied by specific levels of the spinal cord. These are approximations and in practice there is much overlap. The clinical utility of these dermatomes has diminished somewhat with the advent of good magnetic resonance imaging of the spinal cord but it remains important to ascertain the presence of a 'spinal level' of sensation, to remember the supply of saddle area, and to note the cervical descent of some facial spinothalamic pathways.

A Anterior. B Posterior. C3 C2 C4 C5 T2 T1 C6 C7 C8 T3 T4 T5 T6 T7 T8 T9 T12 T11 T10 L1 L2 S2 S3 S4 S2 L3 L4 L5 S1 S 5 C3 C2 C4 C5 T1 T2 T3 T4 T5 T6 T7 T8 T9 T10 T11 T12 L1 L2 L3 C8 C7 C6 L4 L5 S1 S2, 3 B A

1072 • NEUROLOGY Neuroimaging Neurological imaging has traditionally allowed only assessment of structure but advances are allowing much more sophistication. Imaging modalities can use X-rays (plain X-rays, computed tomography (CT), CT angiography, myelography and angiography), magnetic resonance (MR imaging (MRI), MR angiography (MRA)), ultrasound (Doppler imaging of blood vessels) and nuclear medicine techniques (single photon emission computed tomography (SPECT) and positron emission tomography (PET)). The uses and limitations of each of these are shown in Box 25.4. Different sequences for analysing MRI signals can provide helpful information for characterising tissues and pathologies (Box 25.5). Specialist MR techniques, such as functional MRI (fMRI), MR spectroscopy or diffusion tensor imaging (DTI), can be used to assess brain metabolism and chemical compositions. This may be dynamic and can provide 'maps' of cortical

function to help plan lesionectomy and epilepsy surgery. Similarly, MR spectroscopy can outline the chemical composition of specific regions, providing notions of whether lesions are ischaemic, neoplastic or inflammatory. Some degenerative neurological conditions cause functional rather than structural abnormalities that make metabolic and neurochemical assessment increasingly useful. PET scanning can display glucose metabolism in dementia and epilepsy. SPECT scanning uses the lipid-soluble properties of radioactive tracers to mark cerebral blood flow at the time of injection to help in investigating seizures. Dopaminergic pathway tracers can assess the integrity of the nigrostriatal pathway in patients with possible parkinsonism. which tracts/nuclei are affected, usually invoking the fewest number of lesions. For example, in a patient presenting with sudden onset of upper motor neuron features affecting the right face, arm and leg in association with a left 3rd nerve palsy, the lesion will be in the left cerebral peduncle in the brainstem and the pathology is likely to have been a discrete stroke, as the onset was sudden. This combination of symptoms and signs is known as Weber's syndrome, and is one of several well-described brainstem syndromes, which are listed in Box 25.3. The effects of individual cranial nerve deficits are discussed in the sections on eye movements (p. 1088) and on facial weakness, sensory loss in brainstem lesions, dysphonia and dysarthria, and bulbar symptoms (pp. 1082, 1083, 1087 and 1093). Investigation of neurological disease Experienced clinicians make most neurological diagnoses on history alone, with a lesser contribution from examination and investigation. As investigations become more complex and more easily available, it is tempting to adopt a 'scan first, think later' approach to neurological symptoms. The frequency of 'falsepositive' results, the wide range of normality, and the negative implications for patients (unnecessary expense, inconvenience, discomfort and worry) necessitate a more thoughtful approach. Investigation may include assessment of structure (imaging) and function (neurophysiology). Neurophysiological testing has become so complex that in some countries it constitutes a separate specialty focusing on electroencephalography, evoked potentials, nerve conduction studies and electromyography.

Fig. 25.11 The main somatic sensory pathways. Vestibulospinal tract Lateral spinothalamic tract Pain, temperature and poorly localised touch Joint position, vibration and accurate touch Dorsal column Gracile and cuneate nuclei Thalamus Parietal cortex

25.3 Major focal brainstem syndromes

Name of syndrome	Site of lesions	Clinical features
Weber	Anterior cerebral peduncle (mid-brain)	Ipsilateral 3rd palsy Contralateral upper motor neuron 7th palsy Contralateral hemiplegia
Claude	Cerebral peduncle Involving red nucleus	Ipsilateral 3rd palsy Contralateral cerebellar signs
Parinaud	Dorsal mid-brain (tectum)	Vertical gaze palsy Convergence disorders Convergence retraction nystagmus Pupillary and lid disorders
Millard-Gubler	Ponto-medullary junction	Ipsilateral 6th palsy Ipsilateral lower motor neuron 7th palsy Contralateral hemiplegia
Wallenberg	Lateral medulla	Ipsilateral 5th, 9th, 10th, 11th palsy Ipsilateral Horner's syndrome Ipsilateral cerebellar signs Contralateral spinothalamic sensory loss Vestibular disturbance

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25.5 Different magnetic resonance imaging (MRI) sequences T1 T2 T2-FLAIR A 'Anatomically correct' B 'Reverse T1' C T2 with CSF signal dampened Grey matter (cortex) Grey White White matter White Grey Grey Cerebrospinal fluid (CSF) Black White Black Insets courtesy of Dr Ravi Jampana, Consultant Neuroradiologist, Dept of Neuroradiology, Institute of Neuroscience, Queen Elizabeth University Hospital, Glasgow. of intravenous contrast and thinner slicing but CT is not optimal for lesions of meninges, cranial nerves or subtle parenchymal changes. MRI resolution is unaffected by bone and so is more useful in posterior fossa disease. Its sensitivity for cortical and

white matter changes makes it the modality of choice in inflammatory conditions such as multiple sclerosis and in the investigation of epilepsy. Different MRI techniques can selectively suppress Head and orbit Plain skull X-rays now have a very limited role in neurological disease. CT or MRI is needed for intracranial imaging. CT is good for demonstrating bone and calcification well. It will also detect abnormalities of the brain and ventricles, such as atrophy, tumours, cysts, abscesses, vascular lesions and hydrocephalus. Diagnostic yield may be improved by the use of 25.4 Imaging techniques for the nervous system

Technique	Applications	Advantages	Disadvantages	Comments	
X-ray/CT Plain	X-rays, CT, CTA	Radiculography	Myelography	Intra-arterial angiography	Widely available
		Relatively cheap	Relatively quick	Ionising radiation	Contrast reactions
			Invasive (myelography and angiography)		
X-rays:	used for fractures or foreign bodies				
CT:	first line for stroke				
Intra-arterial angiography:	gold standard for vascular lesions				
MRI	Structural imaging	MRA			
Functional MRI	MR spectroscopy	High-quality soft tissue images, useful for posterior fossa and temporal lobes	No ionising radiation	Non-invasive	Expensive
					Less widely available
MRA	images blood flow, not vessel anatomy		Claustrophobic	Pacemakers are a contraindication	Contrast (gadolinium) reactions
Functional MR and spectroscopy:	mainly research tools				
Ultrasound	Doppler	Duplex scans	Cheap	Quick	Non-invasive
			Operator-dependent	Poor anatomical definition	Screening tool to assess need for carotid endarterectomy
Radioisotope	Isotope brain scan	SPECT	PET	In vivo imaging of functional anatomy (ligand binding, blood flow)	Poor spatial resolution
					Ionising radiation
					Expensive
					Not widely available
Isotope scans:	obsolete				
SPECT:	useful in movement disorders, epilepsy and dementias				
PET:	mainly research tool				

(CT = computed tomography; CTA = computed tomographic angiography; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single photon emission computed tomography)

1074 • NEUROLOGY Neurophysiological testing Electroencephalography The electroencephalogram (EEG) detects electrical activity arising in the cerebral cortex via electrodes placed on the scalp to record the amplitude and frequency of the resulting waveforms. With closed eyes, the normal background activity is 8–13 Hz (known as alpha rhythm), most prominent occipitally and suppressed on eye opening. Other frequency bands seen over different parts of the brain in different circumstances are beta (faster than 13/sec), theta (4–8/sec) and delta (slower than 4/sec). Normal EEG patterns evolve with age and alertness; lower frequencies predominate in the very young and during sleep. In recent years, digital technology has allowed longer, cleaner EEG recordings that can be analysed in a number of ways and recorded alongside contemporaneous video of any clinical ‘event’. Meanwhile, the development of intracranial recording allows more sensitive monitoring via surgically placed electrodes in and around lesions to help increase the efficacy and safety of epilepsy surgery. Abnormal EEGs result from a number of conditions. Examples include an increase in fast frequencies (beta) seen with sedating drugs such as benzodiazepines, or marked focal slowing noted over a structural lesion such as a tumour or an infarct. Improved quality and accessibility of imaging have made EEG redundant in lesion localisation, except in the specialist investigation of epilepsy (p. 1100). EEG remains useful in progressive and continuous disorders such as reduced consciousness (p. 194), encephalitis signal from fluid or fat, for example, and so increase sensitivity for more subtle pathologies. Examples of brain imaged by the various techniques are shown in Figure 25.12. Cervical, thoracic and lumbar spine X-rays are useful for imaging bony structures and can show destruction or damage to vertebrae, for example, but will provide no information about non-bony tissues, such as intervertebral discs, spinal cord and nerve roots. They have some usefulness in dynamic imaging,

e.g. flexion/extension of the spine, in the assessment of instability. MRI has transformed spinal investigation, as it can give information not only about vertebrae and intervertebral discs but also about their effects on the spinal cord and nerve roots. Myelography (usually with CT) is an invasive technique requiring injection of contrast into the lumbar theca. While outlining the nerve roots and spinal cord provides some detail about abnormal structure, the accuracy and availability of MRI have reduced the need for it. Myelography may still be used where MRI is unavailable, contraindicated, or precluded by a patient's claustrophobia. Examples of the cervical spine imaged by plain X-rays, myelography and MRI are shown in Figure 25.13. Blood vessels Imaging of the extra- and intracranial blood vessels and disturbance of arterial or venous blood flow is described on page 1161. Fig. 25.12 Different techniques of imaging the head and brain. A Computed tomogram showing complete middle cerebral artery infarct (arrows). B Magnetic resonance image showing widespread areas of high signal in multiple sclerosis (arrows). C Single photon emission computed tomography scan after caudate infarct showing relative hypoperfusion of overlying right cerebral cortex (arrows). D Normal positron emission tomogram (PET scan) of brain. A-C, Courtesy of Dr D. Collie. D, Courtesy of Dr Ravi Jampana, Consultant Neuroradiologist, Dept of Neuroradiology, Institute of Neuroscience, Queen Elizabeth University Hospital, Glasgow. C A B D

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but, conversely, the presence of epileptiform features does not of itself make a diagnosis. Up to 5% of some normal populations may demonstrate epileptiform discharges on EEG, preventing its use as a screening test for epilepsy, most notably in younger patients with a family history of epilepsy. In view of this, the EEG should not be used where epilepsy is merely 'possible'. (p. 1121), and certain dementias such as Creutzfeldt-Jakob disease (p. 1127). Since sleep induces marked changes in cerebral activity, EEG can be useful in diagnosis of sleep disturbances. In paroxysmal disorders such as epilepsy, EEG is at its most useful when it captures activity during one of the events in question. Over 50% of patients with epilepsy have a normal 'routine' EEG Fig. 25.13 Different techniques of imaging the cervical spine. A Lateral X-ray showing bilateral C6/7 facet dislocation. B Myelogram showing widening of cervical cord due to astrocytoma (arrows). C Magnetic resonance image showing posterior epidural compression from adenocarcinomatous metastasis to the posterior arch of T1 (arrows). A-C, Courtesy of Dr D. Collie. A B C C6 C7 Fig. 25.14 Electroencephalograms in epilepsy. A Generalised epileptic discharge, as seen in epilepsy syndromes such as childhood absence or juvenile myoclonic epilepsy. B Focal sharp waves over the right parietal region (circled), with spread of discharge to cause a generalised tonic-clonic seizure.

A B

15 14 13 12

Secondary generalised seizure

1076 • NEUROLOGY 25.15). These are around 500 times larger than sensory nerve potentials, typically around 1–20 millivolts. Since a proportion of stimulated impulses in motor nerves will 'reflect' back from the anterior horn cell body (forming the 'F' wave), it is also possible to obtain some information about the condition of nerve roots. Repetitive nerve stimulation (RNS) at 3–15/sec provides consistent CMAPs in healthy muscle. In myasthenia gravis (p. 1141), however,

where there is partial blockage of acetylcholine receptors, there is a diagnostic fall (decrement) in CMAP amplitude. In contrast, an increasing CMAP with high-frequency RNS is seen in Lambert-Eaton myasthenic syndrome (p. 1143).

Electromyography Electromyography (EMG) is usually performed alongside NCS and involves needle recording of muscle electrical potential during rest and contraction. At rest, muscle is electrically silent but loss of nerve supply causes muscle membrane to become unstable, manifest as fibrillations, positive sharp waves ('spontaneous activity') or fasciculations. Motor unit action potentials are recorded during muscle contraction. Axonal loss or destruction will result in fewer motor units. Resultant sprouting of remaining units will lead to increasing size of each individual unit on EMG. Myopathy, in contrast, causes muscle fibre splitting, which results in a large number of smaller units on EMG. Other abnormal activity, such as myotonic discharges, may signify abnormal ion channel conduction, as in myotonic dystrophy or myotonia congenita. Specialised single-fibre electromyography (SFEMG) can be used to investigate neuromuscular junction transmission. Measuring 'jitter' and 'blocking' can identify the effect of antibodies in reducing the action of acetylcholine on the receptor. Evoked potentials

The cortical response to visual, auditory or electrical stimulation can be measured on an EEG as an evoked potential (EP). If a stimulus is provided – e.g. to the eye, the tiny EEG response can be discerned when averaging 100–1000 repeated stimuli. Assessing the latency (the time delay) and amplitude can give Therefore the EEG in epilepsy is predominantly used for classification and prognostication, but in some patients can help localise the seat of epileptiform discharges when surgery is being considered. During a seizure, high-voltage disturbances of background activity ('discharges') are often noted. These may be generalised, as in the 3 Hz 'spike and wave' of childhood absence epilepsy, or more focal, as in localisation-related epilepsies (Fig. 25.14). Techniques such as hyperventilation or photic stimulation can be used to increase the yield of epileptiform changes, particularly in the generalised epilepsy syndromes. While some argue that it is possible to detect 'spikes' and 'sharp waves' to lend support to a clinical diagnosis, these are non-specific and therefore not diagnostic, and can lead an unwary clinician to err in ascribing other symptoms to epilepsy.

Nerve conduction studies Electrical stimulation of a nerve causes an impulse to travel both efferently and afferently along the underlying axons. Nerve conduction studies (NCS) make use of this, recording action potentials as they pass along peripheral nerves and (with motor nerves) as they pass into the muscle belly. Digital recording has enhanced sensitivity and reproducibility of these tiny potentials. By measuring the time taken to traverse a known distance, it is possible to calculate nerve conduction velocities (NCVs). Healthy nerves at room temperature will conduct at a speed of 40–50 m/sec. If the recorded potential is smaller than expected, this provides evidence of a reduction in the overall number of functioning axons. Significant slowing of conduction velocity, in contrast, suggests impaired conduction due to peripheral nerve demyelination. Such changes in NCS may be diffuse (as in a hereditary demyelinating peripheral neuropathy, p. 1138), focal (as in pressure palsies, p. 1139) or multifocal (e.g. Guillain-Barré syndrome, p. 1140; mononeuritis multiplex, p. 1140). The information gained can allow the disease responsible for peripheral nerve dysfunction to be better deduced (see Box 25.84, p. 1139). Stimulation of motor nerves allows for the recording of compound muscle action potentials (CMAPs) over muscles (Fig. Fig. 25.15 Motor nerve conduction tests. Electrodes (R) on the muscle (abductor pollicis here) record the compound muscle action potential (CMAP) after stimulation at the median nerve at the wrist (S1) and from the elbow (S2). The velocity from elbow to wrist can be determined if the distance between the two stimulating electrodes (d) is known. A prolonged L1 (L = latency) would be caused by dysfunction distally in the median nerve (e.g. in carpal tunnel syndrome). A prolonged L2 is caused by slow nerve conduction (as in demyelinating

neuropathy). The F wave is a small delayed response that appears when the electrical signal travels backwards to the anterior horn cell, sparking a second action potential in a minority of fibres (see text). (NCV = nerve conduction velocity)

Anterior horn cells Antidromic conduction: generates F wave Orthodromic conduction F wave CMAP
Abductor pollicis brevis Median nerve NCV = d L2 - L1 S2 S1 L1 L2 R Amplitude d

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causative antibodies (see Boxes 25.52 and 25.53, p. 1111) and it is likely that further conditions will turn out to have an immune basis. Genetic testing This evolving field represents a huge untapped area for neurological exploration, particularly with the development of genome-wide association study (GWAS) and whole-genome sequencing. Relevant subsections will detail the increasing numbers of inherited neurological conditions that can now be diagnosed by DNA analysis (p. 56). These include diseases caused by increased numbers of trinucleotide repeats, such as Huntington's disease (p. 1114); myotonic dystrophy (p. 1143); and some types of spinocerebellar ataxia (p. 1115). Mitochondrial DNA can also be sequenced to diagnose relevant disorders (p. 1144). Lumbar puncture Lumbar puncture (LP) is the technique used to obtain both a CSF sample and an indirect measure of intracranial pressure. After local anaesthetic injection, a needle is inserted between lumbar spinous processes (usually between L3 and L4) through the dura and into the spinal canal. Intracranial pressure can be deduced (if patients are lying on their side) and CSF removed for analysis. CSF pressure measurement is important in the diagnosis and monitoring of idiopathic intracranial hypertension (p. 1133). In this condition, the LP itself is therapeutic. CSF is normally clear and colourless, and the tests that are usually performed include a naked eye examination of the CSF and centrifugation to determine the colour of the supernatant (yellow, or xanthochromic, some hours after subarachnoid haemorrhage; p. 1160). Measurement of absorption of specific light wavelengths helps quantify the amount of haem metabolites in CSF. Routine analysis involves a cell count, as well as glucose and protein concentrations. CSF assessment is important in investigating infections (meningitis or encephalitis), subarachnoid haemorrhage and inflammatory conditions (multiple sclerosis, sarcoidosis and cerebral lupus). Normal values and abnormalities found in specific conditions are shown in Box 25.6. More sophisticated analysis allows measurement of antibody formation solely within the CNS (oligoclonal bands), genetic analysis (e.g. polymerase chain reaction (PCR) for herpes simplex or tuberculosis), immunological tests (paraneoplastic antibodies) and cytology (to detect malignant cells). If there is a cranial space-occupying lesion causing raised intracranial pressure, LP presents a theoretical risk of downward shift of intracerebral contents, a potentially fatal process known as coning (p. 1128). Consequently, LP is contraindicated if there is any clinical suggestion of raised intracranial pressure (papilloedema), depressed level of consciousness, or focal neurological signs suggesting a cerebral lesion, until imaging (by CT or MRI) has excluded a space-occupying lesion or hydrocephalus. When there is a risk of local haemorrhage (thrombocytopenia, disseminated intravascular coagulation or anticoagulant treatment), then caution should be exercised or specific measures should be taken. LP can be safely performed in patients on antiplatelet drugs or low-dose heparin, but may be unsafe in patients who are fully anticoagulated due to the increased risk of epidural haematoma. About 30% of LPs are followed by a postural headache, due to reduced CSF pressure. The frequency of headache information about the integrity of the relevant pathway. MRI now provides more information about CNS pathways, thus reducing reliance on EPs. In practice, visual evoked

potentials (VEPs) are most commonly used to help differentiate CNS demyelination from small-vessel white-matter changes (Fig. 25.16). Magnetic stimulation Central conduction times can also be measured using electromagnetic induction of action potentials in the cortex or spinal cord by the local application of specialised coils. Again, MRI has made this technique largely redundant, other than for research. Routine blood tests Many systemic conditions that can affect the nervous system can be identified by simple blood tests. Nutritional deficiencies, metabolic disturbances, inflammatory conditions or infections may all present or be associated with neurological symptoms, and basic blood tests (full blood count, erythrocyte sedimentation rate, C-reactive protein, biochemical screening) may provide clues. Specific blood tests will be highlighted in the relevant subsections of this chapter. Human immunodeficiency virus (HIV) infection is increasingly recognised as a cause of neurological disease and the clinician should have a low threshold for checking this. Immunological tests Recent developments have seen a host of new immune-mediated conditions emerge in clinical neurology, with antibody targets ranging from muscle and neuromuscular junction disturbance (causing weakness and muscle pain) to specific neuronal ion channels (causing cognitive decline, epilepsy and psychiatric changes). The 21st century has seen the identification of many

Fig. 25.16 Visual evoked potential (VEP) recording. The abnormality is in the left hemisphere, with delay in latency and a reduction in signal of the P100. 5 μ V 5 μ V 5 μ V 5 μ V 5 μ V 5 μ V 5 μ V 5 μ V 5 μ V

L R ms ms P100 P100

1078 • NEUROLOGY Presenting problems in neurological disease While history is important in all medical specialties, it is especially key in neurology, where many neurological diagnoses have no confirmatory test. History-taking allows doctor and patient to get to know one another; many neurological diseases follow chronic paths and this may be the first of many such consultations. It also allows the clinician to obtain information about the patient's affect, cognition and psychiatric state. History-taking is a highly active process. While there are generic templates (Box 25.7), each individual story will follow its own course, and diagnostic considerations during the history will guide further questioning. It is important to be clear about what patients mean by certain words. They may find it difficult to describe symptoms: for instance, weakness may be called 'numbness', while there are many possible interpretations of 'dizziness'. These must be clarified; even in emergency situations, a clear, accurate history is the foundation of any management plan. While the story should come primarily from the patient, input from eye-witnesses and family members is crucial if the patient is unable to provide details or if there has been loss of consciousness. This need for corroboration and clarification means the telephone is as important as any investigation. The aim of the history is to address two key issues: where is the lesion and what is the lesion (Box 25.8)? These should remain uppermost in the doctor's mind while the history is being elicited. Some common combinations of symptoms may suggest particular locations for a lesion (Box 25.10). Enquiry about handedness is important; lateralisation of the dominant hand helps designate the dominant hemisphere, which in turn may help to localise any pathologies, or to plan rehabilitation or treatment strategies in asymmetrical disorders such as stroke or Parkinson's disease. Epidemiology must be borne in mind. How likely is it that this particular patient has any specific condition under consideration? can be reduced by using smaller or atraumatic needles. Rarer complications involve transient radicular pain, and pain over the lumbar region during the procedure. Aseptic technique renders secondary infections such as meningitis extremely rare. Biopsy Biopsies of nervous tissue (peripheral nerve, muscle, meninges or brain) are occasionally

required for diagnosis. Nerve biopsy can help in the investigation of peripheral neuropathy. Usually, a distal sensory nerve (sural or radial) is targeted. Histological examination can help identify underlying causes, such as vasculitides or infiltrative disorders like amyloid. Nerve biopsy should not be undertaken lightly since there is an appreciable morbidity; it should be reserved for cases where the diagnosis is in doubt after routine investigations and where it will influence management. Muscle biopsy is performed more frequently and is indicated for the differentiation of myositis and myopathies. These conditions can usually be distinguished by histological examination, and enzyme histochemistry can be useful when mitochondrial diseases and storage diseases are suspected. The quadriceps muscle is most commonly biopsied but other muscles may also be sampled if they are involved clinically. Although pain and infection can follow the procedure, these are less of a problem than after nerve biopsy. Brain biopsy is required when imaging fails to clarify the nature of intracerebral lesions, e.g. in unexplained degenerative diseases such as unusual cases of dementia and in patients with brain tumours. Most biopsies are performed stereotactically through a burr hole in the skull, which lowers complication rates. Nevertheless, haemorrhage, infection and death still occur and brain biopsy should be considered only if a diagnosis is otherwise elusive. Biopsy of other organs can be useful in the diagnosis of systemic disorders presenting as neurological problems, such as tonsillar biopsy (diagnosis of prion diseases), or rectal or fat biopsy (for assessment of amyloid).

25.6 How to interpret cerebrospinal fluid results

	Normal	Subarachnoid haemorrhage	Acute bacterial meningitis	Viral meningitis	Tuberculous meningitis	Multiple sclerosis	Pressure
50–250 mm of water	Increased	Normal	Normal	Normal	Normal	Normal	Normal
Colour	Clear	Blood-stained	Xanthochromic	Cloudy	Clear	Clear/cloudy	Clear
Red cell count ($\times 10^6/L$)	0–4	Raised	Normal	Normal	Normal	Normal	Normal
White cell count ($\times 10^6/L$)	0–4	Normal/raised	1000–5000 polymorphs	10–2000 lymphocytes	50–5000 lymphocytes	0–50 lymphocytes	Glucose

“ 50–60% of blood level Normal Decreased Normal Decreased Normal Protein < 0.45 g/L Increased Increased Normal/increased Increased Normal/increased Microbiology Sterile Sterile Organisms on Gram stain and/or culture Sterile/virus detected Ziehl-Neelsen/auramine stain or tuberculosis culture positive Sterile Oligoclonal bands Negative Negative Can be positive Can be positive Can be positive Often positive

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Evolution over several days, however, might make demyelination (multiple sclerosis) a possible diagnosis, or perhaps a subdural haematoma if the weakness was preceded by a head injury in an older person taking warfarin. Progression over weeks might bring an intracranial mass lesion or motor neuron disease into the differential. Slow progression over a year or so, with difficulty in using the hand, could suggest a degenerative process such as Alzheimer's disease. For example, a 20-year-old with right-sided headache and tenderness will not have temporal arteritis, but this is an important possibility if such symptoms present in a 78-year-old female. Determining the evolution, speed of onset and progression of a disease is important (Box 25.11). For example, if right-hand weakness occurred overnight, it would suggest a stroke in an older person or an acute entrapment neuropathy in a younger one.

25.7 How to take a neurological history

Introduction • Age and sex • Handedness

Presenting complaint • Symptoms (clarify: see text) • Overall pattern: intermittent or persistent? • If intermittent, how often do symptoms occur and how long do they last? • Speed of onset: seconds, minutes, hours, days, weeks, months, years, decades? • Better, worse or the same over time? • Associated symptoms (including non-neurological) • Disability caused by symptoms • Change in walking • Difficulty with fine hand movements, e.g. writing, fastening buttons, using cutlery • Effect on work, family life and leisure Background • Previous neurological symptoms and whether similar to current symptoms • Previous medical history • Domestic situation • Driving licence status • Medications (current and at time of symptom onset) • Alcohol/smoking habits • Recreational drug and other toxin exposure • Family history and developmental history • What are patient's thoughts/fears/concerns?

25.8 The key diagnostic questions Where is the lesion? • Is it neurological? • If so, to which part of the nervous system does it localise? Central versus peripheral Sensory versus motor versus both What is the lesion? • Hereditary or congenital • Acquired: Traumatic Infective Neoplastic Degenerative Inflammatory or immune-mediated Vascular Functional

25.10 How to 'localise' neurological disease

Combination of symptoms/signs	Probable site	Possible pathology	Other important information
Painless loss of hemilateral function	Cerebral cortex	Usually vascular, inflammatory or neoplastic	Associated systemic symptoms
Tempo of evolution	Pyramidal weakness of all four limbs or both legs, bladder signs, sensory loss	Spinal cord	Usually vascular, inflammatory or neoplastic
Associated systemic symptoms	Tempo of evolution	Cranial nerve lesions, with limb pyramidal signs or sensory loss ± sphincter disturbance	Brainstem
Mid-brain	Pons	Medulla	Usually vascular or inflammatory
Rarely neoplastic	Associated systemic symptoms	Tempo of evolution	Visual loss + pyramidal signs and/or cerebellar signs
Widespread cerebral lesions	Usually inflammatory	Less commonly vasculitic	Tempo of evolution
Weakness and/or sensory loss in a combination of individual peripheral nerves	Several peripheral nerves ('mononeuritis multiplex')	Usually inflammatory or diabetic	Associated systemic symptoms
Widespread LMN and UMN signs	Upper and lower motor neurons	Motor neuron disease	Cervical myeloradiculopathy
Associated localised cervical symptoms	Distal loss of sensation and/or weakness	Generalised peripheral nerves	See causes of neuropathy (p. 1138)
Associated systemic symptoms (LMN/UMN = lower/upper motor neuron)			

25.9 Neurological examination in old age • Pupils: tend to be smaller, making fundoscopy more difficult. • Limb tone: more difficult to assess because of poor relaxation and concomitant joint disease. • Ankle reflexes: may be absent. • Gait assessment: more difficult because of concurrent musculoskeletal disease and pre-existing neurological deficits. • Sensory testing: especially difficult when there is cognitive impairment. • Vibration sense: may be reduced distally in the legs.

1080 • NEUROLOGY frequently felt in the second and third divisions of the nerve and often triggered by talking or chewing. Facial shingles most commonly affects the first (ophthalmic) division of the trigeminal nerve, and pain usually precedes the rash. Post-herpetic neuralgia may follow, typically a continuous burning pain throughout the affected territory, with marked sensitivity to light touch (allodynia) and resistance to treatment. Destructive lesions of the trigeminal nerve usually cause numbness rather than pain. Persistent idiopathic facial pain is most frequently seen in middle-aged women, who report persistent pain, with no abnormal signs or investigations, and is similar to other forms of idiopathic chronic pain. Dizziness, blackouts and 'funny turns' Acute onset of dizziness or blackouts will present to the acute medical department. In neurological practice, it is common to deal with patients presenting with a history of multiple events. While detailed questioning will be dealt with in the relevant section (p. 181), the neurologist will have to tease out the pattern of each of the different attack types experienced by

the patient to be able to form a treatment and investigation plan, one of the challenges of clinical neurology.

Status epilepticus Status epilepticus is seizure activity not resolving spontaneously, or recurrent seizure with no recovery of consciousness in between. Persisting seizure activity has a recognised mortality and is a medical emergency. Diagnosis is usually clinical and can be made on the basis of the description of prolonged rigidity and/or clonic movements with loss of awareness. As seizure activity becomes prolonged, movements may become more subtle. Cyanosis, pyrexia, acidosis and sweating may occur, and complications include aspiration, hypotension, cardiac arrhythmias and renal or hepatic failure. In patients with pre-existing epilepsy, the most likely cause is a fall in antiepileptic drug levels. In de novo status epilepticus, it is essential to exclude precipitants such as infection (meningitis, encephalitis), neoplasia and metabolic derangement (hypoglycaemia, hyponatraemia or hypocalcaemia). Treatment and investigation are outlined in Box 25.12.

Coma Coma and loss of consciousness usually present to the acute medical admissions department (p. 194). Clarification of cause and prognosis may require specialist neurological input.

Delirium Delirium describes cortical dysfunction and replaces the older term 'acute confusional state'. It has a range of primary causes, and given its role in precipitating acute admission, it is covered in detail on page 183.

Amnesia Memory disturbance is a common symptom. In the absence of significant functional impairment (e.g. inability to work, dyspraxias, loss of daily function), many patients will prove to have benign memory dysfunction related to age, mood or psychiatric disorders. as Parkinson's disease. The impact on day-to-day activities, such as walking, climbing stairs and carrying out fine hand movements, should also be established in order to gauge the level of associated disability. Estimates of the frequency and duration of specific events are essential when taking details of a paroxysmal disorder such as migraine and epilepsy. Vague terms such as 'a lot' or 'sometimes' are unhelpful, and it can assist the patient if choices are given to estimate numbers, such as once a day, week or month. Many neurological symptoms are not explained by disease. Describing these as 'functional' is less pejorative and more acceptable to patients than 'psychogenic' or 'hysterical'. Functional symptoms require considerable experience in diagnosis and are frequently missed (p. 1094).

Headache and facial pain Most headaches are chronic disorders but acute presentation of headaches is an important aspect of emergency medical care. Headache may be divided into primary (benign) or secondary, and most patients, whether presenting in clinic or as emergencies, have primary syndromes (see Box 10.10, p. 184). The emergency clinical assessment of headaches is dealt with on page 185.

Ocular pain Assuming that ocular disease (such as acute glaucoma) has been excluded, ocular pain may be due to trigeminal autonomic cephalalgias (TACs) or, rarely, inflammatory or infiltrative lesions at the apex of the orbit or the cavernous sinus, when 3rd, 4th, 5th or 6th cranial nerve involvement is usually evident. Ocular pain and headache are also discussed on page 1170.

Facial pain Pain in the face can be due to dental or temporomandibular joint problems. Acute sinusitis is usually apparent from other features of sinus congestion/infection and may cause localised pain over the affected sinus, but is almost never the explanation for persistent facial pain or headache. Facial pain is not uncommon in migraine but some syndromes can present solely with facial pain. The most common neurological causes of facial pain are trigeminal neuralgia, herpes zoster (shingles) and post-herpetic neuralgia, all characterised by their extreme severity. In trigeminal neuralgia, the patient describes bouts of brief (seconds), lancinating pain ('electric shocks'), most 25.11

The evolution of symptoms

Onset	Evolution	Possible causes
Sudden (minutes to hours)	Stable/improvement	Vascular (stroke/transient ischaemic attack (TIA))
Nerve entrapment syndromes	Functional	Gradual
Progressive over days	Demyelination	Infection
Gradual	Progressive over weeks to months	Neoplastic/paraneoplastic
Gradual	Progressive over months to years	Genetic
Degenerative		

amnesia recurs in only around 10–20% of cases. A vascular aetiology is unlikely (TGA is not a risk factor for subsequent vascular disease) and amnesia may be due to a benign process similar to migraine, occurring in the hippocampus. TGA causes no physical signs and, provided there is a typical history (which requires a witness), no investigation is necessary and patients may be reassured. Persistent amnesia Serious neurological disease must be excluded in patients with persistent memory disturbance, although many will prove to have benign symptoms. Symptoms corroborated by relatives or colleagues are likely to be more significant than those noted by the patient only. Where poor concentration is at the heart of cognitive deterioration, it is more likely to be due to an underlying mood disorder. It is important to assess the timing of onset and to establish which aspects of memory are affected. Complaints of getting lost or of losing complex abilities are more pathological than wordfinding difficulties. Disturbance of episodic or working memory (previously called ‘short-term memory’) must be distinguished from semantic memory (memory for concept-based knowledge unrelated to specific experiences). Episodic memory is selectively impaired in Korsakoff’s syndrome (often secondary to alcohol) or bilateral temporal lobe damage. It can also be seen in conjunction with other types of dementia. Progressive deterioration over months suggests an underlying dementia, and a full medical assessment must be performed to detect any underlying medical problem. It is important to identify and treat depression (p. 1185) in patients with memory loss. Depression may present as a ‘pseudo-dementia’, with concentration and memory impairment as dominant features, and this is often reversible with antidepressant medication. Any patient with dementia (particularly of Alzheimer’s type) may develop depression in the early stages of their illness, however. Specific causes of progressive dementia, with their investigation and treatment, are described elsewhere (p. 1191).

Weakness The assessment of weakness requires the application of basic anatomy, physiology and some pathology to the interpretation of the history and clinical findings. Points to consider are shown on Figure 25.17 and in Boxes 25.13 and 25.14. The pattern and evolution of weakness and the clinical signs provide clues to the site and nature of the lesion. It is important to establish whether the patient has loss of power rather than reduced sensation or generalised fatigue. Pain may restrict movement and thus mimic weakness. Paradoxically, sensory neglect (p. 1083) may leave patients unaware of severe weakness. Patients with parkinsonism may complain of weakness; extrapyramidal signs of rigidity (cogwheel or lead pipe) and bradykinesia should be evident, and a resting tremor (usually asymmetrical) may provide a further clue (p. 1112). Simple observation of the patient walking into the consulting room may be diagnostic, and is as important as formal strength testing. Movement restricted by pain should be apparent, and other features (contractures, wasting, fasciculations, abnormal movements/postures) all provide diagnostic clues. Weakness is a common symptom arising without an underlying degenerative or destructive cause (functional symptom).

25.12 Management of status epilepticus

Initial

- Ensure airway is patent; give oxygen to prevent cerebral hypoxia
- Check pulse, blood pressure, BM stix and respiratory rate
- Secure intravenous access
- Send blood for: Glucose, urea and electrolytes, calcium and magnesium, liver function, antiepileptic drug levels

Full blood count and coagulation screen

Storing a sample for future analysis (e.g. drug misuse)

- If seizures continue for > 5 mins: give midazolam 10 mg buccally or nasally or lorazepam 4 mg IV if access available or diazepam 10 mg rectally or IV if necessary; repeat once only after 15 mins
- Correct any metabolic trigger, e.g. hypoglycaemia

Ongoing

- If seizures continue after 30 mins
- IV infusion (with cardiac monitoring) with one of:
 - Phenytoin: 15 mg/kg at 50 mg/min
 - Sodium valproate: 20–30 mg/kg IV at 40 mg/min
 - Phenobarbital: 10 mg/kg at

100 mg/min • Cardiac monitor and pulse oximetry: Monitor neurological condition, blood pressure, respiration; check blood gases If seizures still continue after 30–60 mins • Transfer to intensive care: Start treatment for refractory status with intubation, ventilation and general anaesthesia using propofol or thiopental EEG monitor Once status controlled • Commence longer-term antiepileptic medication with one of: Sodium valproate 10 mg/kg IV over 3–5 mins, then 800–2000 mg/day Phenytoin: give loading dose (if not already used as above) of 15 mg/kg, infuse at < 50 mg/min, then 300 mg/day Carbamazepine 400 mg by nasogastric tube, then 400–1200 mg/day • Investigate cause The increasing publicity given to dementia, combined with a natural fear of losing one's mind, has led to an increase in patients presenting with memory loss but many will have benign symptoms. Investigation and treatment of the dementias are discussed elsewhere (p. 1191). Temporary loss of memory may be due to a transient delirium related to infection, the post-ictal period after seizure, or transient global amnesia. These are usually distinguished on the basis of the history. Transient amnesia resulting directly from a seizure (transient epileptic amnesia) is a rare result of temporal lobe epilepsy. Transient global amnesia Transient global amnesia (TGA) predominantly affects middle-aged people, with an abrupt, discrete loss of anterograde memory function lasting up to a few hours. During the episode, patients are unable to record new memories, resulting in repetitive questioning, the hallmark of this condition. Consciousness is preserved and patients may perform even complex motor acts normally. During the attack there is retrograde amnesia for the events of the past few days, weeks or years. After 4–6 hours, memory function and behaviour return to normal but the patient has persistent, complete amnesia for the duration of the attack itself. There are no seizure markers and, unlike epileptic amnesia, transient global

1082 • NEUROLOGY Facial weakness Facial nerve palsy (Bell's palsy) One of the most common causes of facial weakness is Bell's palsy, a lower motor neuron lesion of the 7th (facial) nerve, affecting all ages and both sexes. It is more common following upper respiratory tract infections, during pregnancy, and in patients with diabetes, immunosuppression and hypertension. weakness does not conform to typical organic patterns, and the signs in Box 25.13 are absent. Clinical examination is often variable (e.g. the patient can walk but appears to have no leg movement when assessed on the couch), and strength may appear to 'give way', with the patient able to achieve full power for brief bursts, which does not occur in disease. Hoover's sign is useful to confirm functional weakness, and relies on eliciting the normal phenomenon of simultaneous hip extension when the contralateral hip flexes. In functional weakness, hip extension weakness may be seen; this then returns to full strength when contralateral hip flexion is tested. This sign may be demonstrated to the patient in a non-confrontational manner, to show that the potential limb power is intact. 25.14 How to assess weakness Clinical finding Likely level of lesion/diagnosis Pattern and distribution Isolated muscles Radiculopathy or mononeuropathy Both limbs on one side (hemiparesis) Cerebral hemisphere, less likely cord or brainstem One limb Neuronopathy, plexopathy, cord/brain Both lower limbs (paraparesis) Spinal cord; look for a sensory level Fatigability Myasthenia gravis Bizarre, fluctuating, not following anatomical rules Functional Signs Upper motor neuron Brain/spinal cord Lower motor neuron Peripheral nervous system Evolution of the weakness Sudden and improving Stroke/mononeuropathy Evolving over months or years Meningioma, cervical spondylotic myelopathy Gradually worsening over days or weeks Cerebral mass, demyelination Associated symptoms Absence of sensory involvement Motor neuron disease, myopathy, myasthenia 25.13 Distinguishing signs in upper versus lower motor neuron syndromes Upper motor neuron lesion Lower motor neuron lesion Inspection Normal (may be wasting in

chronic lesions) Wasting, fasciculation Tone Increased with clonus Normal or decreased, no clonus
 Pattern of weakness Preferentially affects extensors in arms, flexors in leg Hemiparesis,
 paraparesis or tetraparesis Typically focal, in distribution of nerve root or peripheral nerve, with
 associated sensory changes Deep tendon reflexes Increased Decreased/absent Plantar response
 Extensor (Babinski sign) Flexor Fig. 25.17 Patterns of motor loss according to the anatomical site of
 the lesion. Anterior horn, motor root, plexus and peripheral nerve Upper limbs Contralateral
 hemiplegia Central lesion Peripheral lesion Tetraplegia Paraplegia Upper motor neuron lesion
 Spinal cord Lower motor neuron lesion Lower limbs

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Sensory neurological examination needs to be undertaken and interpreted with care because the findings depend, by definition, on subjective reports. The reported distribution of sensory loss can be useful, however, when combined with the coexisting deficits of motor and/or cranial nerve function (Fig. 25.18). Sensory loss in peripheral nerve lesions Here the symptoms are usually of sensory loss and paraesthesia. Single nerve lesions cause disturbance in the sensory distribution of the nerve, whereas in diffuse neuropathies the longest neurons are affected first, giving a characteristic 'glove and stocking' distribution. If smaller nerve fibres are preferentially affected (e.g. in diabetic neuropathy), temperature and pin-prick (pain) are reduced, whilst vibration sense and proprioception (modalities served by the larger, well-myelinated, sensory nerves) may be relatively spared. In contrast, vibration and proprioception are particularly affected if the neuropathy is demyelinating in character (p. 1138), producing symptoms of tightness and swelling with impairment of proprioception and vibration sensation. Sensory loss in nerve root lesions These typically present with pain as a prominent feature, either within the spine or in the limb plexuses. Pain is often felt in the myotome rather than the dermatome. The nerve root involved may be deduced from the dermatomal pattern of sensory loss (p. 1071), although overlap may lead to this being smaller than expected. Sensory loss in spinal cord lesions Transverse lesions of the spinal cord produce loss of all sensory modalities below that segmental level, although the clinical level may only be manifest 2–3 segments lower than the anatomical site of the lesion. Very often, there is a band of paraesthesia or hyperaesthesia at the top of the area of sensory loss. Clinical examination may reveal dissociated sensory loss, i.e. different patterns in the spinothalamic and dorsal columnar pathways. If the transverse lesion is vascular due to anterior spinal artery thrombosis, the spinothalamic pathways may be affected while the posterior one-third of the spinal cord (the dorsal column modalities) may be spared. Lesions damaging one side of the spinal cord will produce loss of spinothalamic modalities (pain and temperature) on the opposite side, and of dorsal column modalities (joint position and vibration sense) on the same side of the body – the Brown–Séquard syndrome (p. 1084). Lesions in the centre of the spinal cord (such as syringomyelia: see Box 25.83 and Fig. 25.51, pp. 1138 and 1139) spare the dorsal columns but involve the spinothalamic fibres crossing the cord from both sides over the length of the lesion. There is no sensory loss in segments above and below the lesion; this is described as 'suspended' sensory loss. There is sometimes reflex loss at the level of the lesion if afferent fibres of the reflex arc are affected. An isolated lesion of the dorsal columns is not uncommon in multiple sclerosis. This produces a characteristic unpleasant, tight feeling over the limb(s) involved and, while there is no loss of pin-prick or temperature sensation, the associated loss of proprioception may severely limit function of the affected limb(s). Sensory loss in brainstem lesions Lesions in the brainstem can be associated with sensory loss but the distribution depends on the site of the lesion. A lesion

limited to the trigeminal nucleus or its sensory projections will cause The lesion is within the facial canal. Symptoms usually develop subacutely over a few hours, with pain around the ear preceding the unilateral facial weakness. Patients often describe the face as 'numb' but there is no objective sensory loss (except to taste, if the chorda tympani is involved). Hyperacusis may occur if the nerve to stapedius is involved and impairment of parasympathetic fibres may cause diminished salivation and tear secretion. Examination reveals an ipsilateral lower motor neuron facial nerve palsy (no sparing of forehead muscles). Vesicles in the ear or on the palate may indicate primary herpes zoster infection (p. 239). A clinical search for signs of other causes of lower motor neuron facial nerve weakness, such as parotid or scalp lesions, trauma or skull base lesions, is justified. Glucocorticoids improve recovery rates if started within 72 hours of onset but antiviral drugs are not effective. Artificial tears applied regularly prevent corneal drying, and taping the eye shut overnight helps prevent exposure keratitis and corneal abrasion. Patients unable to close the eye should be referred urgently to an ophthalmologist. About 80% of patients recover spontaneously within 12 weeks. Plastic surgery may be considered for the minority left with facial disfigurement after 12 months. Recurrence is unusual and should prompt further investigation. Aberrant re-innervation may occur during recovery, producing unwanted facial movements, such as eye closure when the mouth is moved (synkinesis) or 'crocodile tears' (tearing during salivation). Unlike Bell's palsy, lesions with an upper motor neuron origin may spare the upper face. Cortical lesions may cause a facial weakness either in isolation or with associated hemiparesis and speech difficulties. Sensory disturbance Sensory symptoms are common and frequently benign. Patients often find sensory symptoms difficult to describe and sensory examination is difficult for both doctor and patient. While neurological disease can cause sensory symptoms, systemic disorders can also be responsible. Tingling in both hands and around the mouth can occur as the result of hyperventilation (p. 558) or hypocalcaemia (p. 662). When there is dysfunction of the relevant cerebral cortex, the patient's perception of the wholeness or actual presence of the relevant part of the body may be distorted. Numbness and paraesthesia The history may give the best clues to localisation and pathology. Certain common patterns are recognised: in migraine, the aura may consist of spreading tingling or paraesthesia, followed by numbness evolving over 20–30 minutes over one half of the body, often splitting the tongue. Sensory loss caused by a stroke or transient ischaemic attack (TIA) occurs much more rapidly and is typically negative (numbness) rather than positive (tingling). Rarely, unpleasant paraesthesia of sensory epilepsy spreads within seconds. The sensory alteration of inflammatory spinal cord lesions often ascends from one or both lower limbs to a distinct level on the trunk over hours to days. Psychogenic sensory change can occur as a manifestation of anxiety or as part of a conversion disorder (p. 1202). In such cases, the distribution usually neither conforms to a known anatomical pattern nor fits with any organic disease. Care must be taken in diagnosing non-organic sensory problems; a careful history and examination will ensure there is no other objective neurological deficit.

1084 • NEUROLOGY nociceptive pain, which is secondary to pathological processes such as inflammation. Neuropathic pain has distinctive features and typically provokes a very unpleasant, persistent, burning sensation. There is often increased sensitivity to touch, so that light brushing of the affected area causes exquisite pain (allodynia). Painful stimuli are felt as though they arise from a larger area than that touched, and spontaneous bursts of pain may also occur. Pain may be elicited by other modalities (allodynia) and is considerably affected by emotional influences. The most common causes of neuropathic pain are diabetic neuropathies, trigeminal and post-herpetic neuralgias, and trauma to a peripheral nerve. Treatment of these syndromes can be difficult. Drugs

that modulate various parts of the nociceptive system, such as gabapentin, carbamazepine or tricyclic antidepressants, may help. Localised treatment (topical treatment or nerve blocks) sometimes succeeds but may increase the sensory deficit and worsen the situation. Electrical stimulation has occasionally proved successful. For further information, see page 1347.

Abnormal movements Disorders of movement lead to either extra, unwanted movement (hyperkinetic disorders) or too little movement (hypokinetic disorders) (Box 25.15). In either case, the lesion often localises to the basal ganglia, although some tremors are related to cerebellar or brainstem disturbance. Functional movement disorders are common and may mimic all of the organic syndromes below. The most important hypokinetic disorder is Parkinson's disease (p. 1112). Parkinsonism is a clinical description of a collection of symptoms, including tremor, bradykinesia and rigidity. While the history is always important, observation is clearly vital; much ipsilateral facial sensory disturbance. For example, pain resembling trigeminal neuralgia can be seen in patients with multiple sclerosis. The anatomy of the trigeminal connections means that lesions in the medulla or spinal cord can give rise to 'balaclava' patterns of sensory loss (p. 1070). Sensory pathways running up from the spinal cord can also be damaged in the brainstem, resulting in simultaneous sensory loss in arm(s) and/or leg(s). Sensory loss in hemispheric lesions The temporal, parietal and occipital lobes receive sensory information regarding the various modalities of touch, vision, hearing and balance (see Box 25.2, p. 1066). The initial points of entry into the cortex are the respective primary cortical areas (see Fig. 25.4, p. 1067). Damage to any of these primary areas will result in reduction or loss of the ability to perceive that particular modality: 'negative' symptomatology. Abnormal excitation of these areas can result in a false perception ('positive' symptoms), the most common of which is migrainous visual aura (flashing lights or teichopsia). Cortical lesions are more likely to cause a mixed motor and sensory loss. Substantial lesions of the parietal cortex (as in large strokes) can cause severe loss of proprioception and may even abolish conscious awareness of the existence of the affected limb(s), known as neglect; this can be difficult to distinguish from paralysis. Pathways are so tightly packed in the thalamus that even small lacunar strokes can cause isolated contralateral hemisensory loss.

Neuropathic pain Neuropathic pain is a positive neurological symptom caused by dysfunction of the pain perception apparatus, in contrast to Fig. 25.18 Patterns of sensory loss.

A Generalised peripheral neuropathy.
B Sensory roots: some common examples.
C Single dorsal column lesion (proprioception and some touch loss).
D Transverse thoracic spinal cord lesion.
E Unilateral cord lesion (Brown-Séquard): ipsilateral dorsal column (and motor) deficit and contralateral spinothalamic deficit.
F Central cord lesion: 'cape' distribution of spinothalamic loss.
G Mid-brainstem lesion: ipsilateral facial sensory loss and contralateral loss on body below the vertex.
H Hemisphere (thalamic) lesion: contralateral loss on one side of face and body.

C5 C7 L5 A B C D E F G H Unilateral cord lesion (Brown-Séquard) Central cord lesion Mid-brainstem lesion Hemisphere (thalamic) lesion Transverse thoracic spinal cord lesion Single dorsal column lesion Sensory roots Generalised peripheral neuropathy

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part affected. In the assessment of tremor, the position, body part affected, frequency and amplitude should be considered, as these provide diagnostic clues (Box 25.16). Other hyperkinetic syndromes Non-rhythmic involuntary movements include chorea, athetosis, ballism, dystonia, myoclonus and tics. They are categorised by clinical appearance, and coexistence and overlap are common, such as in choreoathetosis. Chorea Chorea refers to jerky, brief, purposeless involuntary movements, appearing fidgety and affecting different areas. They suggest disease in the caudate

nucleus (as in Huntington's disease, p. 1114) and are a common complication of levodopa treatment for Parkinson's disease. Other causes are shown in Box 25.17.

25.15 Movement disorders

Description	Features	Examples
Hypokinetic disorders	Parkinsonism	Akinesia Rigidity
Tremor	Loss of postural reflexes	Other features depending on cause
Idiopathic Parkinson's disease	Other degenerative syndromes	Drug-induced (See Box 25.54)
Catatonia	Mutism	Sustained posturing and waxy flexibility
Usually psychiatric; if neurological, is most commonly of vascular origin	Hyperkinetic disorders	Tremor
Rhythmical oscillation of body part (see Box 25.16)	Essential tremor	Parkinson's disease
Drug-induced	Chorea	Jerky, brief, involuntary movements
Huntington's disease	Drug-induced	Tics
Stereotyped, repetitive movements, briefly suppressible	Tourette's syndrome	Myoclonus
Shock-like muscle jerks	Epilepsy	Hypnic jerks (p. 1086)
Focal cortical disease	Dystonia	Sustained muscle contraction causing abnormal postures $\pm$ tremor
Genetic	Generalised dystonic syndromes	Focal dystonias in adults (e.g. torticollis)
Others	Various	Paroxysmal hyperkinetic dyskinesias
Hemifacial spasm	Tardive syndromes	

25.16 Causes and characteristics of tremors

Body part affected	Position	Frequency	Amplitude	Character	Physiological
Both arms > legs	Posture, movement	High	Small (fine)	Enhanced by anxiety, emotion, drugs, toxins	Parkinsonism
Unilateral or asymmetrical	Arm > leg, chin, never head	Rest	Postural and re-emergent may occur	Low (3–4 Hz)	Moderate
Typically pill-rolling, thumb and index finger, other features of parkinsonism	Essential tremor	Bilateral arms, head	Movement	High (8–10 Hz)	Low to moderate
Family history; 50% respond to alcohol	Dystonic	Head, arms, legs	Posture	Variable	Variable
Other features of dystonia, often jerky tremors	Functional	Any	Any	Variable	Variable

Distractible of the skill in diagnosing movement disorders lies in pattern recognition. Once it is established whether the problem is hypo- or hyperkinetic, the next task is to categorise the movements further, accepting that there is often overlap. Videoing the movements (with the patient's consent), so that they can be shown to a movement disorder expert, may provide a quick diagnosis in cases of uncertainty.

Tremor Tremor is caused by alternating agonist/antagonist muscle contractions and produces a rhythmical oscillation of the body

25.17 Causes of chorea

- Hereditary • Huntington's disease (HD) and HD-like syndromes • Wilson's disease • Neuroacanthocytosis • Dentato-rubro-pallidoluysian atrophy • Benign hereditary chorea • Paroxysmal dyskinesias
- Cerebral birth injury (including kernicterus) Cerebral trauma
- Drugs • Levodopa (long-term with Parkinson's disease) • Antipsychotics • Antiepileptics • Oral contraceptive
- Metabolic • Disorders affecting thyroid, parathyroid, glucose, sodium, calcium and magnesium balance • Pregnancy
- Autoimmune • Post-streptococcal (Sydenham's chorea) • Antiphospholipid antibody syndrome • Autoimmune encephalitis • Systemic lupus erythematosus
- Structural lesions of basal ganglia (usually caudate) • Vascular • Demyelination • Brain tumour

1086 • NEUROLOGY effects of gravity and alterations in body position and load (and hence centre of gravity) in order to prevent a person from falling. This requires input from a variety of sensory modalities (visual, vestibular and proprioceptive), processing by the cerebellum and brainstem, and output via a number of descending pathways (e.g. vestibulospinal, rubrospinal and reticulospinal tracts). Disorders of balance can therefore arise from any part of this process. Disordered input (loss of vision, vestibular disorders or lack of joint position sense), processing (damage to vestibular nuclei or cerebellum) or motor function (spinal cord lesions, leg weakness of any cause) can all impair balance. The patient may complain of different symptoms, depending on the location of the lesion. For example, loss of joint position sense or cerebellar function may result in a sensation of unsteadiness, while damage to the vestibular nuclei or labyrinth may result in an illusion of movement, such as vertigo (see below). A careful history is vital. Since vision can often

compensate for lack of joint position sense, patients with peripheral neuropathies or dorsal column loss will often find their problem more noticeable in the dark. Examination of such patients may yield physical signs that again depend on the site of the lesion. Sensory abnormalities may be manifest as altered visual acuities or visual fields, possibly with abnormalities on fundoscopy, altered eye movements (including nystagmus, p. 1090), impaired vestibular function (p. 1104) or lack of joint position sense. Disturbance of cerebellar function may be manifest as nystagmus, dysarthria or ataxia, or difficulty with gait (unsteadiness or inability to perform tandem gait; see below). Leg weakness, if present, will be detectable on examination of the limbs. Vertigo Vertigo is defined as an abnormal perception of movement of the environment or self, and occurs because of conflicting visual, proprioceptive and vestibular information about a person's position in space. Vertigo commonly arises from imbalance of vestibular input and is within the experience of most people, since this is the 'dizziness' that occurs after someone has spun round vigorously and then stops. Bilateral labyrinthine dysfunction often causes some unsteadiness. Labyrinthine vertigo usually lasts days at a time, though it may recur, while vertigo arising from central (brainstem) disorders is often persistent and accompanied by other brainstem signs. Benign paroxysmal positional vertigo (p. 1104) lasts a few seconds on head movement. A careful history will reveal the likely cause in most patients. Abnormal gait Many neurological disorders can affect gait. Observing patients as they walk into the consulting room can be very informative, although formal examination is also important. Neurogenic gait disorders need to be distinguished from those due to skeletal abnormalities, usually characterised by pain producing an antalgic gait, or limp. Gait alteration incompatible with any anatomical or physiological deficit may be due to functional disorders. Pyramidal gait Upper motor neuron lesions cause characteristic extension of the affected leg. The resultant tendency for the toes to strike the ground on walking requires the leg to swing outwards at the hip (circumduction). Nevertheless, a shoe on the affected side worn down at the toes may provide evidence of this type of Athetosis Slower, writhing movement of the limbs are often combined with chorea and have similar causes. Ballism This more dramatic form of chorea causes often violent flinging movements of one limb (monoballism) or one side of the body (hemiballism). The lesion localises to the contralateral subthalamic nucleus and the most common cause is stroke. Dystonia Sustained involuntary muscle contraction causes abnormal postures or movement. It may be generalised (usually in childhood onset genetic syndromes) or, more commonly, focal/segmental (such as in torticollis, when the head is twisted repeatedly to one side). Some dystonias occur only with specific tasks, such as writer's cramp or other occupational 'cramps'. Dystonic tremor is associated, and is asymmetrical and of large amplitude. Myoclonus Myoclonus consists of brief, isolated, random jerks of muscle groups. This is physiological at the onset of sleep (hypnic jerks). Similarly, a myoclonic jerk is a component of the normal startle response, which may be exaggerated in some rare (mostly genetic) disorders. Myoclonus may occur in disorders of the cerebral cortex, such as some forms of epilepsy. Alternatively, myoclonus can arise from subcortical structures or, more rarely, from segments of the spinal cord. Tics Tics are stereotyped repetitive movements, such as blinking, winking, head shaking or shoulder shrugging. Unlike dyskinesias, the patient may be able to suppress them, although only for a short time. Isolated tics are common in childhood and usually disappear. Tourette's syndrome is defined by the presence of multiple motor and vocal tics that may evolve over time; it is frequently associated with psychiatric disease, including obsessive compulsions, depression, self-harm or attention deficit disorder. Tics may also occur in Huntington's and Wilson's diseases, or after streptococcal infection. Abnormal perception The parietal lobes are involved in the higher processing and integration of primary sensory information. This takes place in areas referred to as

'association' cortex, damage to which gives rise to sensory (including visual) inattention, disorders of spatial perception, and disruption of spatially orientated behaviour, leading to apraxia. Apraxia is the inability to perform complex, organised activity in the presence of normal basic motor, sensory and cerebellar function (after weakness, numbness and ataxia have been excluded as causes). Examples of complex motor activities include dressing, using cutlery and geographical orientation. Other abnormalities that can result from damage to the association cortex involve difficulty reading (dyslexia) or writing (dysgraphia), or the inability to recognise familiar objects (agnosia). The results of damage to particular lobes of the brain are given in Box 25.2 (p. 1066). Altered balance and vertigo Balance is a complicated dynamic process that requires ongoing modification of both axial and limb muscles to compensate for the

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Marche à petits pas This gait is characterised by small, slow steps and marked instability. It differs from the festination found in Parkinson's disease (see below), in that it lacks increasing pace and freezing. The usual cause is small-vessel cerebrovascular disease and there may be accompanying bilateral upper motor neuron signs. **Extrapyramidal gait** The rigidity and bradykinesia of basal ganglia dysfunction (p. 1112) lead to a stooped posture and characteristic gait difficulties, with problems initiating walking and controlling the pace of the gait. Patients may become stuck while trying to start walking or when walking through doorways ('freezing'). The centre of gravity will be moved forwards to aid propulsion, which, with poor axial control, can lead to an accelerating pace of shuffling and difficulty stopping. This produces the festinant gait: initial stuttering steps that quickly increase in frequency while decreasing in length. **Abnormal speech and language** Speech disturbance may be isolated to disruption of sound output (dysarthria) or may involve language disturbance (dysphasia). Dysphonia (reduction in the sound/volume) is usually due to mechanical laryngeal disruption, whereas dysarthria is more typically neurological in origin. Dysphasia is always neurological and localises to the dominant cerebral hemisphere (usually left, regardless of handedness). Combinations of speech and swallowing problems are explained below (p. 1093). **Dysphonia** Dysphonia describes hoarse or whispered speech. The most common cause is laryngitis, but dysphonia can also result from a lesion of the 10th cranial nerve or disease of the vocal cords, including laryngeal dystonia. Parkinsonism may cause hypophonia with marked reduction in speech volume, often in association with dysarthria, making speech difficult to understand. **Dysarthria** Dysarthria is characterised by poorly articulated or slurred speech and can occur in association with lesions of the cerebellum, brainstem and lower cranial nerves, as well as in myasthenia or myopathic disease. Language function is not affected. The quality of the speech tends to differ, depending on the cause, but gait. In hemiplegia, the asymmetry between affected and normal sides is obvious on walking, but in paraparesis both lower limbs swing slowly from the hips in extension and are dragged stiffly over the ground – described as 'walking in mud'. **Foot drop** In normal walking, the heel is the first part of the foot to hit the ground. A lower motor neuron lesion affecting the leg will cause weakness of ankle dorsiflexion, resulting in a less controlled descent of the foot, which makes a slapping noise as it hits the ground. In severe cases, the foot will have to be lifted higher at the knee to allow room for the inadequately dorsiflexed foot to swing through, resulting in a high-stepping gait. **Myopathic gait** During walking, alternating transfer of the body's weight through each leg requires adequate hip abduction. In proximal muscle weakness, usually caused by muscle disease, the hips are not properly fixed by these muscles and trunk movements are exaggerated, producing a rolling or waddling gait. **Ataxic gait** An ataxic gait can result from

lesions in the cerebellum, vestibular apparatus or peripheral nerves. Patients with lesions of the central portion of the cerebellum (the vermis) walk with a characteristic broad-based gait 'as if drunk' (cerebellar function is particularly sensitive to alcohol). Patients with acute vestibular disturbances walk similarly but the accompanying vertigo is characteristic. Inability to walk heel to toe may be the only sign of less severe cerebellar dysfunction. Proprioceptive defects can also cause an ataxic gait. The impairment of joint position sense makes walking unreliable, especially in poor light. The feet tend to be placed on the ground with greater emphasis, presumably to enhance proprioceptive input, resulting in a 'stamping' gait. Apraxic gait In an apraxic gait, power, cerebellar function and proprioception are normal on examination of the legs. The patient may be able to carry out complex motor tasks (e.g. bicycling motion) while recumbent and yet cannot formulate the motor act of walking. In this higher cerebral dysfunction, the feet appear stuck to the floor and the patient cannot walk. Gait apraxia is a sign of diffuse bilateral hemisphere disease (such as normal pressure hydrocephalus) or diffuse frontal lobe disease.

25.18 Causes of dysarthria

Type	Site	Characteristics	Associated features
Myopathic	Muscles of speech	Indistinct, poor articulation	Weakness of face, tongue and neck
Myasthenic	Motor end plate	Indistinct with fatigue and dysphonia	Fluctuating severity
Ptosis, diplopia, facial and neck weakness	Bulbar	Brainstem	Indistinct, slurred, often nasal
Dysphagia, diplopia, ataxia 'Scanning'	Cerebellum	Slurred, impaired timing and cadence, 'sing-song'	Ataxia of limbs and gait, tremor of head/limbs
Nystagmus	Spastic ('pseudo-bulbar')	Pyramidal tracts	Indistinct, nasal tone, mumbling
Poor rapid tongue movements, increased reflexes and jaw jerk	Parkinsonian	Basal ganglia	Indistinct, rapid, stammering, quiet
Tremor, rigidity, slow shuffling gait	Dystonic	Basal ganglia	Strained, slow, high-pitched
Dystonia, athetosis			

1088 • NEUROLOGY Disturbance of smell Symptomatic olfactory loss is most commonly due to local causes (nasal obstruction) but may follow head injury. Hyposmia may predate motor symptoms in Parkinson's disease by many years, although it is rarely noticed by the patient. Frontal lobe lesions are a rare cause. Positive olfactory symptoms may arise in Alzheimer's disease or epilepsy. Visual disturbance and ocular abnormalities Disturbances of vision may be due to primary ocular disease or to disorders of the central connections and visual cortex. Visual symptoms are usually negative (loss of vision) but sometimes positive, most commonly in migraine. Eye movements may be disturbed, giving rise to double vision (diplopia) or blurred vision. Loss of vision is also discussed on page 1170. Visual loss Visual loss can occur as the result of lesions in any areas between the retina and the visual cortex. Patterns of visual field loss are explained by the anatomy of the visual pathways (see Fig. 25.7, p. 1069). Associated clinical manifestations are described in Box 25.19. Visual symptoms affecting one eye only are due to lesions anterior to the optic chiasm. Transient visual loss is quite common and sudden-onset visual loss lasting less than 15 minutes is likely to have a vascular origin. It may be difficult to know whether the visual loss was monocular (carotid circulation) or binocular (vertebrobasilar circulation), and it is important to ask if the patient tried closing each eye in turn to see whether the symptom affected one eye or both. Visual field testing is an important part of the examination, either at the bedside or formally with perimetry. Field defects become more symmetrical (congruous), the closer the lesion comes to the visual cortex. Migrainous visual symptoms are very common and, when associated with typical headache and other migraine features, rarely pose a diagnostic challenge. They may occur in isolation, however, making distinction from TIA difficult, but TIAs typically cause negative (blindness) symptoms, whereas migraine causes positive phenomena (see below). TIAs often last for a shorter time (a few minutes), compared to the 10-60-

minute duration of migraine aura, and have an abrupt onset and end, unlike the gradual evolution of a migraine aura. Positive visual phenomena The most common cause is migraine; patients may describe silvery zigzag lines (fortification spectra) or flashing coloured lights (teichopsia), usually preceding the headache. Simple flashes of light (phosphenes) may indicate damage to the retina (e.g. detachment) or to the primary visual cortex. Formed visual hallucinations may be caused by drugs or may be due to epilepsy or 'release phenomena' in a blind visual field (Charles Bonnet syndrome). Double vision Diplopia arises from misalignment of the eyes, meaning that the image is not projected to the same points on the two retinas. At its most subtle it may be reported as blurred rather than it can be very difficult to distinguish the different types clinically (Box 25.18). Dysarthria is discussed further in the section on bulbar symptoms (p. 1093). Dysphasia Dysphasia (or aphasia) is a disorder of the language content of speech. It can occur with lesions over a wide area of the dominant hemisphere (Fig. 25.19). Dysphasia may be categorised according to whether the speech output is fluent or non-fluent. Fluent aphasias, also called receptive aphasias, are impairments related mostly to the input or reception of language, with difficulties either in auditory verbal comprehension or in the repetition of words, phrases or sentences spoken by others. Speech is easy and fluent but there are difficulties related to the output of language as well, such as paraphasia (either substitution of similar-sounding non-words, or incorrect words) and neologisms (non-existent words). Examples include Wernicke's aphasia (which localises to the superior posterior temporal lobe), transcortical sensory aphasia, conduction aphasia and anomic aphasia. Non-fluent aphasias, also called expressive aphasias, are difficulties in articulating, but in most cases there is relatively good auditory verbal comprehension. Examples include Broca's aphasia (associated with pathologies in the inferior frontal region), transcortical motor aphasia and global aphasia. 'Pure' aphasias are selective impairments in reading, writing or the recognition of words. These disorders may be quite selective. For example, a person is able to read but not write, or is able to write but not read. Examples include pure alexia, agraphia and pure word deafness. Dysphasia (a focal symptom) is frequently misinterpreted as disorientation (which is non-focal) and it is important always to consider dysphasia as an alternative explanation for the apparently 'confused' patient. Dysphasia can be misheard/ misspelt as dysphagia, and for this reason some prefer to use 'aphasia' to avoid confusion. Fig. 25.19 Classification of cortical speech problems. (1) Wernicke's aphasia: fluent dysphasia with poor comprehension and poor repetition. (2) Conduction aphasia: fluent aphasia with good comprehension and poor repetition. (3) Broca's aphasia: non-fluent aphasia with good comprehension and poor repetition. (4) Transcortical sensory aphasia: fluent aphasia with poor comprehension and good repetition. (5) Transcortical motor aphasia: non-fluent aphasia with good comprehension and good repetition. Large lesions affecting all of regions 1-5 cause global aphasia.

Sylvian fissure Central sulcus

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gaze, whether the images are separated horizontally or vertically, and whether there are any associated symptoms or signs, such as ptosis or pupillary disturbance. Binocular diplopia may result from central disorders or from disturbance of the ocular motor nerves, muscles or the double vision. Monocular diplopia indicates ocular disease, while binocular diplopia suggests a neurological cause. Closing either eye in turn will abort binocular diplopia. Once the presence of binocular diplopia is confirmed, it should be established whether the diplopia is maximal in any particular

direction of 25.19 Clinical manifestations of visual field loss Site of lesion Common causes
 Complaint Visual field loss Associated physical signs Retina/optic disc Vascular disease (including
 vasculitis) Glaucoma Inflammation Partial/complete visual loss depending on site, involving one or
 both eyes Altitudinal field defect Arcuate scotoma Reduced acuity Visual distortion (macula)
 Abnormal retinal appearance Optic nerve Optic neuritis Sarcoidosis Tumour Leber's hereditary
 optic neuropathy Partial/complete loss of vision in one eye Often painful Central vision particularly
 affected Central or paracentral scotoma Monocular blindness Reduced acuity Reduced colour vision
 Relative afferent pupillary defect Optic atrophy (late) Optic chiasm Pituitary tumour
 Craniopharyngioma Sarcoidosis May be none Rarely, diplopia ('hemifield slide') Bitemporal
 hemianopia Pituitary function abnormalities Optic tract Tumour Inflammatory disease Disturbed
 vision to one side of midline Incongruous contralateral homonymous hemianopia Temporal lobe
 Stroke Tumour Inflammatory disease Disturbed vision to one side of midline Contralateral
 homonymous upper quadrantanopia Memory/language disorders Parietal lobe Stroke Tumour
 Inflammatory disease Disturbed vision to one side of midline Bumping into things Contralateral
 homonymous lower quadrantanopia Contralateral sensory disturbance Asymmetry of optokinetic
 nystagmus Occipital lobe Stroke Tumour Inflammatory disease Disturbed vision to one side of
 midline Difficulty reading Bumping into things Homonymous hemianopia (may be macula-sparing)
 Damage to other structures supplied by posterior cerebral circulation 25.20 Common causes of
 damage to cranial nerves 3, 4 and 6 Site Common pathology Nerve(s) involved Associated features
 Brainstem Infarction Haemorrhage Demyelination Intrinsic tumour 3 (mid-brain) 6 (ponto-medullary
 junction) Contralateral pyramidal signs Ipsilateral lower motor neuron facial palsy Other
 brainstem/cerebellar signs Intrameningeal Meningitis (infective/malignant) 3, 4 and/or 6
 Meningism, features of primary disease course Raised intracranial pressure

Papilloedema 3 (uncal herniation) Features of space-occupying lesion Aneurysms 3 (posterior
 communicating artery) 6 (basilar artery) Pain Features of subarachnoid haemorrhage Cerebello-
 pontine angle tumour

8, 7, 5 nerve lesions (order of likelihood) Ipsilateral cerebellar signs Trauma 3, 4 and/or 6 Other
 features of trauma Cavernous sinus Infection/thrombosis Carotid artery aneurysm
 Caroticocavernous fistula 3, 4 and/or 6 May be 5th nerve involvement also Pupil may be fixed, mid-
 position (Sympathetic plexus on carotid may also be affected) Superior orbital fissure Tumour (e.g.
 sphenoid wing meningioma) Granuloma 3, 4 and/or 6 May be proptosis, chemosis Orbit Vascular
 (e.g. diabetes, vasculitis) Infections Tumour Granuloma Trauma 3, 4 and/or 6 Pain Pupil often
 spared in vascular 3rd nerve palsy

1090 • NEUROLOGY contralateral side to cause the eyes to drift towards the side of the lesion. This
 elicits recurrent compensatory fast movements away from the side of the lesion, manifest as
 unidirectional horizontal nystagmus. Vertical and torsional components can be seen with damage
 to other parts of the vestibular apparatus. The nystagmus of peripheral labyrinthine lesions is
 accompanied by vertigo and usually by nausea, vomiting and unsteadiness, but as the CNS
 habituates, the nystagmus disappears (fatigues) quite quickly. Central vestibular nystagmus is
 more persistent. Nystagmus also occurs as a consequence of drug toxicity and nutritional
 deficiency (e.g. thiamin). The severity is variable, and it may or may not result in visual
 degradation, though it may be associated with a sensation of movement of the visual world
 (oscillopsia). Nystagmus may occur as a congenital phenomenon, in which case both phases are

equal and 'pendular', rather than having alternating fast and slow components. Ptosis Various disorders may cause drooping of the eyelids (ptosis) and these are listed in Box 25.21 and shown on Figure 25.21. Abnormal pupillary responses Abnormal pupillary responses may arise from lesions at several points between the retina and brainstem. Lesions of the oculomotor nerve, ciliary ganglion and sympathetic supply produce characteristic ipsilateral disorders of pupillary function. 'Afferent' defects result from damage to an optic nerve, impairing the direct response of a pupil to light, although leaving the consensual response from stimulation of the normal eye intact. Structural damage to the iris itself can also result in pupillary abnormalities. Causes are given in Box 25.22. An example is shown in Figure 25.22. Papilloedema There are several causes of swelling of the optic disc but the term 'papilloedema' is reserved for swelling secondary to raised intracranial pressure, when obstructed axoplasmic flow from retinal ganglion cells results in swollen nerve fibres, which in turn cause capillary and venous congestion, producing papilloedema.

neuromuscular junction (see Fig. 25.8, p. 1070). The pattern of double vision, along with any associated features, usually allows the clinician to infer which nerves/muscles are affected, while the mode of onset and other features (e.g. fatigability in myasthenia) provide further clues to the cause. The causes of ocular motor nerve palsies are listed in Box 25.20. Examination findings are illustrated in Figure 25.20. Nystagmus Nystagmus describes a repetitive to-and-fro movement of the eyes. In central lesions, the slow drifts are the primary abnormal movement, each followed by fast (corrective) phases. Nystagmus occurs because the control systems of the eyes are defective, causing them to drift off target; corrections then become necessary to return fixation to the object of interest, causing nystagmus. The direction of the fast phase is usually designated as the direction of the nystagmus because it is easier to see. Nystagmus may be horizontal, vertical or torsional, and usually involves both eyes synchronously. It may be a physiological phenomenon in response to sustained vestibular stimulation or movement of the visual world (optokinetic nystagmus). There are many causes of pathological nystagmus, the most common sites of lesions being the vestibular system, brainstem and cerebellum. The brainstem and the cerebellum are involved in maintaining eccentric positions of gaze. Lesions will therefore allow the eyes to drift back in towards primary position, producing nystagmus with fast component beats in the direction of gaze (gaze-evoked nystagmus). This is the most common type of 'central' nystagmus; it is most commonly bidirectional and not usually accompanied by vertigo. Other signs of brainstem dysfunction may be evident. Brainstem disease may also cause vertical nystagmus. Unilateral cerebellar lesions may result in gaze-evoked nystagmus when looking in the direction of the lesion, where the fast phases are directed towards the side of the lesion. Cerebellar hemisphere lesions also cause 'ocular dysmetria', an overshoot of target-directed, fast eye movements (saccades) resembling 'past-pointing' in limbs. In vestibular lesions, damage to one of the horizontal canals or its connections will allow the tonic output from the healthy Fig. 25.20 Examination findings in 3rd, 4th and 6th nerve palsy. Diplopia tends to be more obvious on lateral gaze compared to primary position. Cranial nerve palsy Right 3rd nerve palsy Unable to adduct right eye Squint worse Right eye turns down and out N.B. Pupil dilated; ptosis Right 4th nerve palsy (more evident on downgaze) Right eye elevates more as it moves medially Right eye turns slightly up No obvious squint Right 6th nerve palsy Able to adduct right eye No obvious squint Right eye turns medially Unable to abduct right eye Squint worse Direction of gaze Primary position Direction of gaze

The earliest sign is the cessation of venous pulsation seen at the disc, progression causing the disc margins to become red (hyperaemic). Disc margins become indistinct and haemorrhages may occur in the retina (Fig. 25.23). Lack of papilloedema never excludes raised intracranial pressure. Other causes of optic disc swelling are listed in Box 25.23. Some normal variations of disc appearance (e.g. optic nerve drusen, p. 1178) can mimic disc swelling. Optic disc swelling is also discussed on page 1171. Optic atrophy Loss of nerve fibres causes the optic disc to appear pale, as the choroid becomes visible (Fig. 25.24). A pale disc (optic 25.21 Common causes of ptosis Mechanism Causes Associated clinical features 3rd nerve palsy Isolated palsy (see Box 25.20) Central/supranuclear lesion Ptosis is usually complete Extraocular muscle palsy (eye 'down and out') Depending on site of lesion, other cranial nerve palsies (e.g. 4, 5 and 6) or contralateral upper motor neuron signs Sympathetic lesion (Horner's syndrome: see Fig. 25.22) Central (hypothalamus/brainstem) Peripheral (lung apex, carotid artery pathology) Idiopathic Ptosis is partial Lack of sweating on affected side Depending on site of lesion, brainstem signs, signs of apical lung/brachial plexus disease, or ipsilateral carotid artery stroke Myopathic Myasthenia gravis Dystrophia myotonica Extraocular muscle palsies Usually bilateral More widespread muscle weakness, with fatigability in myasthenia Progressive external ophthalmoplegia Other characteristic features of individual causes Other Functional ptosis Pseudo-ptosis (e.g. blepharospasm) Local orbital/lid disease Age-related levator dehiscence Resistance to eye opening Eyebrows depressed rather than raised May be local orbital abnormality Fig. 25.21 Differential diagnosis of unilateral ptosis. (CPEO = chronic progressive external ophthalmoplegia) Neurological causes of unilateral ptosis Smaller pupil Larger pupil Diplopia worse on upgaze Diplopia Diplopia Increasing accommodation ?3rd nerve paralysis 3rd nerve paralysis Normal pupil Normal pupil Horner's syndrome Check for dilated pupil and other signs of 3rd nerve paralysis Fatigable weakness Myasthenia excluded Consider myasthenia gravis Family history Consider mitochondrial disorder, e.g. CPEO Fig. 25.22 Right-sided Horner's syndrome due to paravertebral metastasis at T1. There is ipsilateral partial ptosis and a small pupil.

1092 • NEUROLOGY 25.22 Pupillary disorders Disorder Cause Ophthalmological features Associated features 3rd nerve palsy See Box 25.21 Dilated pupil (especially with external compression) Extraocular muscle palsy (eye is typically 'down and out') Complete ptosis Other features of 3rd nerve palsy (see Box 25.21) Horner's syndrome (see Fig. 25.22) Lesion to sympathetic supply Small pupil Partial ptosis Iris heterochromia (if congenital) Ipsilateral failure of sweating (anhidrosis) Holmes-Adie syndrome (tonic pupil) Lesion of ciliary ganglion (usually idiopathic) Dilated pupil Light-near dissociation (accommodate but do not react to light) Vermiform movement of iris during contraction Disturbance of accommodation Generalised areflexia Argyll Robertson pupil Dorsal mid-brain lesion (syphilis or diabetes) Small, irregular pupils Light-near dissociation Other features of tabes dorsalis (p. 1125) Local pupillary damage Trauma/inflammatory disease Irregular pupils, often with adhesions to lens (synechiae) Variable degree of reactivity Other features of trauma/underlying inflammatory disease (e.g. cataract, blindness etc.) Relative afferent pupillary defect (Marcus Gunn pupil) Damage to optic nerve Pupils symmetrical - swinging torch test reveals dilatation in abnormal eye Decreased visual acuity/colour vision Central scotoma Optic disc swelling or pallor Fig. 25.23 Mechanism of optic disc oedema (papilloedema). A Normal. B Disc oedema (e.g. due to cerebral tumour). C Fundus photograph of the left eye showing optic disc oedema with a small haemorrhage on the nasal side of the disc. (CSF = cerebrospinal fluid) C, Courtesy of Dr B. Cullen. Choroid Optic disc CSF Optic nerve Central retinal vein Meningeal sheath Retinal veins Choroid Increased CSF pressure Optic nerve Venous dilatation Swollen optic disc

Axonal transport block Swollen axons A B C 25.23 Common causes of optic disc swelling Raised intracranial pressure (papilloedema) • Cerebral mass lesion (tumour, abscess) • Obstructive hydrocephalus • Idiopathic intracranial hypertension Obstruction of ocular venous drainage • Central retinal vein occlusion • Cavernous sinus thrombosis Systemic disorders affecting retinal vessels • Hypertension • Vasculitis • Hypercapnia Optic nerve damage • Demyelination (optic neuritis/ papillitis) • Leber's hereditary optic neuropathy • Anterior ischaemic optic neuropathy • Toxins (e.g. methanol) • Infiltration of optic disc • Sarcoidosis • Glioma • Lymphoma Fig. 25.24 Fundus photograph of the left eye of a patient with familial optic atrophy. Note the marked pallor of the optic disc.

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will cause upper motor neuron bulbar paralysis, known as 'pseudobulbar palsy'. Here the tongue is small and contracted, and moves slowly; the jaw jerk is brisk, and there may be associated emotional variability. Causes of these are shown in Box 25.24. Bladder, bowel and sexual disturbance While isolated disturbances of bladder, bowel and sexual function are rarely the sole presenting features of neurological disease, they are common complications of many chronic disorders such as multiple sclerosis, stroke and dementia, and are frequently found post head injury. Abnormalities in these functions considerably reduce quality of life for patients. Incontinence and its management are discussed elsewhere (pp. 397, 835 and 1309). Bladder dysfunction The anatomy and physiology involved in controlling bladder functions are discussed on page 386 but it is worth emphasising the role of the pontine micturition centre, which is itself under higher control via inputs from the pre-frontal cortex, mid-brain and hypothalamus. In the absence of conscious control (e.g. in coma or dementia), distension of the bladder to near capacity evokes reflex detrusor contraction (analogous to the muscle stretch reflex), and reciprocal changes in sympathetic activation and relaxation of the distal sphincter result in coordinated bladder emptying. Damage to the lower motor neuron pathways (the pelvic and pudendal nerves) produces a flaccid bladder and sphincter with overflow incontinence, often accompanied by loss of pudendal sensation. Such damage may be due to disease of the conus medullaris or sacral nerve roots, either within the dura (as in inflammatory or carcinomatous meningitis) or as they pass through the sacrum (trauma or malignancy), or due to damage to the nerves themselves in the pelvis (infection, haematoma, trauma or malignancy). Damage to the pons or spinal cord results in an 'upper motor neuron' pattern of bladder dysfunction due to uncontrolled over-activity of the parasympathetic supply. The bladder is small and highly sensitive to being stretched. This results in frequency, urgency and urge incontinence. Loss of the coordinating control of the pontine micturition centre will also result in the phenomenon of detrusor-sphincter dyssynergia, in which detrusor contraction and sphincter relaxation are not coordinated; the spastic bladder will often try to empty against a closed sphincter. This manifests as both urgency and an inability to pass urine, which is distressing and painful. The resultant incomplete bladder emptying predisposes to urinary infection, and the prolonged high intravesical pressure may result in obstructive uropathy and renal failure; post-micturition bladder ultrasound may confirm incomplete bladder emptying. More severe lesions of the spinal cord, as in spinal cord compression or trauma, can result in painless urinary retention as bladder sensation, normally carried in the lateral spinothalamic tracts, will be disrupted. Damage to the frontal lobes gives rise to loss of awareness of bladder fullness and consequent incontinence. Coexisting cognitive impairment may result in inappropriate micturition. These features may be seen in hydrocephalus, frontal tumours, dementia and bifrontal subdural

haematomas. When a patient presents with bladder symptoms, it is important to localise the lesion on the basis of history and examination, remembering that most bladder problems are not neurological atrophy) follows optic nerve damage; causes include previous optic neuritis or ischaemic damage, long-standing papilloedema, optic nerve compression, trauma and degenerative conditions (e.g. Friedreich's ataxia, p. 1116). Hearing disturbance Each cochlear organ has bilateral cortical representation, so unilateral hearing loss is a result of peripheral organ damage. Bilateral hearing dysfunction is usual and is most commonly due to age-related degeneration or noise damage, although infection and drugs (particularly diuretics and aminoglycoside antibiotics) can be a primary cause. Prominent deafness may suggest a mitochondrial disorder (see Box 25.93, p. 1144). Bulbar symptoms – dysphagia and dysarthria Swallowing is a complex activity involving the coordinated action of lips, tongue, soft palate, pharynx and larynx, which are innervated by cranial nerves 7, 9, 10, 11 and 12. Structural causes of dysphagia are considered on page 778. Neurological mechanisms are vulnerable to damage at different points, resulting in dysphagia that is usually accompanied by dysarthria. Tempo is again crucial: acute onset of dysphagia may occur as a result of brainstem stroke or a rapidly developing neuropathy, such as Guillain-Barré syndrome or diphtheria. Intermittent fatigable muscle weakness (including dysphagia) would suggest myasthenia gravis. Dysphagia developing over weeks or months may be seen in motor neuron disease, basal meningitis and inflammatory brainstem disease. More slowly developing dysphagia suggests a myopathy or possibly a brainstem or skull-base tumour. Pathologies affecting lower cranial nerves (9, 10, 11 and 12) frequently manifest bilaterally, producing dysphagia and dysarthria. The term 'bulbar palsy' is used to describe lower motor neuron lesions, either within the medulla or outside the brainstem. The tongue may be wasted and fasciculating, and palatal movement is reduced. Upper motor neuron innervation of swallowing is bilateral, so persistent dysphagia is unusual with a unilateral upper motor lesion (the exception being in the acute stages of, for example, a hemispheric stroke). Widespread lesions above the medulla

25.24 Causes of pseudobulbar and bulbar palsy

Type	Genetic	Vascular	Degenerative	Motor neuron disease	Inflammatory/ infective	Multiple sclerosis	Cerebral vasculitis	Myasthenia	Guillain-Barré syndrome	Poliomyelitis	Lyme disease	Vasculitis	Neoplastic	High brainstem tumours	Brainstem glioma	Malignant meningitis	
	Kennedy's disease (X-linked bulbospinal neuronopathy)	Bilateral hemisphere (lacunar) infarction	Medullary infarction (see Box 25.3, p. 1072)	Motor neuron disease	Syringobulbia	Inflammatory/ infective	Multiple sclerosis (p. 1106)	Cerebral vasculitis	Myasthenia (p. 1140)	Guillain-Barré syndrome (p. 1140)	Poliomyelitis (p. 1123)	Lyme disease (p. 255)	Vasculitis	Neoplastic	High brainstem tumours	Brainstem glioma	Malignant meningitis

1094 • NEUROLOGY speech, motor planning and organisation. Those with orbitofrontal lesions of the frontal lobes, in contrast, become disinhibited, displaying grandiosity or irresponsible behaviour. Memory is substantially intact but frontal release signs may emerge, such as a grasp reflex, palmomental response or pout. Proximity to the olfactory bulb and tracts means that inferior frontal lobe tumours may be associated with anosmia. Disturbance to the cortical areas responsible for speech or memory can result in changes that may be interpreted as changes in personality. Sleep disturbance Disturbances of sleep are common and are not usually due to neurological disease. Patients may complain of insomnia (difficulty sleeping), excessive daytime sleepiness, disturbed behaviour during night-time sleep, parasomnia (sleep walking and talking, or night terrors) or disturbing subjective experiences during sleep and/or its onset (nightmares, hypnagogic hallucinations, sleep paralysis). A careful history (from bed partner as well as patient) usually allows specific causes of sleep disturbance to be identified and these are discussed in more detail on page 1105. Psychiatric disorders Psychiatric disorders are described in Chapter 28 but may

cause or result from neurological problems. Care is needed in their identification, as effective management will help the underlying neurological illness.

Functional symptoms Many patients presenting with neurological symptoms do not have a defined neurological disease and are best described as having functional symptoms (p. 1187). Some of these are psychogenic (or conversion) disorders. Such patients often have symptoms affecting multiple systems and an impressively long list of consultations and negative tests from other medical specialties when they present. Considering the possibility of a functional origin may save the patient some further anxiety and further investigation (which will be unnecessary, expensive, possibly invasive, and inconvenient), unless there are overt neurological signs. Clinical features and management are summarised in Box 25.25.

Rectal dysfunction The rectum has an excitatory cholinergic input from the parasympathetic sacral outflow, and inhibitory sympathetic supply similar to the bladder. Continence depends largely on skeletal muscle contraction in the puborectalis and pelvic floor muscles supplied by the pudendal nerves, as well as the internal and external anal sphincters. Damage to the autonomic components usually causes constipation (a common early symptom in Parkinson's disease) but diabetic neuropathy can be associated with diarrhoea. Lesions affecting the conus medullaris, the somatic S2–4 roots and the pudendal nerves may cause faecal incontinence.

Erectile failure and ejaculatory failure These related functions are under autonomic control via the pelvic nerves (parasympathetic, S2–4) and hypogastric nerves (sympathetic, L1–2). Descending influences from the cerebrum are important for erection but it can occur as a reflex phenomenon in response to genital stimulation. Erection is largely parasympathetic and may be impaired by a number of drugs, including anticholinergic, antihypertensive and antidepressant agents. Sympathetic activity is important for ejaculation and may be inhibited by α -adrenoceptor antagonists (α -blockers). For further information on erectile dysfunction, see page 440.

Personality change While this is often due to psychiatric illness, neurological conditions that alter the function of the frontal lobes can cause personality change and mood disorder (see Box 25.2, p. 1066). Personality change due to a frontal lobe disorder may occur as the result of structural damage due to stroke, trauma, tumour or hydrocephalus. The nature of any change may help localise the lesion. Patients with mesial frontal lesions become increasingly withdrawn, unresponsive and mute (abulic), often in association with urinary incontinence, gait apraxia and an increase in tone known as gegenhalten, in which the patient varies the resistance to movement in proportion to the force exerted by the examiner. Patients with lesions of the dorsolateral pre-frontal cortex develop a dysexecutive syndrome, which involves difficulties with

25.25 Neurogenic bladder: clinical features and treatment

Type	Site of lesion	Result	Treatment
Atonic (lower motor neuron)	Sacral segments of cord (conus medullaris)	Sacral roots and nerves	Loss of detrusor contraction
		Difficulty initiating micturition	Bladder distension with overflow
		Intermittent self-catheterisation	In-dwelling catheterisation
Hypertonic (upper motor neuron)	Pyramidal tract in spinal cord or brainstem		
		Urgency with urge incontinence	Bladder sphincter incoordination (dyssynergia)
		Incomplete bladder emptying	Anticholinergics: Solifenacin Tolterodine Imipramine
		Intermittent self-catheterisation	
Cortical	Post-central	Pre-central	Frontal
			Loss of awareness of bladder fullness
			Difficulty initiating micturition
			Inappropriate micturition
			Loss of social control
			Intermittent or in-dwelling catheterisation

Headache syndromes • 1095

round the head or pressure at the vertex. It is of constant character and generalised, but often radiates forwards from the occipital region. It may be episodic or persistent, although the severity

may vary, and there is no associated vomiting or photophobia. Tension-type headache is rarely disabling and patients appear well. The pain often progresses throughout the day. Tenderness may be present over the skull vault or in the occiput but is easily distinguished from the triggered pains of trigeminal neuralgia and the exquisite tenderness of temporal arteritis. Analgesics may be taken with chronic regularity, despite little effect, and may perpetuate the symptoms (see 'Medication overuse headache' below). Management Most benefit is derived from a careful assessment, followed by discussion of likely precipitants and reassurance that the prognosis is good. The concept of medication overuse headache needs careful explanation. An important therapeutic step is to allow patients to realise that their problem has been taken seriously and rigorously assessed. Physiotherapy (with muscle relaxation and stress management) may help and low-dose amitriptyline can provide benefit. Investigation is rarely required. The reassurance value of brain imaging needs careful assessment: the pick-up rate of structural abnormalities is exceedingly low, and significantly outweighed by the likelihood of identifying an incidental and irrelevant finding (e.g. an arachnoid cyst, Chiari I malformation or vascular abnormality). The value of such 'reassurance' is usually over-estimated by doctors and patients alike.

Migraine Migraine usually appears before middle age, or occasionally in later life; it affects about 20% of females and 6% of males at some point in life. Migraine is usually readily identifiable from the history, although unusual variants can cause uncertainty. Pathophysiology The cause of migraine is unknown but there is increasing evidence that the aura (see below) is due to dysfunction of ion channels causing a spreading front of cortical depolarisation (excitation) followed by hyperpolarisation (depression of activity). This process (the 'spreading depression of Leão') spreads over the cortex at a rate of about 3 mm/min, corresponding to the aura's symptomatic spread. The headache phase is associated with vasodilatation of extracranial vessels and may be relayed by hypothalamic activity. Activation of the trigeminovascular system is probably important. A genetic contribution is implied by the frequently positive family history, and similar phenomena occurring in disorders such as CADASIL (p. 1052) or mitochondrial disease (p. 1144). The female preponderance and the frequency of migraine attacks at certain points in the menstrual cycle also suggest hormonal influences. Oestrogen-containing oral contraception sometimes exacerbates migraine and increases the very small risk of stroke in patients who suffer from migraine with aura. Doctors and patients often over-estimate the role of dietary precipitants such as cheese, chocolate or red wine. When psychological factors contribute, the migraine attack often occurs after a period of stress, being more likely on Friday evening at the end of the working week or at the beginning of a holiday.

Clinical features Some patients report a prodrome of malaise, irritability or behavioural change for some hours or days. Around 20% of Weakness and sensory change predominate among patients with functional neurological disorders but pain or loss of consciousness can also occur. Associated symptoms, such as tiredness, lethargy, poor concentration, bowel upset (irritable bowel syndrome) and gynaecological complaints, are common. A functional cause should always be considered, as it can allow for more rapid diagnosis and minimise investigation. Some clinical features may hint at a functional origin for symptoms (Box 25.26). It is the clinician's (rewarding, albeit sometimes challenging) job to elicit the context of the patient's symptoms in a sensitive and non-judgemental manner. Whatever the cause of the illness, it is important to acknowledge that mood and sleep disturbance will exacerbate neurological symptoms, thus increasing disability. The best practitioners have the skill to carry the patient with them when describing the patterns of behaviour contributing to worsening symptoms. Assessment to detect an underlying or exacerbating mood disorder is vital in all patients, ensuring that depression and anxiety are managed to minimise their secondary effects on neurological symptoms. Headache syndromes

Acute management of headache is dealt with on page 184 but management of chronic, complex, or refractory headaches may require specialist input. Headaches may be classified as primary or secondary, depending on the underlying cause (see Box 10.10, p. 184). Secondary headache may be due to structural, infective, inflammatory or vascular conditions, discussed later in this chapter. Primary headache syndromes are described here. Tension-type headache This is the most common type of headache and is experienced to some degree by the majority of the population.

Pathophysiology Tension-type headache is incompletely understood, and some consider that it is simply a milder version of migraine; certainly, the original notion that it is due primarily to muscle tension (hence the unsatisfactory name) has long since been dismissed. Anxiety about the headache itself may lead to continuation of symptoms, and patients may become convinced of a serious underlying condition. Clinical features The pain of tension headache is characterised as 'dull', 'tight' or like a 'pressure', and there may be a sensation of a band 25.26 Clinical features suggestive of functional disorder • Inconsistent examination findings (e.g. Hoover's sign, p. 1082) • Situational provocation of events (e.g. in medical settings) • Associated mental health disorders: Anxiety Depression • Lack of anatomical coherence to neurological symptoms • Florid or bizarre descriptions of individual symptoms • History of multiple other systemic symptoms inadequately explained by disease (asthma/breathlessness, fatigue, pain, gastrointestinal symptoms)

1096 • NEUROLOGY Cluster headache Cluster headaches (also known as migrainous neuralgia) are much less common than migraine. Unusually for headache syndromes, there is a significant male predominance and onset is usually in the third decade. Pathophysiology The cause is unknown but this type of headache differs from migraine in many ways, suggesting a different pathophysiological basis. Although uncommon, it is the most common of the trigeminal autonomic cephalalgia syndromes. Functional imaging studies have suggested abnormal hypothalamic activity. Patients are more often smokers with a higher than average alcohol consumption. Clinical features Cluster headache is strikingly periodic, featuring runs of identical headaches beginning at the same time for weeks at a stretch (the 'cluster'). Patients may experience either one or several attacks within a 24-hour period, and typically are awoken from sleep by symptoms ('alarm clock headache'). Cluster headache causes severe, unilateral periorbital pain with autonomic features, such as ipsilateral tearing, nasal congestion and conjunctival injection (occasionally with the other features of a Horner's syndrome). The pain, though severe, is characteristically brief (30–90 minutes). In contrast to the behaviour of those with migraine, patients are highly agitated during the headache phase. The cluster period is typically a few weeks, followed by remission for months to years, but a small proportion do not experience remission. Management Acute attacks can usually be halted by subcutaneous injections of sumatriptan or inhalation of 100% oxygen. The brevity of the attack probably prevents other migraine therapies from being effective. Migraine prophylaxis is often ineffective too but attacks can be prevented in some patients by verapamil, sodium valproate, or short courses of oral glucocorticoids. Patients with severe debilitating clusters can be helped with lithium therapy, although this requires monitoring (p. 1200). Trigeminal neuralgia This is characterised by unilateral lancinating facial pain, most commonly involving the second and/or third divisions of the trigeminal nerve territory, usually in patients over the age of 50 years. Pathophysiology For most, trigeminal neuralgia remains an idiopathic condition but there is a suggestion that it may be due to an irritative lesion involving the trigeminal root zone, in some cases an aberrant loop of artery. Other compressive lesions, usually benign, are occasionally found. Trigeminal neuralgia associated with multiple sclerosis may result from a plaque of demyelination in the brainstem. Clinical features The pain is repetitive, severe and very brief (seconds or less). It

may be triggered by touch, a cold wind or eating. Physical signs are usually absent, although the spasms may make the patient wince and sit silently (*tic douloureux*). There is a tendency for the condition to remit and relapse over many years. Rarely, there patients experience an aura and are said to have migraine with aura (previously known as classical migraine). The aura may manifest as almost any neurological symptom but is most often visual, consisting of fortification spectra, which are usually positive phenomena such as shimmering, silvery zigzag lines marching across the visual fields for up to 40 minutes, sometimes leaving a trail of temporary visual field loss (scotoma). Sensory symptoms characteristically spreading over 20–30 minutes, from one part of the body to another, are more common than motor ones, and language function can be affected, leading to similarities with TIA/stroke. Isolated aura may occur (i.e. the neurological symptoms are not followed by headache). The 80% of patients with characteristic headache but no 'aura' are said to have migraine without aura (previously called 'common' migraine). Migraine headache is usually severe and throbbing, with photophobia, phonophobia and vomiting lasting from 4 to 72 hours. Movement makes the pain worse and patients prefer to lie in a quiet, dark room. In a small number of patients the aura may persist, leaving more permanent neurological disturbance. This persistent migrainous aura may occur with or without evidence of brain infarction. Management Avoidance of identified triggers or exacerbating factors (such as the combined contraceptive pill) may prevent attacks. Treatment of an acute attack consists of simple analgesia with aspirin, paracetamol or non-steroidal anti-inflammatory agents. Nausea may require an antiemetic such as metoclopramide or domperidone. Severe attacks can be aborted by one of the 'triptans' (e.g. sumatriptan), which are potent 5-hydroxytryptamine (5-HT, serotonin) agonists. These can be administered via the oral, subcutaneous or nasal route. Caution is needed with ergotamine preparations because they may lead to dependence. Overuse of any analgesia, including triptans, may contribute to medication overuse headache. If attacks are frequent (more than two per month), prophylaxis should be considered. Many drugs can be chosen but the most frequently used are vasoactive drugs (β -blockers), antidepressants (amitriptyline, dosulepin) and antiepileptic drugs (valproate, topiramate). Women with aura should avoid oestrogen treatment for either oral contraception or hormone replacement, although the increased risk of ischaemic stroke is minimal. Medication overuse headache With increasing availability of over-the-counter medication, headache syndromes perpetuated by analgesia intake are becoming much more common. Medication overuse headache (MOH) can complicate any headache syndrome but is especially common with migraine and chronic tension-type headache. The most frequent culprits are compound analgesics (particularly codeine and other opiate-containing preparations) and triptans, and MOH is usually associated with use on more than 10–15 days per month. Management is by withdrawal of the responsible analgesics. Patients should be warned that the initial effect will be to exacerbate the headache, and migraine prophylactics may be helpful in reducing the rebound headaches. Relapse rates are high, and patients often need help and support in withdrawing from analgesia; a careful explanation of this paradoxical concept is vital.

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Epilepsy A seizure can be defined as the occurrence of signs and/or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain. The lifetime risk of an isolated seizure is about 5%, although incidence is highest at the extremes of age. Epilepsy is the tendency to have unprovoked seizures. While the prevalence of active epilepsy in European countries is about 0.5%, the figure in developing countries may be higher because of parasitic illnesses such as

cysticercosis (p. 298). A recent change in definition allows the diagnosis of epilepsy to be made after a single seizure with a high risk of recurrence (e.g. a single seizure in the presence of a cortical lesion). Such changes may lead to an observed increase in epilepsy incidence. Historical terms such as 'grand mal' (implying tonic-clonic seizures) and 'petit mal' (intended originally to mean 'absence seizures' but commonly misused to describe 'anything other than grand mal') have been superseded. Subsequent revisions, including terms such as 'complex partial' and 'simple partial', have been imprecise and carry little information about underlying pathology, treatment or prognosis. The modern equivalents for these terms will be given below, but it is preferable to adhere to the 2010 iteration of the International League Against Epilepsy's classification (Box 25.28).

Pathophysiology To function normally, the brain must maintain a continual balance between excitation and inhibition, remaining responsive to the environment while avoiding continued unrestrained spontaneous activity. The inhibitory transmitter gamma-aminobutyric acid (GABA) is particularly important, acting on ion channels to enhance chloride inflow and reducing the chances of action potential formation. Excitatory amino acids (glutamate and aspartate) allow influx of sodium and calcium, producing the opposite effect. It is likely that many seizures result from an imbalance may be combined features of trigeminal neuralgia and cluster headache ('cluster-tic').

Management The pain often responds to carbamazepine. It is wise to start with a low dose and increase gradually, according to effect. In patients who cannot tolerate carbamazepine, oxcarbazepine, gabapentin, pregabalin, amitriptyline or glucocorticoids may be effective alternatives, but if medication is ineffective or poorly tolerated, surgical treatment should be considered. Decompression of the vascular loop encroaching on the trigeminal root is said to have a 90% success rate. Otherwise, localised injection of alcohol or phenol into a peripheral branch of the nerve may be effective.

Headaches associated with specific activities These usually affect men in their thirties and forties. Patients develop a sudden, severe headache with exertion, including sexual activity. There is usually no vomiting or neck stiffness, and the headache lasts less than 10–15 minutes, though a less severe dullness may persist for some hours. Subarachnoid haemorrhage needs to be excluded by CT and/or CSF examination (see Fig. 26.14, p. 1162) after a first event. The pathogenesis of these headaches is unknown. Although frightening, attacks are usually brief and patients may need only reassurance and simple analgesia for the residual headache. The syndrome may recur, and prevention may be necessary with propranolol or indometacin.

Other headache syndromes A number of rare headache syndromes produce pains about the eye similar to cluster headaches (Box 25.27). These include chronic paroxysmal hemicrania and SUNCT (short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing). The recognition of these syndromes is useful because they often respond to specific treatments such as indometacin.

25.27	Benign paroxysmal headaches	Type	Character of pain	Duration	Location	Comment
Ice pick	Stabbing	Very brief (split-second)	Variable, usually temporoparietal	Benign, more common in migraine	Ice cream	Sharp, severe 30–120 secs
Bitemporal/occipital	Obvious trigger by cold stimuli	Exertional/sexual activity	Bursting, thunderclap	Severe for mins, then less severe for hours	Generalised	Subarachnoid haemorrhage needs to be excluded
Cough	Bursting	Secs to mins	Occipital or generalised	Intracranial pathology needs to be excluded (especially craniocervical junction)	Cluster headache (migrainous neuralgia)	Severe unilateral, with ptosis, tearing, conjunctival injection, unilateral nasal congestion 30–90 mins 1–3 times per day
Periorbital	Usually in men, occurring in clusters over weeks/months	Chronic paroxysmal hemicrania	Severe unilateral with cluster headache-like autonomic features (see above)	5–20 mins, frequently through day	Periorbital/temporal	Usually in women, responds to indometacin
SUNCT*	Severe, sharp, triggered by touch or neck movements	15–120 secs, repetitive				

through day Periorbital May respond to carbamazepine *Short-lasting, unilateral, neuralgiform headache with conjunctival injection, tearing, rhinorrhoea and forehead sweating.

1098 • NEUROLOGY Clinical features Seizure type and epilepsy type Patients can experience more than one type of seizure attack, and it is important to document each attack type and the patient's age at its onset, along with its frequency, duration and typical features. Any triggers should be identified (Box 25.29). The type of seizure, other clinical features and investigations can then be used to determine the epilepsy syndrome, as discussed below. Where there is doubt about the type, this is best stated and a full classification should be deferred until the evolution of the clinical features clarifies the picture. To classify seizure type, the clinician should ask firstly whether there is a focal onset, and secondly whether the seizures conform to one of the recognised patterns (see Box 25.28). Epilepsy that starts in patients beyond their mid-thirties will almost invariably reflect a focal cerebral event. Where activity remains focal, the classification will be obvious. With generalised tonic-clonic seizures, a focal onset will be heralded by positive neurological symptoms and signs corresponding to the normal function of that area. Occipital onset causes visual changes (lights and blobs of colour), temporal lobe onset causes false recognition (*déjà vu*), sensory strip involvement causes sensory alteration (burning, tingling), and motor strip involvement causes jerking. Alternatively, patients report a previous local cortical insult, and it may be reasonably (but not invariably) inferred that this is the seat of epileptogenesis.

25.28 Classification of seizures (2010 International League Against Epilepsy classification)

Generalised seizures • Tonic-clonic (in any combination) • Absence: Typical Atypical Absence with special features • Myoclonic absence • Eyelid myoclonia • Myoclonic: Myoclonic Myoclonic-atonic Myoclonic-tonic • Clonic • Tonic • Atonic

Focal seizures • Without impairment of consciousness or awareness (was 'simple partial'): Focal motor Focal sensory • With impairment of consciousness or awareness (was 'complex partial') • Evolving to a bilateral, convulsive seizure (was 'secondarily generalised seizure'): Tonic Clonic Tonic-clonic Unknown • Epileptic spasms

Fig. 25.25 The pathophysiological classification of seizures. A A focal seizure originates from a paroxysmal discharge in a focal area of the cerebral cortex (often the temporal lobe); the seizure may subsequently spread to the rest of the brain (secondary generalisation) via diencephalic activating pathways. B In genetic generalised epilepsies (GGEs) the abnormal electrical discharges originate from the diencephalic activating system and spread simultaneously to all areas of the cortex.

A B Focal seizure ± secondary generalisation Primary generalised seizure

25.29 Trigger factors for seizures • Sleep deprivation • Missed doses of antiepileptic drugs in treated patients • Alcohol (particularly withdrawal) • Recreational drug misuse • Physical and mental exhaustion • Flickering lights, including TV and computer screens (generalised epilepsy syndromes only) • Intercurrent infections and metabolic disturbances • Uncommon: loud noises, music, reading, hot baths between this excitation and inhibition. Intracellular recordings during seizures demonstrate a paroxysmal depolarisation shift in neuronal membrane potential, an upshift in internal potential predisposing to recurrent action potentials. In vivo, epileptic cortex shows repetitive discharges involving large groups of neurons. Focal epilepsy Seizures may be related to a localised disturbance in the cortex, becoming manifest in the first instance as focal seizures. Any disturbance of cortical architecture and function can precipitate this, whether focal infection, tumour, hamartoma or trauma-related scarring. If focal seizures remain localised, the symptoms experienced depend on which cortical area is affected. If areas in the temporal lobes become involved, then awareness of the environment becomes impaired but without associated tonic-clonic movements. When both hemispheres become involved, the seizure becomes generalised (Fig. 25.25). Generalised epilepsies The new

terminology is genetic generalised epilepsies (GGEs) (previously idiopathic generalised epilepsies) to reflect their likely cause. These seizures are generalised at onset, abnormal activity probably originating in the central mechanisms controlling cortical activation (Fig. 25.25) and spreading rapidly. This group constitutes around 30% of all epilepsy and is likely to reflect widespread disturbance of structure or function. GGEs almost always become apparent before the age of 35. Seizure activity is usually apparent on EEG as spike and wave discharges (see Fig. 25.14, p. 1075). Other generalised seizures may involve merely brief loss of awareness (absence seizures), single jerks (myoclonus) or loss of tone (atonic seizures), as detailed in Box 25.28.

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originates (as above). The patient then becomes rigid (tonic) and unconscious, falling heavily if standing ('like a log') and risking facial injury. During this phase, breathing stops and central cyanosis may occur. As cortical discharges reduce in frequency, jerking (clonic) movements emerge for 2 minutes at most. Afterwards, there is a flaccid state of deep coma, which can persist for some minutes, and on regaining awareness the patient may be confused, disorientated and/or amnesic. During the attack, urinary incontinence and tongue-biting may occur. A severely bitten, bleeding tongue after an attack of loss of consciousness is pathognomonic of a generalised seizure but less marked lingual injury can occur in syncope. Subsequently, the patient usually feels unwell and sleepy, with headache and myalgia. Witnesses are usually frightened by the event, often believe the person to be dying, and may struggle to give a clear account of the episode. Some may not describe the tonic or clonic phase and may not mention cyanosis or tongue-biting. In less typical episodes, post-ictal delirium, or sequelae such as headache or myalgia, may be the main pointers to the diagnosis. Causes of generalised tonic-clonic seizures are listed in Box 25.31.

Absence seizures Absence seizures (previously 'petit mal') always start in childhood. The attacks are rarely mistaken for focal seizures because of their brevity. They can occur so frequently (20–30 times a day) that they are mistaken for daydreaming or poor concentration in school.

Myoclonic seizures These are typically brief, jerking movements, predominating in the arms. In epilepsy, they are more marked.

Focal seizures The classification of focal seizures is shown in Box 25.28. They are caused by localised cortical activity with retained awareness. The localisation of such symptoms is described above. A spreading pattern of seizure may occur, the abnormal sensation spreading much faster (in seconds) than a migrainous focal sensory attack. Awareness may become impaired if spread occurs to the temporal lobes (previously 'complex partial seizure'). Patients stop and stare blankly, often blinking repetitively, making smacking movements of their lips or displaying other automatisms, such as picking at their clothes. After a few minutes consciousness returns but the patient may be muddled and feel drowsy for a period of up to an hour. The age of onset, preceding aura, longer duration and post-ictal symptoms usually make these easy to differentiate from childhood absence seizures (see below). Seizures arising from the anterior parts of the frontal lobe may produce bizarre behaviour patterns, including limb posturing, sleep walking or even frenetic, ill-directed motor activity with incoherent screaming. Video EEG may be necessary to differentiate these from psychogenic attacks (which are more common) but abruptness of onset, stereotyped nature, relative brevity and nocturnal preponderance may indicate a frontal origin. Causes of focal seizures are given in Box 25.30.

Generalised seizures

Tonic-clonic seizures An initial 'aura' may be experienced by the patient, depending on the cortical area from which the seizure

25.30 Causes of focal seizures

Idiopathic • Benign Rolandic epilepsy of childhood • Benign occipital epilepsy of childhood

Focal structural lesions

Genetic • Tuberous sclerosis (p. 1264) •

Autosomal dominant nocturnal frontal lobe epilepsy • Autosomal dominant partial epilepsy with auditory features (ADPEAF) • von Hippel–Lindau disease (p. 1132) • Neurofibromatosis (p. 1131) • Cerebral migration abnormalities Infantile hemiplegia Dysembryonic • Cortical dysgenesis • Sturge–Weber syndrome Mesial temporal sclerosis (associated with febrile convulsions) Cerebrovascular disease (Ch. 26) • Intracerebral haemorrhage • Cerebral infarction • Arteriovenous malformation • Cavernous haemangioma Tumours (primary and secondary) (p. 1129) Trauma (including neurosurgery) Infective (p. 1117) • Cerebral abscess (pyogenic) • Toxoplasmosis • Cysticercosis • Tuberculoma • Subdural empyema • Encephalitis • Human immunodeficiency virus (HIV) Inflammatory • Autoimmune encephalopathies (e.g. anti-voltage-gated potassium channel antibodies, anti-NMDA receptor antibodies, anti-glycine receptor antibodies) • Sarcoidosis • Vasculitis 25.31 Causes of generalised tonic-clonic seizures Generalisation from focal seizures • See Box 25.30 Genetic • Inborn errors of metabolism (p. 1144) • Storage diseases • Phakomatoses (e.g. tuberous sclerosis, p. 1264) Cerebral birth injury Hydrocephalus Cerebral anoxia Drugs • Antibiotics: penicillin, isoniazid, metronidazole • Antimalarials: chloroquine, mefloquine • Ciclosporin • Amphetamines (withdrawal) • Cardiac anti-arrhythmics: lidocaine, disopyramide • Psychotropic agents: phenothiazines, tricyclic antidepressants, lithium Alcohol (especially withdrawal) Toxins • Organophosphates (sarin) • Heavy metals (lead, tin) Metabolic disease • Hypocalcaemia • Hyponatraemia • Hypomagnesaemia • Hypoglycaemia • Renal failure • Liver failure Infective • Post-infectious encephalopathy • Meningitis (p. 1118) Inflammatory • Multiple sclerosis (uncommon; (p. 1106) • Systemic lupus erythematosus (p. 1034) Diffuse degenerative diseases • Alzheimer’s disease (uncommonly; p. 1992) • Creutzfeldt–Jakob disease (rarely; p. 1127)

1100 • NEUROLOGY to assess prognosis once a firm diagnosis has been made. The recurrence rate after a first seizure is approximately 40% and most recurrent attacks occur within a month or two of the first. Further seizures are less likely if an identified trigger can be avoided (see Box 25.29). Other investigations for infective, toxic and metabolic causes (Box 25.34) may be appropriate. An EEG performed immediately after a seizure may be more helpful in showing focal features than if performed after a delay. in the morning or on awakening from sleep, and tend to be provoked by fatigue, alcohol, or sleep deprivation. Atonic seizures These are seizures involving brief loss of muscle tone, usually resulting in heavy falls with or without loss of consciousness. They occur only in the context of epilepsy syndromes that involve other forms of seizure. Tonic seizures These are associated with a generalised increase in tone and an associated loss of awareness. They are usually seen as part of an epilepsy syndrome and are unlikely to be isolated. Clonic seizures Clonic seizures are similar to tonic-clonic seizures. The clinical manifestations are similar but there is no preceding tonic phase. Seizures of uncertain generalised or focal nature Epileptic spasms While these are highlighted in the classification system, they are unusual in adult practice and occur mainly in infancy. They signify widespread cortical disturbance and take the form of marked contractions of the axial musculature, lasting a fraction of a second but recurring in clusters of 5–50, often on awakening. Epilepsy syndromes Many patients with epilepsy fall into specific patterns, depending on seizure type(s), age of onset and treatment responsiveness: the so-called electroclinical syndromes (Box 25.32). It is anticipated that genetic testing will ultimately demonstrate similarities in molecular pathophysiology. Box 25.33 highlights the more common epilepsy syndromes, which are largely of early onset and are sensitive to sleep deprivation, hyperventilation, alcohol and photic stimulation. Epilepsies that do not fit into any of these diagnostic categories can be delineated firstly on the basis of the presence or absence of a known

structural or metabolic condition (presumed cause), and then on the basis of the primary mode of seizure onset (generalised versus focal). Investigations Single seizure All patients with transient loss of consciousness should have a 12-lead ECG. Where seizure is suspected or definite, patients should have cranial imaging with either MRI or CT, although the yield is low unless focal signs are present. EEG may help

25.32 Electroclinical epilepsy syndromes Adolescence to adulthood • Juvenile absence epilepsy (JAE) • Juvenile myoclonic epilepsy (JME) • Epilepsy with generalised tonic-clonic seizures alone • Progressive myoclonus epilepsies (PMEs) • Autosomal dominant epilepsy with auditory features (ADEAF) • Other familial temporal lobe epilepsies Less specific age relationship • Familial focal epilepsy with variable foci (childhood to adult) • Reflex epilepsies Distinctive constellations • Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS) • Rasmussen's syndrome • Gelastic (from the Greek word for laughter) seizures with hypothalamic hamartoma • Hemiconvulsion-hemiplegia-epilepsy Epilepsies with structural-metabolic causes • Malformations of cortical development (hemimegalencephaly, heterotopias etc.) • Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber etc.) • Tumour • Infection • Trauma • Angioma • Perinatal insults • Stroke etc. Epilepsies of unknown cause Conditions with epileptic seizures not needing long-term treatment • Benign neonatal seizures (BNS) • Febrile seizures (FS)

25.33 Common generalised epilepsy syndromes Syndrome Age of onset Type of seizure EEG features Treatment Prognosis Childhood absence epilepsy 4–8 years Frequent brief absences 3/sec spike and wave Ethosuximide Sodium valproate Levetiracetam 40% develop GTCS, 80% remit in adulthood Juvenile absence epilepsy 10–15 years Less frequent absences than childhood absence Poly-spike and wave Sodium valproate Levetiracetam 80% develop GTCS, 80% seizure-free in adulthood Juvenile myoclonic epilepsy 15–20 years GTCS, absences, morning myoclonus Poly-spike and wave, photosensitivity Sodium valproate Levetiracetam 90% remit with AEDs but relapse if AED withdrawn GTCS on awakening 10–25 years GTCS, sometimes myoclonus Spike and wave on waking and sleep onset Sodium valproate Levetiracetam 65% controlled with AEDs but relapse off treatment (AED = antiepileptic drug; GTCS = generalised tonic-clonic seizure)

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Immediate care Little can or needs to be done for a person during a convulsive seizure except for first aid and common-sense manœuvres to limit damage or secondary complications (see Box 25.36). Advice should be given that on no account should anything be inserted into the patient's mouth. The management of status epilepticus is described on page 1080. Lifestyle advice Patients should be advised to avoid activities where they might place themselves or others at risk if they have a seizure. This applies at work, at home and at leisure. At home, only shallow baths (or showers) should be taken. Prolonged cycle journeys should be discouraged until reasonable freedom from seizures has been achieved. Activities involving prolonged proximity to water (swimming, fishing or boating) should always be carried out in the company of someone who is aware of the risks and the potential need for rescue measures. Driving regulations vary between countries and the patient should be made aware of these (Box 25.38). Certain occupations, such as firefighter or airline pilot, are not open to those with a previous or active diagnosis of epilepsy; further information is available from epilepsy support organisations. The risk of harm from epilepsy should be discussed around the time of diagnosis. This should be done with care and sensitivity, and with the aim of motivating the patient to adapt habits and lifestyle to optimise epilepsy control and minimise risks of serious complications. Antiepileptic drugs Antiepileptic drugs (AEDs) should

be considered where risk of seizure recurrence is high. A diagnosis of two or more seizures is justification enough but a prolonged inter-seizure interval may deter some patients and physicians. Treatment decisions should always be shared with the patient, to enhance adherence. A wide range of drugs is available. These agents either increase inhibitory neurotransmission in the brain or alter neuronal sodium channels to prevent abnormally rapid transmission of impulses. In the majority of patients, full control is achieved with a single drug. Dose regimens should be kept as simple as possible. Guidelines Epilepsy The same investigations are required in a patient with epilepsy (Box 25.34). The EEG may help to establish the type of epilepsy and guide therapy. Investigations should be revisited if the epilepsy is intractable to treatment. Inter-ictal EEG is abnormal in only about 50% of patients with recurrent seizures, so it cannot be used to exclude epilepsy. The sensitivity can be increased to about 85% by prolonging recording time and including a period of natural or drug-induced sleep, but this does not replace a well-taken history. Ambulatory EEG recording or video EEG monitoring may help with differentiation of epilepsy from other disorders if attacks are sufficiently frequent. Indications for imaging are summarised in Box 25.35. Imaging cannot establish a diagnosis of epilepsy but identifies any structural cause. It is not required if a confident diagnosis of a recognised GGE syndrome (e.g. juvenile myoclonic epilepsy) is made. While CT excludes a major structural cause of epilepsy, MRI is required to demonstrate subtle changes such as hippocampal sclerosis, which may direct or inform surgical intervention. Management It is important to explain the nature and cause of seizures to patients and their relatives, and to instruct relatives in the first aid management of seizures (Box 25.36). Many people with epilepsy feel stigmatised and may become unnecessarily isolated from work and social life. It is important to emphasise that epilepsy is a common disorder that affects 0.5–1% of the population, and that full control of seizures can be expected in approximately 70% of patients (Box 25.37).

25.36 How to administer first aid for seizures • Move the person away from danger (fire, water, machinery, furniture) • After convulsions cease, turn the person into the 'recovery' position (semi-prone) • Ensure the airway is clear but do NOT insert anything in the mouth (tongue-biting occurs at seizure onset and cannot be prevented by observers) • If convulsions continue for more than 5 mins or recur without the person regaining consciousness, summon urgent medical attention • Do not leave the person alone until fully recovered (drowsiness and delirium can persist for up to 1 hr)

25.35 Indications for brain imaging in epilepsy • Epilepsy starting after the age of 16 years • Seizures having focal features clinically • Electroencephalogram showing a focal seizure source • Control of seizures difficult or deteriorating

25.34 Investigation of epilepsy From where is the epilepsy arising? • Standard EEG • Sleep EEG • EEG with special electrodes (foramen ovale, subdural) What is the cause of the epilepsy? Structural lesion? • CT • MRI Metabolic disorder? • Urea and electrolytes • Liver function tests • Blood glucose • Serum calcium, magnesium Inflammatory or infective disorder? • Full blood count, erythrocyte sedimentation rate, C-reactive protein • Chest X-ray • Serology for syphilis, HIV, collagen disease • CSF examination Are the attacks truly epileptic? • Ambulatory EEG • Videotelemetry (CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalography; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging)

25.37 Epilepsy: outcome after 20 years • 50% are seizure-free, without drugs, for the previous 5 years • 20% are seizure-free for the previous 5 years but continue to take medication • 30% continue to have seizures in spite of antiepileptic therapy

1102 • NEUROLOGY pharmacokinetics than the older ones and the only indication for measuring serum levels is if there is doubt about adherence. Blood levels need to be interpreted carefully and dose changes made to treat the patient rather than to bring a serum level into the 'therapeutic

range'. Some centres advocate serum level monitoring during pregnancy (notably with lamotrigine) but the evidence of benefit for this is not strong. Epilepsy surgery Some patients with drug-resistant epilepsy benefit from surgical resection of epileptogenic brain tissue. Less invasive treatments, including vagal nerve stimulation or deep brain stimulation, may also be helpful in some patients. All those who continue to experience seizures despite appropriate drug treatment should be considered for surgical treatment. Planning such interventions requires intensive specialist assessment and investigation to identify the site of seizure onset and the dispensability of any target areas for resection, i.e. whether the area of brain involved is necessary for a critical function such as vision or motor function. Withdrawing antiepileptic therapy Withdrawal of medication may be considered after a patient has been seizure-free for more than 2 years. Childhood-onset epilepsy, particularly classical absence seizures, carries the best prognosis for successful drug withdrawal. Other epilepsy syndromes, such as juvenile myoclonic epilepsy, have a marked tendency to recur after drug withdrawal. Focal epilepsies that begin in adult life are also likely to recur, especially if there is an identified structural lesion. Overall, the recurrence rate after drug withdrawal depends on the individual's epilepsy history. An individualised estimate may be gained from the SIGN guideline tables (see 'Further information', p. 1146). Patients should be advised of the risks of recurrence, to allow them to decide whether or not they wish to withdraw. If undertaken, withdrawal should be done slowly, reducing the drug dose gradually over weeks or months. Withdrawal See *Scottish Intercollegiate Guidelines Network SIGN 143 – Diagnosis and management of epilepsy in adults (May 2015)*. 25.39 Guidelines for antiepileptic drug therapy • Start with one first-line drug (see Box 25.40) • Start at a low dose; gradually increase dose until effective control of seizures is achieved or side-effects develop • Optimise adherence (use minimum number of doses per day) • If first drug fails (seizures continue or side-effects develop), start second first-line drug, followed if possible by gradual withdrawal of first • If second drug fails (seizures continue or side-effects develop), start second-line drug in combination with the preferred baseline drug at maximum tolerated dose (beware interactions) • If this combination fails (seizures continue or side-effects develop), replace second-line drug with alternative second-line drug • If this combination fails, check adherence and reconsider diagnosis (Are events seizures? Occult lesion? Treatment adherence/alcohol/ drugs confounding response?) • Consider alternative, non-drug treatments (e.g. epilepsy surgery, vagal nerve stimulation) • Use minimum number of drugs in combination at any one time 25.38 UK driving regulations The physician's prime duty is to ensure the patient is aware of the legal obligation to inform the driving authority Private use Single seizure • Cease driving for 6 months; a longer period may be required if risk of recurrence is high Epilepsy (i.e. more than one seizure over the age of 5 years) • Cease driving immediately • Licence restored when patient is seizure-free for 1 year, or an initial sleep seizure is followed by exclusively sleep seizures for 1 year, or mixed awake and sleep seizures are followed by 3 years of exclusively sleep seizures • Licence will require renewal every 3 years thereafter until patient is seizure-free for 10 years Withdrawal of antiepileptic drugs • Cease driving during withdrawal period and for 6 months thereafter Vocational drivers (heavy goods and public service vehicles) • No licence permitted if any seizure has occurred after the age of 5 years until patient is off medication and seizure-free for more than 10 years, and has no potentially epileptogenic brain lesion are listed in Box 25.39. For focal epilepsies, one large study suggests that lamotrigine is the best-tolerated monotherapy, which, alongside its favourable adverse-effect profile and relative lack of pharmacokinetic interactions, makes it a good first-line drug, although caution must be exercised with oral contraceptive use. Unclassified or genetic generalised epilepsies respond best to valproate, although pregnancy-related problems mean that valproate should not be used in women

of reproductive age unless the benefits outweigh the risks. The initial choice should be an established first-line drug (Box 25.40), with more recently introduced drugs as second choice. Monitoring therapy Some practitioners confuse epilepsy care with serum level monitoring. The newer drugs have much more predictable 25.40 Guidelines for choice of antiepileptic drug¹

Epilepsy type	First-line	Second-line	Third-line
Focal onset and/or secondary GTCS	Lamotrigine	Carbamazepine	Levetiracetam
Sodium valproate	Topiramate	Zonisamide	Lacosamide
Clobazam	Gabapentin	Oxcarbazepine	Phenobarbital
Phenytoin	Pregabalin	Primidone	Tiagabine
GTCS ²	Sodium valproate	Levetiracetam	Lamotrigine
Topiramate	Zonisamide	Carbamazepine	Phenytoin
Primidone	Phenobarbital	Acetazolamide	Absence ²
Ethosuximide	Sodium valproate	Lamotrigine	Clonazepam
Myoclonic ²	Sodium valproate	Levetiracetam	Clonazepam
Lamotrigine	Phenobarbital	N.B.	Use as few drugs as possible at the lowest possible dose. (GTCS = generalised tonic-clonic seizure) ¹ See Scottish Intercollegiate Guidelines Network SIGN 143 – Diagnosis and management of epilepsy in adults (May 2015). ² Genetic generalised epilepsies.

Epilepsy • 1103

Prognosis The outcome of newly diagnosed epilepsy is generally good. Overall, generalised epilepsies and generalised seizures are more readily controlled than focal seizures. The presence of a structural lesion reduces the chances of freedom from seizures. The overall prognosis for epilepsy is shown in Box 25.37. The particular problems that epilepsy poses in the elderly and in adolescents are summarised in Boxes 25.42 and 25.43, respectively. Status epilepticus Presentation and management are described on page 1080. While generalised status epilepticus is most easily recognised, non-convulsive status may be less dramatic and less easily diagnosed. It may cause only altered awareness, delirium or wandering with automatisms. In an intensive care unit setting, EEG monitoring is essential to ensure that diagnosis and treatment are optimised.

Non-epileptic attack disorder ('dissociative attacks') The difficulty with nomenclature is discussed on page 1097. Patients may present with attacks that resemble epileptic seizures but are caused by psychological phenomena and may necessitate precautions around driving or occupation (see Box 25.38).

Contraception Some AEDs induce hepatic enzymes that metabolise synthetic hormones, increasing the risk of contraceptive failure. This is most marked with carbamazepine, phenytoin and barbiturates, but clinically significant effects can be seen with lamotrigine and topiramate. If the AED cannot be changed, this can be overcome by giving higher-dose preparations of the oral contraceptive. Sodium valproate and levetiracetam have no interaction with hormonal contraception.

Pregnancy and reproduction Epilepsy presents specific management problems during pregnancy (Box 25.41). There is usually concern about teratogenesis associated with AEDs. It is important to recognise proportionate risks: background risk of severe fetal malformation in the general population is around 2–3%, while the AED most associated with teratogenesis is sodium valproate, which, at high dose, increases the risk to around 6–7%. Long-term observational studies show that most of the commonly used AEDs can be given safely in pregnancy. Pre-conception treatment with folic acid (5 mg daily), along with use of the smallest effective doses of as few AEDs as possible, may reduce the risk of fetal abnormalities. The risks of abrupt AED withdrawal to the mother should be stressed. Seizures may become more frequent during pregnancy, particularly if pharmacokinetic changes decrease serum levels of AEDs (see Box 25.41). Menstrual irregularities and reduced fertility are more common in women with epilepsy, and are also increased by sodium valproate. Patients with epilepsy are at greater risk of osteoporosis, apparently independently of the drug used. Some centres advocate vitamin D

supplementation in any patient with epilepsy but the higher female risk of osteoporosis makes this most important in women. Oral contraception can interact with individual AEDs (Box 25.41).

25.41 Epilepsy in pregnancy • Provision of pre-conception counselling is best practice: start folic acid (5 mg daily for 2 months) before conception to reduce the risk of fetal malformations. • Fetal malformation: risk is minimised if a single drug is used. Carbamazepine and lamotrigine have the lowest incidence of major fetal malformations. The risk with sodium valproate is higher but should be carefully balanced against its benefits. Levetiracetam may be safe but avoid other newer drugs if possible. • Learning difficulties in children: IQ may be lower when children are exposed to valproate in utero, so its use should always be considered carefully. • Haemorrhagic disease of the newborn: enzyme-inducing antiepileptic drugs increase risk. Give oral vitamin K (20 mg daily) to the mother during the last month of pregnancy and IM vitamin K (1 mg) to the infant at birth. • Increased frequency of seizures: where breakthrough seizures occur, monitor antiepileptic drug levels and adjust the dose regimen accordingly. • Pharmacokinetic effects of pregnancy: carbamazepine levels may fall in the third trimester. Lamotrigine and levetiracetam levels may fall early in pregnancy. Some advocate monitoring of levels.

25.43 Epilepsy in adolescence • Effect on school/education: seizures, antiepileptic drugs (AEDs) and psychological complications of epilepsy may hamper education. Fear may make some educational institutions unduly restrictive. • Effect on family relationships: parents may adopt a protective role, which can lead to epilepsy (and AEDs) becoming a point of assertion and rebellion. • Effect on career choice: epilepsy may exclude or restrict employment in the emergency services and armed forces. • Alcohol: may affect sleep pattern; excess may be associated with poor AED adherence. • Illicit drugs: may affect seizure threshold and be associated with poor AED adherence. • Sleep disturbance: may be worsened by social activities and computer games. • Oral contraception: interactions with AED can occur. Use may not always be disclosed to parents.

25.42 Epilepsy in old age • Incidence and prevalence: late-onset epilepsy is very common and the annual incidence in those over 60 years is rising. • Fits and faints: the features that usually differentiate these may be less definitive than in younger patients. • Non-convulsive status epilepticus: can present as delirium in the elderly. • Cerebrovascular disease: the underlying cause of seizures in 30–50% of patients over the age of 50 years. A seizure may occur with an overt stroke or with occult vascular disease. • Antiepileptic drug regimens: keep as simple as possible and take care to avoid interactions with other drugs being prescribed. • Carbamazepine-induced hyponatraemia: increases significantly with age; this is particularly important in patients on diuretics or those with heart failure. • Withdrawal of antiepileptic therapy: drug withdrawal should be attempted only where benefits exceed risk of harm from seizures.

1104 • NEUROLOGY within a few days, though head movement may continue to provoke transient symptoms (positional vertigo) for some time. During the acute attack, nystagmus (p. 1090) will be present for a few days. Cinnarizine, prochlorperazine or betahistine provide symptomatic relief but should not be used long-term, as this may delay recovery. A small proportion of patients fail to recover fully and complain of ongoing imbalance and dysequilibrium rather than vertigo; vestibular rehabilitation by a physiotherapist may help. Benign paroxysmal positional vertigo Benign paroxysmal positional vertigo (BPPV) is due to the presence of otolithic debris from the saccule or utricle affecting the free flow of endolymph in the semicircular canals (cupulolithiasis). It may follow minor head injury but typically is spontaneous. The history is diagnostic, with transient (seconds) vertigo precipitated by movement (typically, rolling over in bed or getting into or out of bed). Although it is benign, and usually self-limiting after weeks or months, patients are often alarmed by the symptoms. The diagnosis can be confirmed by the 'Hallpike manoeuvre' to

demonstrate positional nystagmus (Fig. 25.26). Treatment comprises explanation and reassurance, along with positioning procedures designed to return otolithic debris from the semicircular canal to saccule or utricle (such as the Epley manoeuvre) and/or to re-educate the brain to cope with the inappropriate signals from the labyrinth (such as Cawthorne–Cooksey exercises: see ‘Further information’, p. 1146).

Ménière’s disease This is due to an abnormality of the endolymph that causes episodes of vertigo accompanied by tinnitus and fullness in the ear, each attack typically lasting a few hours. Over the years, patients may develop progressive deafness (typically low-tone on audiometry). Examination is typically normal in between attacks. The diagnosis is clinical, supported by abnormal audiometry. Ménière’s disease is idiopathic but a similar syndrome may have no abnormal EEG discharges. Such attacks may be very prolonged, sometimes mimicking status epilepticus. Epileptic and non-epileptic attacks may coexist and time and effort are needed to clarify the relative contribution of each, allowing more accurate and comprehensive treatment. Non-epileptic attack disorder (NEAD) may be accompanied by dramatic flailing of the limbs and arching of the back, with side-to-side head movements and vocalising. Cyanosis and severe biting of the tongue are rare but incontinence can occur. Distress and crying are common following non-epileptic attacks. The distinction between epileptic attacks originating in the frontal lobes and non-epileptic attacks may be especially difficult, and may require videotelemetry with prolonged EEG recordings. Non-epileptic attacks are three times more common in women than in men and have been linked with a history of past or ongoing life trauma. They are not necessarily associated with formal psychiatric illness. Patients and carers may need reassurance that hospital admission is not required for every attack. Prevention requires psychotherapeutic interventions rather than drug therapy (p. 1202).

Vestibular disorders Vertigo is the typical symptom caused by vestibular dysfunction, and most patients with vertigo have acute vestibular failure, benign paroxysmal positional vertigo or Ménière’s disease. Central (brain) causes of vertigo are rare by comparison, with the exception of migraine (p. 1095).

Acute vestibular failure Although commonly called ‘labyrinthitis’ or ‘vestibular neuronitis’, acute vestibular failure is a more accurate term, as most cases are idiopathic. It usually presents as isolated severe vertigo with vomiting and unsteadiness. It begins abruptly, often on waking, and many patients are initially bed-bound. The vertigo settles Fig. 25.26

The Hallpike manoeuvre for diagnosis of benign paroxysmal positional vertigo (BPPV). Patients are asked to keep their eyes open and look at the examiner as their head is swung briskly backwards through 120° to overhang the edge of the couch. A Perform first with the right ear down. B Perform next with the left ear down. The examiner looks for nystagmus (usually accompanied by vertigo). In BPPV, the nystagmus typically occurs in A or B only and is torsional, the fast phase beating towards the lower ear. Its onset is usually delayed a few seconds and it lasts 10–20 seconds. As the patient is returned to the upright position, transient nystagmus may occur in the opposite direction. Both nystagmus and vertigo typically decrease (fatigue) on repeat testing. B A

Disorders of sleep • 1105

Parasomnias Parasomnias are abnormal motor behaviours that occur around sleep. They may arise in either REM or non-REM sleep, with characteristic features and timing. Non-REM parasomnias tend to occur early in sleep. Parasomnias should be distinguished from other motor disturbances (such as periodic limb movements, hypnic jerks or sleep talking) and sleep-onset epileptic seizures (p. 1101). History from a sleeping partner or other witness is essential. Non-REM parasomnias These are due to incomplete arousal from non-REM sleep and manifest as night terrors, sleep

walking and confusional arousals (sleep drunkenness). They typically occur within an hour or two of sleep onset, and are common in children and usually of no pathological significance. Rarely, they persist into adulthood and may become increasingly complex, including dressing, moving objects, eating, drinking or even acts of violence. Patients have little or no recollection of the episodes, even though they appear 'awake'. The episodes may be triggered by alcohol or unfamiliar sleeping situations, and can be familial. Treatment is usually not required but clonazepam can be used.

REM sleep behaviour disorder In REM sleep behaviour disorder (RBD), patients 'act out' their dreams during REM sleep, due to failure of the usual muscle atonia. Sleep partners provide typical histories of patients 'fighting' or 'struggling' in their sleep, sometimes causing injury to themselves or to their partner. They are easily roused from this state, with recollection of their dream, unlike in non-REM states. RBD is more common in men and may be an early symptom of neurodegenerative diseases such as alpha synucleinopathies (p. 1111), perhaps preceding more typical symptoms of these conditions by years. Polysomnography will confirm absence of atonia during REM sleep. Clonazepam is the most successful treatment.

Restless legs syndrome Restless legs syndrome (RLS) is common, with a prevalence of up to 10%, but many patients never seek medical attention. It is characterised by unpleasant leg (rarely, arm) sensations that are eased by movement (motor restlessness); the diagnosis is caused by middle ear trauma or infection. Imaging may be indicated to exclude other focal brainstem or cerebellopontine angle pathology but will be normal in Ménière's disease. Management includes a low-salt diet, vestibular sedatives for acute attacks (e.g. cinnarizine or prochlorperazine), and occasionally surgery to increase endolymphatic drainage from the vestibular system. Migraine may also cause episodic vertigo, and can be confused with Ménière's disease, although usually other migrainous features will appear in the history.

Disorders of sleep Sleep disturbances include too much sleep (hypersomnolence or excessive daytime sleepiness), insufficient or poor-quality sleep (insomnia), and abnormal behaviour during sleep (parasomnias). Insomnia is usually caused by psychological or psychiatric disorders, shift work and other environmental causes, pain and so on, and will not be discussed further. Many symptoms and disorders may affect sleep and sleep quality (e.g. pain, depression/anxiety, parkinsonism).

Excessive daytime sleepiness (hypersomnolence) There are primary and secondary causes (Box 25.44). The most common causes are impaired sleep due to lifestyle issues or sleep-disordered breathing (p. 622). Sleepiness may be measured using the Epworth Sleepiness Score (see Box 17.86, p. 623). Most causes will be identified by a detailed history from the patient and their bed partner, and a 2-week sleep diary.

Narcolepsy This has a prevalence of about 1 in 2000, with peak onset in adolescence and early middle age. The key symptom is sudden, irresistible 'sleep attacks', often in inappropriate circumstances such as while eating or talking. Other characteristic features help distinguish this from excessive daytime sleepiness (Box 25.45). Symptoms may be due to loss of hypocretin-secreting hypothalamic neurons. Diagnosis requires sleep study with sleep latency testing (demonstrating rapid onset of REM sleep). Narcolepsy may respond to stimulants such as modafinil but more severe cases may require sodium oxybate, dexamfetamine, methylphenidate or selective serotonin reuptake inhibitor (SSRIs). Cataplexy can be debilitating and can respond to sodium oxybate or to antidepressants, such as clomipramine or venlafaxine.

25.44 Causes of hypersomnolence

- Primary causes • Narcolepsy • Idiopathic hypersomnolence • Brain injury
- Secondary causes (due to poor-quality sleep) • Obstructive sleep apnoea • Pain • Restless legs/periodic limb movements of sleep • Parkinsonism and other neurodegenerative diseases • Depression/anxiety • Medication • Environmental factors (noise, temperature etc.)

25.45 Narcolepsy symptoms

- Sleep attacks • Brief, frequent and unlike normal somnolence
- Cataplexy • Sudden loss of muscle tone triggered by surprise, laughter, strong emotion etc.
- Hypnagogic or

hypnopompic hallucinations • Frightening hallucinations experienced during sleep onset or waking due to intrusion of REM sleep during wakefulness (can occur in normal people) Sleep paralysis • Brief paralysis on waking (can occur in normal people)

1106 • NEUROLOGY A) and CD226 genes. An immune hypothesis is supported by increased levels of activated T lymphocytes in the CSF and increased immunoglobulin synthesis within the CNS. Initial CNS inflammation in MS involves entry of activated T lymphocytes across the blood-brain barrier. These recognise myelin-derived antigens on the surface of the nervous system's antigen-presenting cells, the microglia, and undergo clonal proliferation. The resulting inflammatory cascade releases cytokines and initiates destruction of the oligodendrocyte-myelin unit by macrophages. Histologically, the resultant lesion is a plaque of inflammatory demyelination, most commonly in the periventricular regions of the brain, the optic nerves and the subpial regions of the spinal cord (Fig. 25.27). This begins as a circumscribed area of disintegration of the myelin sheath, accompanied by infiltration by activated lymphocytes and macrophages, often with conspicuous perivascular inflammation. After the acute attack, gliosis follows, leaving a shrunken scar. Much of the initial acute clinical deficit is caused by the effect of inflammatory cytokines on transmission of the nervous impulse rather than structural disruption of myelin, and may explain the rapid recovery of some deficits and probably the acute benefit from glucocorticoids. In the long term, accumulating myelin loss reduces the efficiency of impulse propagation or causes complete conduction block, contributing to sustained impairment of CNS functions. Inflammatory mediators released during the acute attack (particularly nitric oxide) probably also initiate axonal damage, which is a feature of the latter stages of the disease. In established MS there is progressive axonal loss, probably due to the successive damage from acute attacks and the subsequent loss of neurotrophic factors from oligodendrocytes. This axonal loss may account for the phase of the disease characterised by progressive and persistent disability (Fig. 25.28). Clinical features The diagnosis of MS requires the demonstration of otherwise unexplained CNS lesions separated in time and space (Box 25.47); traditionally, this meant two or more clinical relapses affecting different parts of the nervous system, and the first ever episode was labelled 'clinically isolated syndrome' (CIS). Recent changes to diagnostic criteria mean that MS may be diagnosed after an isolated episode (i.e. at the CIS stage), provided that certain criteria are met (Box 25.47) The peak age of onset of MS is the fourth decade; onset before puberty or after the age of 60 years is rare. Symptoms and signs of MS usually evolve over days or weeks, resolving over weeks or months. Rarely, a more rapid stroke-like presentation may occur. About 85–90% of patients have an initial relapsing and remitting clinical course with variable intervening recovery, although the majority will eventually enter a secondary progressive phase. Most of the rest follow a slowly progressive clinical course (so-called primary progressive MS), while rare patients have a fulminant variety leading to early death (see Fig. 25.28). Frequent relapses with incomplete recovery indicate a poor prognosis. Some milder cases have an interval of years or even decades between attacks, while in others (particularly if optic neuritis is the initial manifestation) there is no recurrence of disease. There are a number of clinical symptoms and syndromes suggestive of MS, occurring either at presentation or during the course of the illness (Box 25.48). The physical signs observed in MS are determined by the anatomical site of demyelination. Combined spinal cord and brainstem signs are common, although evidence of previous optic neuritis may be found in the form of an afferent pupillary deficit. Significant intellectual impairment clinical (Box 25.46). It has a strong familial tendency and can present with daytime somnolence due to poor sleep. It is usually idiopathic but may be associated with iron deficiency, pregnancy, peripheral neuropathy, Parkinson's disease or

uraemia. It should be distinguished from akathisia, the daytime motor restlessness that is an adverse effect of antipsychotic drugs. Treatment, if required, is with dopaminergic drugs (dopamine agonists or levodopa, p. 1113) or benzodiazepines. Periodic limb movements in sleep Unlike RLS, periodic limb movements in sleep (PLMS) only occur during sleep and cause repetitive flexion movements of the limbs, usually in the early (non-REM) stages of sleep. Although patients are unaware of the symptoms, they may disrupt sleep quality and often disturb partners. The pathological significance of PLMS is uncertain and it often occurs in normal health. There is an overlap with RLS. Treatment is most successful with clonazepam or dopaminergic drugs.

Neuro-inflammatory diseases

Multiple sclerosis Multiple sclerosis (MS) is an important cause of long-term disability in adults, especially in the UK, where the prevalence is approximately 120 per 100 000. The annual incidence is around 7 per 100 000, while the lifetime risk of developing MS is about 1 in 400. The incidence of MS is higher in Northern Europeans and the disease is about twice as common in females.

Pathophysiology There is evidence that both genetic and environmental factors play a causative role. The prevalence of MS is low near the equator and increases in the temperate zones of both hemispheres. People retain the risk of developing the disease in the zone in which they grew up, indicating that environmental exposures during growth and development are important. Prevalence also correlates with environmental factors, such as sunlight exposure, vitamin D (a controversial association) and exposure to Epstein-Barr virus (EBV), although causative mechanisms remain unclear. Genetic factors are also relevant; the risk of familial occurrence in MS is 15%, with highest risk in first-degree relatives (age-adjusted risk 4–5% for siblings and 2–3% for parents or offspring). Monozygotic twins have a concordance rate of 30%. The genes that predispose to MS are incompletely defined but inheritance appears to be polygenic, with influences from genes for human leucocyte antigen (HLA) typing, interleukin receptors, CLEC16A (C-type lectin domain family 16 member 25).

46 Diagnostic criteria for restless legs syndrome

A need to move the legs, usually accompanied or caused by uncomfortable, unpleasant sensations in the legs, with the following features:

- only present or worse during periods of rest or inactivity such as lying or sitting
- partially or totally relieved by movement such as walking or stretching, at least as long as the activity continues
- generally worse or occurs only in the evening or night.

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Fig. 25.27 Multiple sclerosis. A Photomicrograph from demyelinating plaque, showing perivascular cuffing of blood vessel by lymphocytes. B Brain magnetic resonance imaging in multiple sclerosis. Multiple high-signal lesions (arrows) seen particularly in the paraventricular region on T2 image. C In T1 image with gadolinium enhancement, recent lesions (A arrows) show enhancement, suggesting active inflammation (enhancement persists for 4 weeks); older lesions (B arrows) show no enhancement but low signal, suggesting gliosis.

25.47 The Macdonald criteria for the diagnosis of multiple sclerosis (2011)

- 1 Clinical presentation
- 2 Additional evidence required for diagnosis of MS

Two or more attacks with either objective clinical evidence of at least 2 lesions or Objective clinical evidence of 1 attack with reasonable evidence (on clinical history) of at least 1 prior attack

None Two or more attacks with objective clinical evidence of 1 lesion

Dissemination in 'space' demonstrated by magnetic resonance imaging (MRI) ≥ 1 lesion in at least 2 of the MS-typical regions

- 3 (multiple lesions in different sites) or Await further clinical attack at different anatomical site

One attack with objective clinical evidence of ≥ 2 lesions

Dissemination in 'time' demonstrated by evolving MRI showing combined enhancing (new) and non-enhancing (old) lesions

or New T2 or enhancing lesion on repeat MRI or Await further (second) clinical attack at different anatomical site One attack with clinical evidence of only 1 lesion (clinically isolated syndrome) Dissemination in 'space' demonstrated by ≥ 1 T2 lesion in at least 2 MS-typical regions or Dissemination in 'time', demonstrated by simultaneous enhancing and non-enhancing lesions or New T2 or enhancing lesions on repeat MRI or Await further (second) clinical attack Insidious neurological progression suggestive of MS 1 year of progression plus 2 of the following: Evidence for dissemination in space with ≥ 1 T2 lesions in MS-typical regions Evidence for dissemination in space based on ≥ 2 lesions in the spinal cord Positive cerebrospinal fluid (evidence of oligoclonal band and/or elevated immunoglobulin G index) 1If the clinical presentation in the left-hand column is associated with the features in the right-hand column, the diagnosis is MS. If there is incomplete association, the diagnosis is 'possible MS'. 2Assumes other possible causes for central nervous system inflammation (e.g. sarcoidosis, systemic lupus erythematosus) have been excluded. 3MS-typical regions = periventricular, juxtacortical, infratentorial, spinal cord. From Polman CH, Reingold SC, Branwell B, et al. Diagnostic criteria for multiple sclerosis. *Ann Neurol* 2011; 69:292-302.

1108 • NEUROLOGY Fig. 25.28 The progression of disability in fulminant, relapsing-remitting and progressive multiple sclerosis. Courtesy of Prof. D.A.S. Compston. Fulminant (< 10%) Relapsing-remitting (80%) Primary progressive (10-20%) Secondary progressive Disability Time Fig. 25.29 Investigations in a patient suspected of having multiple sclerosis. Exclude other structural disease and identify plaques of demyelination Image area of clinical involvement (magnetic resonance imaging, myelography) Demonstrate other sites of involvement Imaging (MRI) Visual evoked potentials Other evoked potentials Demonstrate inflammatory nature of lesion(s) Cerebrospinal fluid examination Cell count Protein electrophoresis (oligoclonal bands) Exclude other conditions Chest X-ray Serum angiotensin-converting enzyme Serum vitamin B12 Antinuclear antibodies Antiphospholipid antibodies 25.48 Clinical features of multiple sclerosis Common presentations of multiple sclerosis • Optic neuritis • Relapsing/remitting sensory symptoms • Subacute painless spinal cord lesion • Acute brainstem syndrome • Subacute loss of function of upper limb (dorsal column deficit) • 6th cranial nerve palsy Other symptoms and syndromes suggestive of central nervous system demyelination • Afferent pupillary defect and optic atrophy (previous optic neuritis) • Lhermitte's symptom (tingling in spine or limbs on neck flexion) • Progressive non-compressive paraparesis • Partial Brown-Séquard syndrome (p. 1083) • Internuclear ophthalmoplegia with ataxia • Postural ('rubral', 'Holmes') tremor • Trigeminal neuralgia (p. 1096) under the age of 50 • Recurrent facial palsy appears only late in the disease, when loss of frontal lobe functions and impairment of memory are common. The prognosis for patients with MS is difficult to predict with confidence, especially early in the disease. Those with relapsing and remitting MS experience, on average, 1-2 relapses every 2 years, although this may decline with time. Approximately 5% of patients die within 5 years of disease onset, and slightly more have very good long-term outcome with little or no disability. Prognosis is good for patients with optic neuritis and only sensory relapses. Overall, about one-third of patients are disabled to the point of needing help with walking after 10 years, and this proportion rises to about half after 15 years. It would appear likely (though this is as yet unproven) that disease-modifying drugs will have an effect on long-term disability. Investigations There is no single diagnostic test that is definitive for MS and the results of investigation need to be combined with the clinical picture in order to make a diagnosis; MRI is the most important investigation (Fig. 25.29). MS mimics should be excluded (see below). Following the first clinical event (CIS), investigations may help prognosis by confirming the

disseminated nature of the disease. MRI is the most sensitive technique for imaging lesions in brain and spinal cord (Fig. 25.30) and for excluding other causes that have provoked the neurological deficit. However, the MRI appearances in MS may be confused with those of small-vessel disease or cerebral vasculitis, and these diagnoses should be considered and excluded. Evoked potentials (visual, auditory or somatosensory) may detect clinically silent lesions but are rarely used nowadays with the advent of MRI. The CSF may show a lymphocytic pleocytosis in the acute phase and unique (i.e. absent from the serum) oligoclonal bands of IgG in 70–90% of patients between attacks. Oligoclonal bands are not specific for MS and denote only intrathecal inflammation, provided they are unique for the CSF. These can appear in other disorders, which should be excluded by examination and investigation. It is important to exclude other potentially treatable conditions, such as infection, vitamin B12 deficiency and spinal cord compression.

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These drugs – available orally, as regular subcutaneous injections or as pulsed intravenous treatments – may be divided into two groups (Box 25.49). All DMTs have strict licensing criteria and are associated with a range of adverse effects, some occasionally fatal, especially the more effective drugs. Careful selection and counselling of patients are necessary and these drugs should be supervised by teams experienced in their use, as recommended in national guidelines. Clinical trials suggest that DMT options for primary and secondary progressive MS will be available in coming years. Clinical trials involving stem cells are ongoing. Special diets, including gluten-free regimens or linoleic acid supplements, and hyperbaric oxygen therapy are popular with patients but their efficacy has not been demonstrated. Treatment of symptoms, complications and disability

Treatments for the complications of MS are summarised in Box 25.50. It is important to provide patients with a careful explanation of the nature of the disease and its outcome. When and if disability occurs, patients and their relatives need appropriate support. Specialist nurses working in a multidisciplinary team of health-care professionals are of great value in managing the chronic phase of the disease. Periods of physiotherapy and occupational therapy may improve functional capacity in those who become disabled, and guidance can be provided on the Management

The management of MS involves four different strands: treatment of the acute episode, prevention of future relapses, treatment of complications, and management of the patient's disability. The acute episode In a disabling exacerbation of MS, pulses of high-dose glucocorticoid, given either intravenously or orally over 3–5 days, will shorten the duration of the acute episode. Prolonged administration of glucocorticoids does not alter the long-term outcome and is associated with severe adverse effects; it should therefore be avoided. Pulses of glucocorticoids can be given up to three times in a year but use should be restricted to those individuals with significant function-threatening deficits. Prophylaxis to prevent glucocorticoid-induced osteoporosis (p. 1045) should be considered in patients requiring multiple courses of glucocorticoids. Disease-modifying treatment

Until the 1990s, there were no effective disease-modifying treatments (DMTs) for MS; azathioprine showed some promise but this was offset by adverse effects and the drug was rarely used. The introduction of, initially, beta-interferons and glatiramer acetate paved the way for a new and exciting era of DMTs, which is still evolving. All reduce annual relapse rates and the number and size of lesions on MRI, and some may reduce disability. They are not indicated for treatment of early or pre-clinical MS. Fig. 25.30 Multiple sclerosis: demyelinating lesion in cervical spinal cord, high-signal T2 images (arrows). A Sagittal plane. B Axial plane. A B 25.49 Disease-modifying treatments in multiple sclerosis

Treatment	Route of administration/dosing	Comment
Moderate		

efficacy for less severe cases: average relapse rate reduction 30–50% Interferon-beta Alternate-day or weekly intramuscular or subcutaneous injection In widespread use for reducing relapse rate Glatiramer acetate Alternate-day subcutaneous injection Similar efficacy to interferon-beta Teriflunomide Daily oral May cause diarrhoea, alopecia, hepatotoxicity Highly teratogenic Dimethyl fumarate Daily oral May cause flushing and gastrointestinal disturbance Risk of PML Fingolimod Daily oral Superior efficacy to interferon-beta in randomised trials Cardiac conduction defects, especially with first dose High efficacy for severe cases: average relapse rate reduction

“ 50% Alemtuzumab Intravenous infusion over two courses separated by 12 months; 5-day infusion initially, second course 3 days May precipitate autoimmune reactions, e.g. thyroid disease, ITP Natalizumab 4-weekly intravenous infusion Recently introduced; may be more effective than interferon-beta and glatiramer acetate Risk of PML (ITP = idiopathic thrombocytopenic purpura; PML = progressive multifocal leucoencephalopathy)

1110 • NEUROLOGY Investigations MRI shows multiple high-signal areas in a pattern similar to that of MS, although often with large confluent areas of abnormality. CSF may be normal or show an increase in protein and lymphocytes (occasionally $> 100 \times 10^6$ cells/L). Oligoclonal bands may be found in the acute episode but, in contrast to MS, do not persist beyond clinical recovery. The clinical picture may be very similar to a first relapse of MS. Management The prognosis for acute disseminated encephalomyelitis is generally good, although occasionally it may be fatal (probably less than 10%). Treatment with high-dose intravenous methylprednisolone, using the same regimen as for a relapse of MS, is recommended. Transverse myelitis Transverse myelitis is an acute, usually monophasic, demyelinating disorder affecting the spinal cord. It is usually thought to be post-infectious in origin. It occurs at any age and presents with a subacute paraparesis with a sensory level, accompanied by severe pain in the neck or back at the onset. MRI should distinguish this from an external lesion affecting the spinal cord. CSF examination shows cellular pleocytosis, often with polymorphs at the onset. Oligoclonal bands are usually absent. Treatment is with high-dose intravenous methylprednisolone. The outcome is variable: one-third have static deficit, one-third go on to develop MS and one-third recover with no subsequent relapse. Some clinical features may suggest a higher risk of MS after transverse myelitis. Neuromyelitis optica Neuromyelitis optica (previously Devic's disease) is the occurrence of transverse myelitis and bilateral optic neuritis. The disease has been recognised for many years, particularly in Asia. The majority of cases are associated with an antibody to a neuronal membrane channel, aquaporin 4. If changes are seen on brain MRI (this is variable), they are typically high-signal lesions restricted to periventricular regions. Spinal MRI scans show lesions that are typically longer than three spinal segments (unlike the shorter lesions of MS). Clinical deficits tend to recover less well than in MS, and the disease may be more aggressive with more frequent relapses. Treatment with glucocorticoids, azathioprine or cyclophosphamide, and/or plasmapheresis seems to be more effective than in MS. Paraneoplastic neurological disorders Neurological disease may occur with systemic malignant tumours in the absence of cerebral metastases. It is now recognised that, in the majority of these cases, antigen production in the body of the tumour leads to development of antibodies to parts of the CNS. Paraneoplastic conditions are increasingly recognised and the number of antibodies identified is also growing (Boxes 25.52 and 25.53). These syndromes are

particularly associated with small-cell carcinoma of lung, ovarian tumours and lymphomas. Autoantibodies are found in the serum and/or CSF, and biopsy will show a lymphocytic infiltrate of the neural tissue affected. provision of aids at home, reducing handicap. Bladder care is particularly important. Urgency and frequency can be treated pharmacologically (see Box 25.25, p. 1094) but this may lead to a degree of retention with an attendant risk of infection. Urinary retention can be managed initially by intermittent urinary catheterisation (performed by the patient, if possible) but an in-dwelling catheter may become necessary. Sexual dysfunction is a frequent source of distress. Sildenafil or tadalafil helps impotence in men, and skilled counselling and prosthetic aids may be beneficial. Pregnancy does not increase the risk of progression of MS but relapses may occur post-partum (Box 25.51). Acute disseminated encephalomyelitis This is an acute monophasic demyelinating condition in which areas of perivenous demyelination are widely disseminated throughout the brain and spinal cord. The illness may arise spontaneously but often occurs a week or so after a viral infection, especially measles or chickenpox, or following vaccination, suggesting that it is immunologically mediated. Clinical features Headache, vomiting, pyrexia, delirium and meningism may be presenting features, often with focal or multifocal brain and spinal cord signs. Seizures or coma may occur. A minority of patients who recover have further episodes.

25.51 Multiple sclerosis in pregnancy • Counselling: provision of pre-conception counselling is best practice. • Relapse risk: endocrine effects on the immune system ensure that relapse risk drops during pregnancy. • Disease-modifying drugs: risk of teratogenicity means that all disease-modifying drugs should ideally be stopped 6–8 weeks before conception and recommenced after breastfeeding has stopped. • Post-partum relapse rate: rebound of immune system activity means that the highest risk of relapse is in the first year after delivery.

25.50 Treatment of complications in multiple sclerosis Spasticity • Physiotherapy • Baclofen (usually oral) • Dantrolene • Gabapentin • Sativex • Tizanidine • Intrathecal baclofen • Local (intramuscular) injection of botulinum toxin • Chemical neuronectomy Dysaesthesia • Carbamazepine • Gabapentin • Phenytoin • Amitriptyline Bladder symptoms • See Box 25.25 (p. 1094) Fatigue • Amantadine • Modafinil • Amitriptyline Erectile dysfunction • Sildenafil 50–100 mg/day • Tadalafil

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disease has been proven, rather than when it is suspected. The CSF often shows an increased protein and lymphocyte count with oligoclonal bands. Treatment is directed at the primary tumour. Occasionally, successful therapy of the tumour is associated with improvement of the paraneoplastic syndrome. Some improvement may occur following administration of intravenous immunoglobulin.

Neurodegenerative diseases While MS is the most common cause of disability in young people in the UK, vascular and neurodegenerative diseases are increasingly important in later life. The neurodegenerative diseases are united in having a pathological process that leads to specific neuronal death, causing relentlessly progressive symptoms, with Clinical features Clinical presentations are summarised in Boxes 25.52 and 25.53. In most instances, the neurological condition progresses quite rapidly over a few months, preceding the malignant disease in around half of cases. The range of clinical patterns is so wide that paraneoplastic disease should be considered in the diagnosis of any unusual progressive neurological syndrome. The paraneoplastic disorders of the peripheral nervous system particularly affect the synaptic cleft (p. 1065).

Investigations and management The presence of characteristic autoantibodies in the context of a suspicious clinical picture may be diagnostic. The causative tumour may be very small and therefore CT of the chest or abdomen or PET scanning may be necessary to find it. These

investigations should be pursued only when paraneoplastic

25.52 Paraneoplastic disorders of the central nervous system

Clinical presentation Associated tumour Antibodies demonstrated

Limbic encephalitis SCLC Anti-Hu, anti-CV2, PCA-2, anti-VGKC, anti-Ma1, anti-amphiphysin, anti-Ri, ANNA-3, anti-VGCC, anti-Zic4, anti-GluR1/2, anti-GABAR

Testicular, breast Anti-Ma2, anti-GluR1/2

Thymoma Anti-VGKC, anti-CV2, anti-GluR1/2

Ovarian/testicular teratoma Anti-NMDAR

Myelopathy SCLC, thymoma, others Anti-CV2, anti-amphiphysin, anti-aquaporin

Motor neuron disease SCLC, others Anti-Hu

Stiff person syndrome Breast, SCLC, thymoma, others Anti-amphiphysin, anti-Ri, anti-GAD, anti-GlyR

Cerebellar degeneration Breast, ovarian, others Anti-Yo, anti-Ma1, anti-Ri

SCLC, others Anti-Hu, anti-CV2, PCA-2, ANNA-3, anti-amphiphysin, anti-VGCC, anti-Ri, anti-Zic4, anti-GAD

Lymphoma Anti-Tr, anti-mGluR1

Multifocal encephalomyelitis SCLC, thymoma Anti-Hu, anti-CV2, anti-VGKC, anti-Ma1, anti-amphiphysin, anti-Ri, ANNA-3

Opsoclonus-myoclonus Breast, ovarian Anti-Ri, anti-Yo, anti-amphiphysin

SCLC Anti-Hu, anti-Ri, anti-CV2, anti-amphiphysin, anti-VGCC

Neuroblastoma Anti-Hu

Testicular Anti-Ma1/2, anti-CV2

Extrapyramidal encephalitis SCLC, thymoma, testicular Anti-CV2, anti-Hu, anti-VGKC, anti-Ma

Optic neuritis SCLC Anti-CV2, anti-aquaporin

Retinal degeneration SCLC Anti-recoverin (ANNA = anti-neuronal nucleolar antibody; GABAR = GABA receptor; GAD = glutamic acid decarboxylase; GluR = glutamate receptor; GlyR = glycine receptor; NMDAR = N-methyl-D-aspartate receptor; PCA = Purkinje cell antibody; SCLC = small-cell lung cancer; VGCC = voltage-gated calcium channel; VGKC = voltage-gated potassium channel)

25.53 Paraneoplastic disorders of the peripheral nervous system

Clinical presentation Associated tumour Antibodies demonstrated

Neuromyotonia Thymoma, SCLC, others Anti-VGKC

Myasthenia gravis Thymoma Anti-Achr, anti-MuSK

Sensorimotor polyneuropathy Lymphoma, SCLC, others Anti-Hu, anti-CV2, ANNA-3, anti-Ma1, anti-amphiphysin

Lambert-Eaton syndrome SCLC Anti-VGCC

Motor neuropathy Lymphoma, SCLC, others Anti-Hu, anti-Yo, anti-CV2

Sensory neuropathy Lymphoma, SCLC, others Anti-Hu, anti-Yo, anti-CV2

Polymyositis/dermatomyositis Lung, breast Anti-Jo1 (MuSK = muscle-specific kinase; for other abbreviations, see Box 25.52)

1112 • **NEUROLOGY** be due to an environmental toxin but none has been convincingly identified. The pathological hallmarks of PD are depletion of the pigmented dopaminergic neurons in the substantia nigra and the presence of α -synuclein and other protein inclusions in nigral cells (Lewy bodies; Fig. 25.31). It is thought that environmental or genetic factors alter the α -synuclein protein, rendering it toxic and leading to Lewy body formation within the nigral cells. Lewy bodies are also found in the basal ganglia, brainstem and cortex, and increase with disease progression. PD is recognised as a synucleinopathy alongside multiple system atrophy and dementia with Lewy bodies. The loss of dopaminergic neurotransmission is responsible for many of the clinical features. Clinical features

Non-motor symptoms, including reduction in sense of smell (hyposmia), anxiety/depression, constipation and REM sleep behavioural disturbance (RBD), may precede the development of typical motor features by many years but patients rarely present at this stage. The motor symptoms are almost always initially asymmetrical. The hallmark is bradykinesia, leading to classic symptoms such as increasingly small handwriting ('micrographia'), difficulty tying shoelaces or buttoning clothes, and difficulty rolling over in bed. Tremor is an early feature but may not be present in at least 20% of people with PD. It is typically a unilateral rest tremor (p. 1085) affecting limbs, jaw and chin but not the head. In some patients, tremor remains the dominant symptom for many years. Rigidity causes stiffness and a flexed posture. Although postural righting reflexes are impaired early on in the disease, falls tend not to occur until later. As the disease advances, speech becomes softer and indistinct. There are a number of abnormalities on neurological examination (Box 25.55). Although features are initially unilateral, gradual bilateral involvement evolves with

time. Cognition is spared in early disease; if impaired, it should trigger consideration of alternative diagnoses, such as dementia with Lewy bodies. Non-motor symptoms While non-motor symptoms may precede the onset of more typical symptoms by many years, for most patients these features become increasingly common and disabling as PD progresses. Cognitive impairment, including dementia, is the symptom most likely to impair quality of life for patients and their carers. Estimates of dementia frequency range from 30% to 80%, depending on definitions and length of follow-up. Other distressing Fig. 25.31 Parkinson's disease. High power ($\times 400$) view of substantia nigra of a patient with Parkinson's disease showing classical Lewy body (haematoxylin and eosin). Courtesy of Dr J. Xuereb. 25.54 Causes of parkinsonism Idiopathic Parkinson's disease (at least 80% of parkinsonism) Cerebrovascular disease Drugs and toxins • Antipsychotic drugs (older and 'atypical') • Metoclopramide, prochlorperazine • Tetrabenazine • Sodium valproate • Lithium • Manganese • MPTP Other degenerative diseases • Dementia with Lewy bodies • Progressive supranuclear palsy • Multiple system atrophy • Corticobasal degeneration • Alzheimer's disease Genetic • Huntington's disease • Fragile X tremor ataxia syndrome • Dopa-responsive dystonia • Spinocerebellar ataxias (particularly SCA 3) • Wilson's disease Anoxic brain injury (MPTP = methyl-phenyl-tetrahydropyridine) incidence rising with age. The causes are not yet known, although genetic influences are important. Alzheimer's disease (p. 1192) and Parkinson's disease are the most common. Movement disorders Movement disorders present with a wide range of symptoms. They may be genetic or acquired, and the most important is Parkinson's disease. Most movement disorders are categorised clinically, with few confirmatory investigations available other than for those with a known gene abnormality. Idiopathic Parkinson's disease Parkinsonism is a clinical syndrome characterised primarily by bradykinesia (p. 1084), with associated increased tone (rigidity), tremor and loss of postural reflexes. There are many causes (Box 25.54) but the most common is Parkinson's disease (PD). PD has an annual incidence of about 18/100 000 in the UK and a prevalence of about 180/100 000. Age has a critical influence on incidence and prevalence, the latter rising to 300–500/100 000 after 80 years of age. Average age of onset is about 60 years and fewer than 5% of patients present under the age of 40. Genetic factors are increasingly recognised and several single genes causing parkinsonism have been identified, although they account for a very small proportion of cases overall. Having a first-degree relative with PD confers a 2–3 times increased risk of developing the disorder. It is progressive and incurable, with a variable prognosis. While motor symptoms are the most common presenting features, non-motor symptoms (particularly cognitive impairment, depression and anxiety) become increasingly prominent as the disease progresses, and significantly reduce quality of life. Pathophysiology Although mutations in several genes have been identified in a few cases, in most patients the cause remains unknown. The discovery that methyl-phenyl-tetrahydropyridine (MPTP) caused severe parkinsonism in young drug users suggested that PD might

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are neuroprotective. Levodopa (LD) remains the most effective treatment available but other agents include dopamine agonists, anticholinergics, inhibitors of monoamine oxidase (MAOI)-B and catechol-O-methyl-transferase (COMT), and amantadine. Debate continues about when and what treatment should be started. In general, most specialists recommend initiating treatment when symptoms are impacting on everyday life although some favour treatment as soon as the diagnosis is made. Whether it is best to start with LD, a dopamine agonist or MAOI-B remains unclear but most accept that the most effective, best-tolerated and cheapest drug is LD. Many motor

symptoms, such as tremor, freezing, falling, head-drop and abnormal flexion, are quite resistant to treatment. Some non-motor symptoms, such as anxiety or depression, may respond to drug or non-drug treatments. In the UK, rivastigmine is licensed for use in PD-associated dementia, although its effect is modest. Many other non-motor symptoms are resistant to treatment. Drugs for PD should not be stopped abruptly, as this can precipitate malignant hyperthermia. Levodopa is the precursor to dopamine. When administered orally, more than 90% is decarboxylated to dopamine peripherally in the gastrointestinal tract and blood vessels, and only a small proportion reaches the brain. This peripheral conversion is responsible for the high frequency of adverse effects. To avoid this, LD is combined with a dopa decarboxylase inhibitor (DDI); the inhibitor does not cross the blood-brain barrier, thus avoiding unwanted decarboxylation-blocking in the brain. Two DDIs, carbidopa and benserazide, are available as combination preparations with LD (Sinemet and Madopar, respectively). LD is most effective for relieving akinesia and rigidity; tremor response is often less satisfactory and it has no effect on many motor (posture, freezing) and non-motor symptoms. Failure of akinesia/rigidity to respond to LD (1000 mg/day) should prompt reconsideration of the diagnosis. Although controlled-release versions of LD exist, these are usually best reserved for use overnight, as their variable bioavailability makes them difficult to use throughout the day. Madopar is also available as a dispersible tablet for more rapid-onset effect. Adverse effects include postural hypotension, nausea and vomiting, which may be offset by domperidone. LD may exacerbate or trigger hallucinations, and abnormal LD-seeking behaviour (dopamine dysregulation syndrome), in which the patient takes excessive doses of LD, may occur uncommonly. As PD progresses, the response to LD becomes less predictable in many patients, leading to motor fluctuations. This end-of-dose deterioration is due to progressive loss of dopamine storage capacity by dwindling numbers of striatonigral neurons.

25.55 Physical signs in Parkinson's disease

General

- Expressionless face (hypomimia)
- Soft, rapid, indistinct speech (dysphonia)
- Flexed (stooped) posture
- Impaired postural reflexes
- Gait**
- Slow to start walking (failure of gait ignition)
- Rapid, short stride length, tendency to shorten (festination)
- Reduction of arm swing
- Impaired balance on turning
- Tremor**
- Resting** (3–4 Hz, moderate amplitude): most common
- Asymmetric, usually first in arm/hand ('pill rolling')
- May affect legs, jaw and chin but not head
- Intermittent, present at rest, often briefly abolished by movement of limb, exacerbated by walking
- Postural** (6–8 Hz, moderate amplitude)
- Present immediately on stretching out arms
- Re-emergent tremor** (3–4 Hz, moderate amplitude)
- Initially no tremor on stretching arms out, rest tremor re-emerges after a few seconds
- Rigidity**
- Cogwheel type, mostly upper limbs (due to tremor superimposed on rigidity)
- Lead pipe type
- Akinesia** (fundamental feature)
- Slowness of movement
- Fatiguing and decrease in size of repetitive movements

Normal findings (if abnormal, consider other causes)

- Power, deep tendon reflexes, plantar responses
- Eye movements

Sensory and cerebellar examination

non-motor symptoms include neuropsychiatric features (anxiety, depression, apathy, hallucinosis/psychosis), sleep disturbance and hypersomnolence, fatigue, pain, sphincter disturbance and constipation, sexual problems (erectile failure, loss of libido or hypersexuality), drooling and weight loss.

Investigations

The diagnosis is clinical. Structural imaging (CT or MRI) is usually normal for age and thus rarely helpful, although it may support a suspected vascular cause of parkinsonism. Functional dopaminergic imaging (SPECT or PET) is abnormal, even in the early stages (Fig. 25.32), but does not differentiate between the different forms of degenerative parkinsonism (see Box 25.54) and so is not specific for PD. In younger patients, specific investigations may be appropriate (e.g. exclusion of Huntington's or Wilson's diseases). Some patients with family histories may wish to consider genetic testing, although the role of genetic counselling is uncertain at present.

Management

Drug therapy

Drug

treatment for PD remains symptomatic rather than curative, and there is no evidence that any of the currently available drugs Fig. 25.32 Imaging in Parkinson's disease. A Single photon emission computed tomography (SPECT) in Parkinson's disease showing reduced dopamine activity in the basal ganglia. B Normal. A B

1114 • NEUROLOGY lack of efficacy (apart from an effect on tremor sometimes) and adverse effects, including dry mouth, blurred vision, constipation, urinary retention, delirium and hallucinosis, as well as long-term concerns regarding cognitive impairment. Several anticholinergics are available, including trihexyphenidyl (benzhexol) and orphenadrine. Surgery Destructive neurosurgery was commonly used before the introduction of LD. In the last 20 years, stereotactic surgery has emerged and most commonly involves deep brain stimulation (DBS), rather than the destructive approach of previous eras. Various targets have been identified, including the thalamus (only effective for tremor), globus pallidus and subthalamic nucleus. DBS is usually reserved for individuals with medically refractory tremor or motor fluctuations, and careful patient selection is vital to success. Intracranial delivery of fetal grafts or specific growth factors remains experimental. Physiotherapy, occupational therapy and speech therapy Patients at all stages of PD benefit from physiotherapy, which helps reduce rigidity and corrects abnormal posture. Occupational therapists can provide equipment to help overcome functional limitations, such as rails for stairs and the toilet, and bathing equipment. Speech therapy can help where dysarthria and dysphonia interfere with communication, and advice may also be provided to those with dysphagia. As with many complex neurological disorders, patients with PD should ideally be managed by a multidisciplinary team, including PD specialist nurses. Other parkinsonian syndromes Cerebrovascular disease and drug-induced parkinsonism are the most common alternative causes of parkinsonism (see Box 25.54). There are several degenerative conditions that cause parkinsonism, including multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration. They typically have a more rapid progression than PD and tend to be resistant to treatment with LD. They are defined pathologically and identification during life is difficult. There are other conditions that may rarely manifest as parkinsonism, including Huntington's and Wilson's diseases. Multiple system atrophy Multiple system atrophy (MSA) is characterised by parkinsonism, autonomic failure and cerebellar symptoms, with either parkinsonism (MSA-P) or cerebellar features (MSA-C) predominating. It is much less common than PD, with a prevalence of about 4/100 000. Although early distinction between PD and MSA-P may be difficult, early falls, postural instability and lack of response to LD are clues. The pathological hallmark is α -synuclein-containing glial cytoplasmic inclusions found in the basal ganglia, cerebellum and motor cortex. Management is symptomatic and the prognosis is less good than for PD, with mean survival from symptom onset of fewer than 10 years and early disability. Cognition is usually unaffected. Progressive supranuclear palsy Progressive supranuclear palsy (PSP) presents with symmetrical parkinsonism, cognitive impairment, early falls and bulbar symptoms. The characteristic eye movement disorder, with slowed vertical saccades leading to impairment of up- and downgaze, may take years to emerge. PSP has different pathological LD-induced involuntary movements (dyskinesia) may occur as a peak-dose phenomenon or as a biphasic phenomenon (occurring during both the build-up and wearing-off phases). More complex fluctuations present as sudden, unpredictable changes in response, in which periods of parkinsonism ('off' phases) alternate with improved mobility but with dyskinesias ('on' phases). Motor complication management is difficult; wearing-off effects may respond to increased dose or frequency of LD or the addition of a COMT inhibitor (see below). More complex fluctuations may be improved by the

addition of dopamine agonists (including continuous infusion of apomorphine), use of intrainestinal LD via a percutaneous endoscopic jejunostomy, or deep brain stimulator implantation. Dopamine receptor agonists Originally introduced in the hope of delaying the initiation of LD and thus delaying motor complications, several dopamine agonists are available, and may be delivered orally, transdermally or subcutaneously (Box 25.56). The ergot-derived agonists are no longer recommended because of rare but serious fibrotic effects. With the exception of apomorphine, all the agonists are considerably less effective than LD in relieving parkinsonism, have more adverse effects (nausea, vomiting, disorientation and hallucinations, impulse control disorders) and are more expensive. Their role in the management of PD (monotherapy or adjunctive) remains uncertain, and evidence suggests that their usefulness as initial monotherapy is short-lasting.

MAOI-B inhibitors Monoamine oxidase type B facilitates breakdown of excess dopamine in the synapse. Two inhibitors are used in PD: selegiline and rasagiline. The effects of both are modest, although usually well tolerated. Neither is neuroprotective, despite initial hopes.

COMT inhibitors Catechol-O-methyl-transferase (along with dopa decarboxylase) is involved in peripheral breakdown of LD. Two inhibitors are available: entacapone and tolcapone (which also inhibits central COMT). Entacapone has a modest effect and is most useful for early wearing-off. It is available either as a single tablet taken with each LD/DDI dose, or as a combination tablet with LD and DDI. The more potent tolcapone is less used because of rare but serious hepatotoxicity.

Amantadine This has a mild, usually short-lived effect on bradykinesia and is rarely used unless patients are unable to tolerate other drugs. It is more commonly employed as a treatment for LD-induced dyskinesias, although again benefit is modest and short-lived. Adverse effects include livedo reticularis, peripheral oedema, delirium and other anticholinergic effects.

Anticholinergic drugs These were the main treatment for PD prior to the introduction of LD. Their role now is limited by *Oral unless otherwise stated*.

25.56 Dopamine agonists

- Ergot-derived • Bromocriptine • Lisuride • Pergolide • Cabergoline
- Non-ergot-derived • Ropinirole • Pramipexole • Rotigotine (transdermal patch) • Apomorphine (subcutaneous)

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is wide (Boxes 25.57 and 25.58), and diagnosis is guided by age of onset, evolution and clinical features. A significant proportion of cases remain idiopathic despite investigation. The hereditary ataxias are a group of inherited disorders in which degenerative changes occur to varying extents in the cerebellum, brainstem, pyramidal tracts, spinocerebellar tracts and optic and peripheral nerves, and influence the clinical manifestations. Onset ranges from infancy to adulthood, with recessive, sex-linked or dominant inheritance (see Box 25.58). While the genetic abnormality has been identified for some, allowing diagnostic testing, this is not currently the case for many of the hereditary ataxias.

Tremor disorders Tremor (p. 1085) is a feature of many disorders but the most important clinical syndromes are PD, essential tremor, drug-induced tremors (Box 25.59) and functional (psychogenic) tremors.

Essential tremor This has a prevalence of about 300/100 000 and may display a dominant pattern of inheritance, although no genes have thus far been identified. It may present at any age with a bilateral arm tremor (8–10 Hz), rarely at rest but typical with movement. The head and voice may be involved. The tremor improves in about 50% of patients with small amounts of alcohol. There are no specific tests and essential tremor should be distinguished from other tremor syndromes, including dystonic tremor. Beta-blockers and primidone are sometimes helpful, and DBS of the thalamus is an effective treatment for severe cases.

features, being associated with abnormal accumulation of tau (τ) proteins and degeneration

of the substantia nigra, subthalamic nucleus and mid-brain. It is therefore a tauopathy rather than synucleinopathy. The prevalence is about 5/100 000, with average survival similar to that in MSA. There is no treatment, and the parkinsonism usually does not respond to LD. Corticobasal degeneration Corticobasal degeneration (CBD) is less common than MSA or PSP, and the clinical manifestations are variable, including parkinsonism, dystonia, myoclonus and 'alien limb' phenomenon, whereby a limb (usually upper) moves about or interferes with the other limb without apparent conscious control. Cortical symptoms, including dementia and especially apraxia, are common and may be the only features in some cases. A number of other diseases may present with a corticobasal syndrome, including other dementias. CBD is a tauopathy with widespread deposition throughout the brain, and has similar survival rates to MSA and PSP. Wilson's disease This is an autosomal recessive disorder resulting from mutation in the ATP7B gene, causing a defect of copper metabolism (p. 896). It is a treatable cause of various movement disorders, including tremor, dystonia, parkinsonism and ataxia; psychiatric symptoms may also occur. Wilson's disease should always be excluded in patients under the age of 50 presenting with any movement disorder. Huntington's disease Huntington's disease (HD) is an autosomal dominant disorder, presenting in adults usually but occasionally in children. It is due to expansion of a trinucleotide CAG repeat in the Huntingtin gene on chromosome 4 (p. 43). The disease frequently demonstrates the phenomenon of anticipation, in which there is a younger age at onset as the disease is passed through generations, due to progressive expansion of the repeat. The prevalence is about 4-8/100 000. Clinical features HD typically presents with a progressive behavioural disturbance, abnormal movements (usually chorea), and cognitive impairment leading to dementia. Onset under 18 years is rare but patients may then present with parkinsonism rather than chorea (the 'Westphal variant'). There is always a family history, although this may be concealed. Investigations and management The diagnosis is confirmed by genetic testing; pre-symptomatic testing for other family members is available but must be preceded by appropriate counselling (p. 59). Brain imaging may show caudate atrophy but is not a reliable test. There are a number of HD mimics. Management is symptomatic. The chorea may respond to neuroleptics such as risperidone or sulpiride, or tetrabenazine. Depression and anxiety are common and may be helped by medication. Ataxias The ataxias are a heterogeneous group of inherited and acquired disorders, presenting either with pure ataxia or in association with other neurological and non-neurological features. The differential 25.57 Causes of acquired ataxia Structural • Brain tumour • Brain abscess Toxic • Drugs: lithium, phenytoin, amiodarone, toluene, 5-fluorouracil, cytosine arabinoside • Alcohol • Heavy metals/chemicals: mercury, lead, thallium Infection/post-infectious • HIV • Varicella zoster • Whipple's disease • Miller Fisher syndrome (p. 1140) Degenerative • Multiple system atrophy • Sporadic Creutzfeldt-Jakob disease • Idiopathic (or sporadic) late-onset cerebellar ataxia Inflammatory/immune-mediated • Multiple sclerosis • Gluten ataxia (coeliac disease) • Paraneoplastic ataxia • Hashimoto encephalopathy Metabolic • Vitamin B1 or E deficiency • Hypothyroidism • Hypoparathyroidism Vascular • Stroke (ischaemic or haemorrhagic) • Vascular malformations • Superficial siderosis

1116 • NEUROLOGY arterial loop irritating the 7th nerve just outside the pons. It may, however, be symptomatic and secondary to structural lesions. Drug treatment is not effective but injections of botulinum toxin into affected muscles help, although these usually have to be repeated every 3 months or so. In refractory cases, microvascular decompression may be considered. Motor neuron disease Motor neuron disease (MND) is a neurodegenerative condition caused by loss of upper and lower motor neurons in the spinal cord, cranial nerve nuclei and motor cortex. Annual incidence is

about 2/100 000, with a prevalence of about 7/100 000. Most cases are sporadic but 10% of cases are familial. Abnormalities in the superoxide dismutase (SOD1) gene account for about 20% of such cases, and an expanded repeat sequence in the C9orf72 gene on chromosome 9 is associated with MND and frontotemporal dementia. The most common form of MND (Fig. 25.33) is amyotrophic lateral sclerosis (ALS), and many use the terms MND and ALS interchangeably. ALS is characterised by a combination of upper and lower motor neuron signs; there are rarer, pure lower (progressive muscular atrophy) or upper (progressive lateral sclerosis) motor neuron variants of MND. The average age of onset is 65, with 10% presenting before 45 years. Clinical features Diagnosis can be difficult and is often delayed. MND typically presents focally, either with limb onset (e.g. foot drop or loss of manual dexterity) or with bulbar symptoms (dysarthria, swallowing difficulty); respiratory onset is rare but type II respiratory failure is a common terminal event. Sensory, autonomic and visual symptoms do not occur, although cramp is common (Box 25.60). Examination reveals a combination of lower and upper

Dystonia Dystonia is characterised by a focal increase in tone affecting muscles in the limbs or trunk. It may be a feature of a number of neurological conditions (PD, Wilson's disease), or occur secondary to brain damage (trauma, stroke) or drugs (tardive syndromes). Dystonia also occurs as a primary disorder. With childhood onset the cause is usually genetic and dystonia is generalised, but adult onset is usually focal; examples include a twisted neck (torticollis), repetitive blinking (blepharospasm) or tremor. Task-specific symptoms (e.g. writer's cramp, musician's dystonia) are often dystonic. Treatment is difficult but botulinum toxin injections or DBS may be useful.

Hemifacial spasm This usually presents after middle age with intermittent twitching around one eye, spreading ipsilaterally to other facial muscles. The spasms are exacerbated by talking, eating and stress. Hemifacial spasm is usually idiopathic, similar to trigeminal neuralgia; it has been suggested that it may be due to an aberrant

Drugs causing parkinsonism and associated tremor are listed in Box 25.54.

25.59 Drug-induced tremor (usually postural)

- β -agonists (e.g. salbutamol)
- Theophylline
- Sodium valproate
- Thyroxine
- Lithium
- Tricyclic antidepressants
- Recreational drugs (e.g. amphetamines)
- Alcohol
- Caffeine

25.58 Inherited ataxias

Inheritance pattern	Age of onset	Clinical features
Autosomal dominant	Episodic	ataxias
Childhood and early adulthood	Brief episodes of ataxia, sometimes induced by stress or startle. May develop progressive ataxia	Spinocerebellar ataxias (SCAs)
Childhood to middle age	Over 30 subtypes identified thus far. Progressive ataxia, sometimes associated with other features, including retinitis pigmentosa, pyramidal tract abnormalities, peripheral neuropathy and cognitive deficits	Dentato-rubro-pallidoluysian atrophy (DRPLA)
Childhood to middle age	Children present with myoclonic epilepsy and progressive ataxia. Adults have progressive ataxia with psychiatric features, dementia and choreoathetosis	Autosomal recessive Friedreich's ataxia
Childhood/adolescence (late onset possible)	Ataxia, nystagmus, dysarthria, spasticity, areflexia, proprioceptive impairment, diabetes mellitus, optic atrophy, cardiac abnormalities. Usually chair-bound	Ataxia telangiectasia
Childhood	Progressive ataxia, athetosis, telangiectasia on conjunctivae, impaired DNA repair, immune deficiency, tendency to malignancies	Abetalipoproteinaemia
Childhood	Steatorrhoea, sensorimotor neuropathy, retinitis pigmentosa, malabsorption of vitamins A, D, E and K	Hereditary ataxia with vitamin E deficiency
< 20 years	Similar to Friedreich's ataxia, visual loss or retinitis pigmentosa, chorea	Others
Usually young onset	Numerous, with genes identified only in some	X-linked Fragile X tremor ataxia syndrome

50 years Tremor, ataxia, parkinsonism, autonomic failure, cognitive impairment and dementia Adrenoleukodystrophy Childhood to adult Impaired adrenal and cognitive function, sometimes spastic paraparesis Mitochondrial disease Various Ataxia features in several mitochondrial diseases, including Kearns–Sayre syndrome, MELAS, MERRF, Leigh’s syndrome (p. 49) (MELAS = mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MERRF = myoclonic epilepsy with ragged red fibres)

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tests are usually normal, other than a mildly raised creatine kinase. Sensory and motor nerve conduction studies are normal but there may be reduction in amplitude of motor action potentials due to axonal loss. EMG will usually confirm the typical features of widespread denervation and re-innervation. Spinal fluid analysis is not usually necessary. Genetic testing is increasing in importance, with mutations found in SOD1, FUS, TARDBP and C9orf72 that may help predict risk and phenotype of disease in those with a family history of MND. Management Patients should be managed within a multidisciplinary service, including physiotherapists, speech and occupational therapists, dietitians, ventilatory and feeding support, and palliative care teams, with neurological and respiratory input. Riluzole, a glutamate release antagonist, is licensed for ALS but has only a modest effect, prolonging median survival by about 2–3 months. Non-invasive ventilation significantly prolongs survival and improves or maintains quality of life in people with ALS. Survival and some measures of quality of life are significantly improved in the subgroup of people with better baseline bulbar function but not in those with severe bulbar impairment. Feeding by percutaneous gastrostomy may improve quality of life and prolong survival, even when done at a late stage. Rapid access to palliative care teams is essential for patients as they enter the terminal stages of MND. Spinal muscular atrophy This is a group of genetically determined disorders affecting spinal and cranial lower motor neurons, characterised by proximal and distal wasting, fasciculation and weakness of muscles. Involvement is usually symmetrical but occasional localised forms occur. With the exception of the infantile form, progression is slow and the prognosis better than for MND. Infections of the nervous system The clinical features of nervous system infections depend on the location of the infection (the meninges or the parenchyma of the brain and spinal cord), the causative organism (virus, bacterium, 25.60 Clinical features of motor neuron disease Onset • Usually after the age of 50 years • Very uncommon before the age of 30 years • Affects males more commonly than females Symptoms • Limb muscle weakness, cramps, occasionally fasciculation • Disturbance of speech/swallowing (dysarthria/dysphagia) • Cognitive and behavioural features common (similar to frontotemporal dementia) Signs • Wasting and fasciculation of muscles • Weakness of muscles of limbs, tongue, face and palate • Pyramidal tract involvement, causing spasticity, exaggerated tendon reflexes, extensor plantar responses • External ocular muscles and sphincters usually remain intact • No objective sensory deficit • Evidence of cognitive impairment with frontotemporal dominance Course • Symptoms often begin focally in one part and spread gradually but relentlessly to become widespread Fig. 25.33 Patterns of involvement in motor neuron disease. (LMN = lower motor neuron; UMN = upper motor neuron) Motor neuron disease Primary lateral sclerosis Progressive muscular atrophy Predominantly LMN Weakness and wasting of distal limb muscles initially Fasciculation Tendon reflexes may be present

Mixed LMN and UMN Distal and proximal muscle wasting and weakness Fasciculation Spasticity, exaggerated reflexes, extensor plantars Bulbar and pseudobulbar palsy follow eventually Pyramidal tract features may predominate Predominantly UMN Spasticity-few lower motor neuron signs Gradual progression Predominantly cranial nerves Early involvement of tongue, palate and pharyngeal muscles Dysarthria/dysphagia Wasting and fasciculation of tongue Pyramidal signs may be present Progressive bulbar palsy Amyotrophic lateral sclerosis motor neuron signs (e.g. brisk reflexes in wasted, fasciculating muscles) without sensory involvement (Fig. 25.33). Cognitive impairment is under-recognised in MND: up to 50% will have a mainly executive impairment on formal testing, and around 10% develop a frontotemporal dementia (FTD). About 10% of patients presenting with FTD will develop ALS within a few years of dementia onset. Even with treatment, MND is relentlessly progressive, but median survival is improved with specialist follow-up offering non-invasive ventilation, feeding measures and access to pharmacological treatment. Investigations Clinical features are often typical but alternative diagnoses should be excluded. Exclusion of treatable causes, such as immunemediated multifocal motor neuropathy with conduction block (p. 1140) and cervical myeloradiculopathy, is essential. Blood

1118 • NEUROLOGY Where specific immunisation is not employed, the mumps virus is a common cause. Clinical features Viral meningitis occurs mainly in children or young adults, with acute onset of headache and irritability and the rapid development of meningism. The headache is usually the most severe feature. There may be a high pyrexia but focal neurological signs are rare. Investigations The diagnosis is made by lumbar puncture. CSF usually contains an excess of lymphocytes. While glucose and protein levels are commonly normal, the latter may be raised. It is important to verify that the patient has not received antibiotics (for whatever cause) prior to the lumbar puncture, as CSF lymphocytosis can also be found in partially treated bacterial meningitis. Management There is no specific treatment and the condition is usually benign and self-limiting. The patient should be treated symptomatically in a quiet environment. Recovery usually occurs within days, although a lymphocytic pleocytosis may persist in the CSF. Meningitis may also occur as a complication of a systemic viral infection such as mumps, measles, infectious mononucleosis, herpes zoster and hepatitis. Whatever the virus, complete recovery without specific therapy is the rule. Bacterial meningitis Many bacteria can cause meningitis but geographical patterns vary, as does age-related sensitivity (Box 25.63). In the 'meningitis belt' of sub-Saharan Africa, drought and dust storms are often associated with meningococcal outbreaks (Harmattan meningitis). Bacterial meningitis is usually part of a bacteraemic illness, although direct spread from an adjacent focus of infection in the ear, skull fracture or sinus can be causative. Antibiotics have rendered this less common but mortality and morbidity remain high (fungus or parasite), and whether the infection is acute or chronic. The major infections of the nervous system are listed in Box 25.61. The frequency of these varies geographically. Helminthic infections, such as cysticercosis and hydatid disease, and protozoal infections are described in Chapter 11. Meningitis Acute infection of the meninges presents with a characteristic combination of pyrexia, headache and meningism. Meningism consists of headache, photophobia and stiffness of the neck, often accompanied by other signs of meningeal irritation, including Kernig's sign (extension at the knee with the hip joint flexed causes spasm in the hamstring muscles) and Brudzinski's sign (passive flexion of the neck causes flexion of the hips and knees). Meningism is not specific to meningitis and can occur in patients with subarachnoid haemorrhage. The severity of clinical features varies with the causative organism, as does the presence of other features such as a rash. Abnormalities in the CSF (see Box 25.6, p. 1078) are important in distinguishing the cause of meningitis. Causes of meningitis are listed in

Box 25.62. Viral meningitis Viruses are the most common cause of meningitis, usually resulting in a benign and self-limiting illness requiring no specific therapy. It is much less serious than bacterial meningitis unless there is associated encephalitis. A number of viruses can cause meningitis (see Box 25.62), the most common being enteroviruses. 25.62 Causes of meningitis Infective Bacteria (see Box 25.63) Viruses • Enteroviruses (echo, Coxsackie, polio) • Mumps • Influenza • Herpes simplex • Varicella zoster • Epstein–Barr • HIV • Lymphocytic choriomeningitis • Mollaret’s meningitis (herpes simplex virus type 2) Protozoa and parasites • Cysticerci • Amoeba Fungi • Cryptococcus neoformans • Candida • Histoplasma • Blastomyces • Coccidioides • Sporothrix Non-infective (‘sterile’) Malignant disease • Breast cancer • Bronchial cancer • Leukaemia • Lymphoma Inflammatory disease (may be recurrent) • Sarcoidosis • Systemic lupus erythematosus • Behçet’s disease 25.61 Infections of the nervous system Bacterial infections • Meningitis • Suppurative encephalitis • Brain abscess • Paravertebral (epidural) abscess • Tuberculosis (p. 588) • Neurosyphilis • Leprosy (Hansen’s disease) (peripheral nerves)* • Diphtheria (peripheral nerves)* • Tetanus (motor cells) Viral infections • Meningitis • Encephalitis • Transverse myelitis • Progressive multifocal leucoencephalopathy • Poliomyelitis • Subacute sclerosing panencephalitis (late sequel) • Rabies • HIV infection (Ch. 12) Prion diseases • Creutzfeldt–Jakob disease • Kuru Protozoal infections • Malaria* • Toxoplasmosis (in immune-suppressed)* • Trypanosomiasis* • Amoebic abscess* Helminthic infections • Schistosomiasis (spinal cord)* • Cysticercosis* • Hydatid disease* • Strongyloidiasis* Fungal infections • Candida meningitis or brain abscess • Cryptococcal meningitis *These infections are discussed in Chapter 11.

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with recurrent fever, sweating, joint pains and transient rash. It usually occurs in the middle-aged and elderly, and in those who have previously had a splenectomy. In pneumococcal and Haemophilus infections there may be an accompanying otitis media. Pneumococcal meningitis may be associated with pneumonia and occurs especially in older patients and alcoholics, as well as those with hyposplenism. Listeria monocytogenes is an increasing cause of meningitis and rhombencephalitis (brainstem encephalitis) in the immunosuppressed, people with diabetes, alcoholics and pregnant women (p. 259). It can also cause meningitis in neonates. Investigations Lumbar puncture is mandatory unless there are contraindications (p. 1077). If the patient is drowsy and has focal neurological signs or seizures, is immunosuppressed, has undergone recent neurosurgery or has suffered a head injury, it is wise to obtain a CT to exclude a mass lesion (such as a cerebral abscess) before lumbar puncture because of the risk of coning. This should not, however, delay treatment of presumed meningitis. If lumbar puncture is deferred or omitted, it is essential to take blood cultures and to start empirical treatment (Fig. 25.34). Lumbar 25.63 Bacterial causes of meningitis Age of onset Common Less common Neonate Gram-negative bacilli (Escherichia coli, Proteus) Group B streptococci Listeria monocytogenes Pre-school child Haemophilus influenzae Neisseria meningitidis (subtypes B, C, Y, W) Streptococcus pneumoniae Mycobacterium tuberculosis Older child and adult N. meningitidis (subtypes B, C, Y, W) Strep. pneumoniae L. monocytogenes M. tuberculosis Staphylococcus aureus (skull fracture) H. influenzae significant. An important factor in determining prognosis is early diagnosis and the prompt initiation of appropriate therapy. The meningococcus and other common causes of meningitis are normal commensals of the upper respiratory tract. New and potentially pathogenic strains are acquired by the air-borne route but close contact is necessary. Epidemics of meningococcal meningitis occur, particularly in cramped living conditions or where the climate is hot and dry. The

organism invades through the nasopharynx, producing sepsis and leading to meningitis.

Pathophysiology The meningococcus (*Neisseria meningitidis*) is now the most common cause of bacterial meningitis in Western Europe after *Streptococcus pneumoniae*, while in the USA *Haemophilus influenzae* remains common. In India, *H. influenzae* B and *Strep. pneumoniae* are probably the most common causes of bacterial meningitis, especially in children. *Streptococcus suis* is a rare zoonotic cause of meningitis associated with porcine contact. Infection stimulates an immune response, causing the pia-arachnoid membrane to become congested and infiltrated with inflammatory cells. Pus then forms in layers, which may later organise to form adhesions. These may obstruct the free flow of CSF, leading to hydrocephalus, or they may damage the cranial nerves at the base of the brain. Hearing loss is a frequent complication. The CSF pressure rises rapidly, the protein content increases, and there is a cellular reaction that varies in type and severity according to the nature of the inflammation and the causative organism. An obliterative endarteritis of the leptomeningeal arteries passing through the meningeal exudate may produce secondary cerebral infarction. Pneumococcal meningitis is often associated with a very purulent CSF and a high mortality, especially in older adults. Clinical features Headache, drowsiness, fever and neck stiffness are the usual presenting features. In severe bacterial meningitis the patient may be comatose, later developing focal neurological signs. Ninety per cent of patients with meningococcal meningitis will have two of the following: fever, neck stiffness, altered consciousness and rash. When accompanied by sepsis, presenting signs may evolve rapidly, with abrupt onset of obtundation due to cerebral oedema. Complications of meningococcal sepsis are listed in Box 25.64. Chronic meningococcaemia is a rare condition in which the patient can be unwell for weeks or even months

25.64 Complications of meningococcal sepsis

- Meningitis
- Rash (morbilliform, petechial or purpuric)
- Shock
- Intravascular coagulation
- Renal failure
- Peripheral gangrene
- Arthritis (septic or reactive)
- Pericarditis (septic or reactive)

Fig. 25.34 The investigation of meningitis.

Resuscitate and stabilise patient Initial tests (blood culture and polymerase chain reaction, throat swab) Empirical antibiotics (Box 25.65) Transfer to critical care facility Drowsy, focal signs? (possible mass lesion, hydrocephalus or cerebral oedema) No Yes Lumbar puncture No other contraindication to lumbar puncture Computed tomography brain No mass lesion, hydrocephalus or other contraindication to lumbar puncture seen

1120 • NEUROLOGY The only contraindication is a history of penicillin anaphylaxis. Recommended empirical therapies are outlined in Box 25.65, and the preferred antibiotic when the organism is known after CSF examination is stipulated in Box 25.66. Adjunctive glucocorticoid therapy is useful in reducing hearing loss and neurological sequelae in both children and adults in developed countries where the incidence of penicillin resistance is low, but its role where there are high rates of resistance or in countries where there are high rates of untreated HIV is unclear. In meningococcal disease, mortality is doubled if the patient presents with features of sepsis rather than meningitis. Individuals likely to require intensive care facilities and expertise include those with cardiac, respiratory or renal involvement, and those with CNS depression prejudicing the airway. Early endotracheal intubation and mechanical ventilation protect the airway and may prevent the development of the acute respiratory distress syndrome (ARDS, p. 198). Adverse prognostic features include hypotensive shock, a rapidly developing rash, a haemorrhagic diathesis, multisystem failure and age over 60 years. Prevention of meningococcal infection Close contacts of patients with meningococcal infection (Box 25.67) should be given 2 days of oral rifampicin. In adults, a single dose of ciprofloxacin is an alternative. If not treated with ceftriaxone, the index case should be given similar treatment to clear infection from the nasopharynx before

hospital discharge. Vaccines are available for most meningococcal subgroups but not group B, which is one of the most common serogroups isolated in many countries. Tuberculous meningitis is now uncommon in developed countries except in immunocompromised individuals, although it is still seen in those born in endemic areas and in developing countries. It is seen more frequently as a secondary infection in patients with the acquired immunodeficiency syndrome (AIDS). Pathophysiology Tuberculous meningitis most commonly occurs shortly after a primary infection in childhood or as part of miliary tuberculosis (p. 588). The usual local source of infection is a caseous focus in puncture will help differentiate the causative organism: in bacterial meningitis the CSF is cloudy (turbid) due to the presence of many neutrophils (often $> 1000 \times 10^6$ cells/L), the protein content is significantly elevated and the glucose reduced. Gram film and culture may allow identification of the organism. Blood cultures may be positive. PCR techniques can be used on both blood and CSF to identify bacterial DNA. These methods are useful in detecting meningococcal infection and in typing the organism. Management There is an untreated mortality rate of around 80%, so action must be swift. In suspected bacterial meningitis the patient should be given parenteral benzylpenicillin immediately (intravenous is preferable) and prompt hospital admission should be arranged.

25.65

Treatment of pyogenic meningitis of unknown cause

1. Adults aged 18–50 years with or without a typical meningococcal rash • Cefotaxime 2 g IV 4 times daily or • Ceftriaxone 2 g IV twice daily
2. Patients in whom penicillin-resistant pneumococcal infection is suspected, or in areas with a significant incidence of penicillin resistance in the community As for (1) but add: • Vancomycin 1 g IV twice daily or • Rifampicin 600 mg IV twice daily
3. Adults aged > 50 years and those in whom *Listeria monocytogenes* infection is suspected (brainstem signs, immunosuppression, diabetic, alcoholic) As for (1) but add: • Ampicillin 2 g IV 6 times daily or • Co-trimoxazole 5 mg/kg IV daily in two divided doses
4. Patients with a clear history of anaphylaxis to β -lactams • Chloramphenicol 25 mg/kg IV 4 times daily plus • Vancomycin 1 g IV twice daily
5. Adjunctive treatment (see text) • Dexamethasone 0.15 mg/kg 4 times daily for 2–4 days

25.66 Chemotherapy of bacterial meningitis when the cause is known Pathogen Regimen

of choice Alternative agents
Neisseria meningitidis Benzylpenicillin 2.4 g IV 6 times daily for 5–7 days Cefuroxime, ampicillin Chloramphenicol*
Streptococcus pneumoniae (sensitive to β -lactams, MIC < 1 mg/L) Cefotaxime 2 g IV 4 times daily or Ceftriaxone 2 g IV twice daily for 10–14 days Chloramphenicol*
Strep. pneumoniae (resistant to β -lactams) As for sensitive strains but add: Vancomycin 1 g IV twice daily or Rifampicin 600 mg IV twice daily
 Vancomycin plus rifampicin*
Moxifloxacin *Gatifloxacin* *Haemophilus influenzae* Cefotaxime 2 g IV 4 times daily or Ceftriaxone 2 g IV twice daily for 10–14 days
 Chloramphenicol*
Listeria monocytogenes Ampicillin 2 g IV 6 times daily plus Gentamicin 5 mg/kg IV daily
 Ampicillin 2 g IV 4-hourly plus Co-trimoxazole 50 mg/kg daily in two divided doses
Streptococcus suis Cefotaxime 2 g IV 4 times daily or Ceftriaxone 2 g IV twice daily for 10–14 days
 Chloramphenicol*
 *For patients with a history of anaphylaxis to β -lactam antibiotics. (MIC = minimum inhibitory concentration)

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protein and a marked fall in glucose. The tubercle bacillus may be detected in a smear of the centrifuged deposit from the CSF but a negative result does not exclude the diagnosis. The CSF

should be cultured but, as this result will not be known for up to 6 weeks, treatment must be started without waiting for confirmation. Brain imaging may show hydrocephalus, brisk meningeal enhancement on enhanced CT or MRI, and/or an intracranial tuberculoma. Management As soon as the diagnosis is made or strongly suspected, chemotherapy should be started using one of the regimens that include pyrazinamide, described on page 592. The use of glucocorticoids in addition to antituberculous therapy has been controversial. Recent evidence suggests that it improves mortality, especially if given early, but not focal neurological damage. Surgical ventricular drainage may be needed if obstructive hydrocephalus develops. Skilled nursing is essential during the acute phase of the illness, and adequate hydration and nutrition must be maintained. Other forms of meningitis

Fungal meningitis (especially cryptococcosis; p. 302) usually occurs in patients who are immunosuppressed and is a recognised complication of HIV infection (p. 321). The CSF findings are similar to those of tuberculous meningitis, but the diagnosis can be confirmed by microscopy or specific serological tests. In some areas, meningitis may be caused by spirochaetes (leptospirosis, Lyme disease and syphilis; pp. 257, 255 and 337), rickettsiae (typhus fever; p. 270) or protozoa (amoebiasis; p. 286). Meningitis can also be due to non-infective pathologies. This is seen in recurrent aseptic meningitis resulting from systemic lupus erythematosus (SLE), Behçet's disease or sarcoidosis, as well as a condition of previously unknown origin known as Mollaret's syndrome, in which the recurrent meningitis is associated with epithelioid cells in the spinal fluid ('Mollaret' cells). Recent evidence suggests that this condition may be due to herpes simplex virus type 2 and is therefore infective after all. Meningitis can also be caused by direct invasion of the meninges by neoplastic cells ('malignant meningitis'; see Box 25.62).

Parenchymal viral infections Infection of the substance of the nervous system will produce symptoms of focal dysfunction (deficits and/or seizures) with general signs of infection, depending on the acuteness of the infection and the type of organism.

Viral encephalitis A range of viruses can cause encephalitis but only a minority of patients report recent systemic viral infection. In Europe, the most serious cause of viral encephalitis is herpes simplex (p. 247), which probably reaches the brain via the olfactory nerves. Varicella zoster is also an important cause. The development of effective therapy for some forms of encephalitis has increased the importance of clinical diagnosis and virological examination of the CSF. In some parts of the world, viruses transmitted by mosquitoes and ticks (arboviruses) are an important cause of encephalitis. The epidemiology of some of these infections is changing.

Japanese encephalitis (p. 249) has spread relentlessly across Asia to Australia, and there have been outbreaks of West Nile encephalitis in Romania, Israel and New York. Zika virus has the meninges or brain substance adjacent to the CSF pathway. The brain is covered by a greenish, gelatinous exudate, especially around the base, and numerous scattered tubercles are found on the meninges.

Clinical features The clinical features and staging criteria are listed in Box 25.68. Onset is much slower than in other bacterial meningitis – over 2–8 weeks. If untreated, tuberculous meningitis is fatal in a few weeks but complete recovery is usual if treatment is started at stage I (Box 25.68). When treatment is initiated later, the rate of death or serious neurological deficit may be as high as 30%.

Investigations Lumbar puncture should be performed if the diagnosis is suspected. The CSF is under increased pressure. It is usually clear but, when allowed to stand, a fine clot ('spider web') may form. The fluid contains up to 500×10^6 cells/L, predominantly lymphocytes, but can contain neutrophils. There is a rise in

25.67 Chemoprophylaxis following meningococcal exposure Close contacts warranting chemoprophylaxis

- Household contacts (including persons who ate or slept in the same dwelling as the patient during the 7 days prior to disease onset)
- Child-care and nursery-school contacts
- Persons having contact with patient's oral secretions during the 7 days prior to disease onset: Kissing Sharing of toothbrushes Sharing of

eating utensils Mouth-to-mouth resuscitation Unprotected contact during endotracheal intubation • Aircraft contacts for persons seated next to the patient for > 8 hrs Persons at low risk in whom chemoprophylaxis is not recommended • Casual contact (e.g. at school or work) without direct exposure to patient's oral secretions • Indirect contact only (contact with a high-risk contact and not a case) • Health-care worker without direct exposure to patient's oral secretions 25.68 Clinical features and staging of tuberculous meningitis Symptoms • Headache • Vomiting • Low-grade fever • Lassitude • Depression • Delirium • Behaviour changes Signs • Meningism (may be absent) • Oculomotor palsies • Papilloedema • Depression of conscious level • Focal hemisphere signs Staging of severity • Stage I (early): non-specific symptoms and signs without alteration of consciousness • Stage II (intermediate): altered consciousness without coma or delirium plus minor focal neurological signs • Stage III (advanced): stupor or coma, severe neurological deficits, seizures or abnormal movements

1122 • NEUROLOGY usually conveyed by saliva through bites or licks on abrasions or on intact mucous membranes. Humans are most frequently infected from dogs and bats. In Europe, the maintenance host is the fox. The incubation period varies in humans from a minimum of 9 days to many months but is usually between 4 and 8 weeks. Severe bites, especially if on the head or neck, are associated with shorter incubation periods. Human rabies is a rare disease, even in endemic areas. However, because it is usually fatal, major efforts are directed at limiting its spread and preventing its importation into uninfected countries, such as the UK. Clinical features At the onset there may be fever, and paraesthesia at the site of the bite. A prodromal period of 1–10 days, during which the patient becomes increasingly anxious, leads to the characteristic 'hydrophobia'. Although the patient is thirsty, attempts at drinking provoke violent contractions of the diaphragm and other inspiratory muscles. Delusions and hallucinations may develop, accompanied by spitting, biting and mania, with lucid intervals in which the patient is markedly anxious. Cranial nerve lesions develop and terminal hyperpyrexia is common. Death ensues, usually within a week of the onset of symptoms. Investigations During life, the diagnosis is usually made on clinical grounds but rapid immunofluorescent techniques can detect antigen in corneal impression smears or skin biopsies. Management Established disease Only a few patients with established rabies have survived. All received some post-exposure prophylaxis (see below) and needed intensive care facilities to control cardiac and respiratory failure. Otherwise, only palliative treatment is possible once symptoms have appeared. The patient should be heavily sedated with diazepam, supplemented by chlorpromazine if needed. Nutrition and fluids should be given intravenously or through a gastrostomy. Pre-exposure prophylaxis Pre-exposure prophylaxis is required by those who handle potentially infected animals professionally, work with rabies virus in laboratories or live at special risk in rabies-endemic areas. Protection is afforded by intradermal injections of human diploid cell strain vaccine, or two intramuscular injections given 4 weeks apart, followed by yearly boosters. Post-exposure prophylaxis The wounds should be thoroughly cleaned, preferably with a quaternary ammonium detergent or soap; damaged tissues should be excised and the wound left unsutured. Rabies can usually be prevented if treatment is started within a day or two of biting. Delayed treatment may still be of value. For maximum protection, hyperimmune serum and vaccine are required. The safest antirabies antiserum is human rabies immunoglobulin. The dose is 20 IU/kg body weight; half is infiltrated around the bite and half is given intramuscularly at a different site from the vaccine. Hyperimmune animal serum may be used but hypersensitivity reactions, including anaphylaxis, are common. The safest vaccine, free of complications, is human diploid cell strain vaccine; 1.0 mL is given intramuscularly on days 0, 3, 7, 14, 30 and 90. In

developing countries, where human rabies globulin may not be obtainable, 0.1 mL of vaccine may be given intramuscularly in the last decades and become a more significant global health problem. HIV may cause encephalitis with a subacute or chronic presentation but occasionally has an acute presentation with seroconversion. Pathophysiology The infection provokes an inflammatory response that involves the cortex, white matter, basal ganglia and brainstem. The distribution of lesions varies with the type of virus. For example, in herpes simplex encephalitis, the temporal lobes are usually primarily affected, whereas cytomegalovirus can involve the areas adjacent to the ventricles (ventriculitis). Inclusion bodies may be present in the neurons and glial cells, and there is an infiltration of polymorphonuclear cells in the perivascular space. There is neuronal degeneration and diffuse glial proliferation, often associated with cerebral oedema. Clinical features Viral encephalitis presents with acute onset of headache, fever, focal neurological signs (aphasia and/or hemiplegia, visual field defects) and seizures. Disturbance of consciousness ranging from drowsiness to deep coma supervenes early and may advance dramatically. Meningism occurs in many patients. Rabies presents a distinct clinical picture and is described below. Investigations Imaging by CT scan may show low-density lesions in the temporal lobes but MRI is more sensitive in detecting early abnormalities. Lumbar puncture should be performed once imaging has excluded a mass lesion. The CSF usually contains excess lymphocytes but polymorphonuclear cells may predominate in the early stages. The CSF may be normal in up to 10% of cases. Some viruses, including the West Nile virus, may cause a sustained neutrophilic CSF. The protein content may be elevated but the glucose is normal. The EEG is usually abnormal in the early stages, especially in herpes simplex encephalitis, with characteristic periodic slowwave activity in the temporal lobes. Virological investigations of the CSF, including PCR, may reveal the causative organism but treatment initiation should not await this. Management Optimum treatment for herpes simplex encephalitis (aciclovir 10 mg/kg IV 3 times daily for 2–3 weeks) has reduced mortality from 70% to around 10%. This should be given early to all patients suspected of having viral encephalitis. Some survivors will have residual epilepsy or cognitive impairment. For details of post-infectious encephalomyelitis, see page 1110. Antiepileptic treatment may be required (p. 1101) and raised intracranial pressure may indicate the need for dexamethasone. Brainstem encephalitis This presents with ataxia, dysarthria, diplopia or other cranial nerve palsies. The CSF is lymphocytic, with a normal glucose. The causative agent is presumed to be viral. However, *Listeria monocytogenes* may cause a similar syndrome with meningitis (and often a polymorphonuclear CSF pleocytosis) and requires specific treatment with ampicillin (500 mg 4 times daily; see Box 25.66). Rabies Rabies is caused by a rhabdovirus that infects the central nervous tissue and salivary glands of a wide range of mammals. It is

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not regain useful function. Second attacks are very rare but occasionally patients show late deterioration in muscle bulk and power many years after the initial infection (this is termed the 'post-polio syndrome'). Investigations The CSF shows a lymphocytic pleocytosis, a rise in protein and a normal sugar content. Poliomyelitis virus may be cultured from CSF and stool. Management Established disease In the early stages, bed rest is imperative because exercise appears to worsen the paralysis or precipitate it. At the onset of respiratory difficulties, a tracheostomy and ventilation are required. Subsequent treatment is by physiotherapy and orthopaedic measures. Prophylaxis Prevention of poliomyelitis is by immunisation with live (Sabin) vaccine. In developed countries where polio is now very rare, the live vaccine has been replaced by the killed vaccine in childhood

immunisation schedules. Herpes zoster (shingles) Herpes zoster is the result of reactivation of the varicella zoster virus that has lain dormant in a nerve root ganglion following chickenpox earlier in life. Reactivation may be spontaneous (as usually occurs in the middle-aged or elderly) or due to immunosuppression (as in patients with diabetes, malignant disease or AIDS). Full details are given on page 239.

Subacute sclerosing panencephalitis This is a rare, chronic, progressive and eventually fatal complication of measles, presumably a result of an inability of the nervous system to eradicate the virus. It occurs in children and adolescents, usually many years after the primary virus infection. There is generalised neurological deterioration and onset is insidious, with intellectual deterioration, apathy and clumsiness, followed by myoclonic jerks, rigidity and dementia. The CSF may show a mild lymphocytic pleocytosis and the EEG demonstrates characteristic periodic bursts of triphasic waves. Although there is persistent measles-specific IgG in serum and CSF, antiviral therapy is ineffective and death ensues within a few years.

Progressive multifocal leucoencephalopathy This was originally described as a rare complication of lymphoma, leukaemia or carcinomatosis but has become more frequent as a feature of AIDS (p. 319) or secondary to immunosuppression, e.g. following organ transplantation or use of disease-modifying drugs for MS. It is an infection of oligodendrocytes by human polyomavirus JC, causing widespread demyelination of the white matter of the cerebral hemispheres. Clinical signs include dementia, hemiparesis and aphasia, which progress rapidly, usually leading to death within weeks or months. Areas of low density in the white matter are seen on CT but MRI is more sensitive, showing diffuse high signal in the cerebral white matter on T2-weighted images. The only treatment available is restoration of the immune response (by treating AIDS or reversing immunosuppression).

intradermally into eight sites on day 1, with single boosters on days 7 and 28. Where human products are not available and when risk of rabies is slight (licks on the skin, or minor bites of covered arms or legs), it may be justifiable to delay starting treatment while observing the biting animal or awaiting examination of its brain, rather than use the older vaccine.

Poliomyelitis Pathophysiology Disease is caused by one of three polioviruses, which constitute a subgroup of the enteroviruses. Poliomyelitis has become much less common in developed countries following the widespread use of oral vaccines but is still a problem in the developing world, especially parts of Africa. Infection usually occurs through the nasopharynx. The virus causes a lymphocytic meningitis and infects the grey matter of the spinal cord, brainstem and cortex. There is a particular propensity to damage anterior horn cells, especially in the lumbar segments. Clinical features The incubation period is 7–14 days. Figure 25.35 illustrates the various features of the infection. Many patients recover fully after the initial phase of a few days of mild fever and headache. In other individuals, after a week of well-being, there is a recurrence of pyrexia, headache and meningism. Weakness may start later in one muscle group and can progress to widespread paresis. Respiratory failure may supervene if intercostal muscles are paralysed or the medullary motor nuclei are involved. Epidemics vary widely in terms of the incidence of non-paralytic cases and in mortality rate. Death occurs from respiratory paralysis. Muscle weakness is maximal at the end of the first week and gradual recovery may then take place over several months. Muscles showing no signs of recovery after a month will probably Fig. 25.35 Poliomyelitis. Possible consequences of infection.

Infection	Asymptomatic seroconversion	Aseptic meningitis (encephalitis)	Febrile illness
Anterior horn cell infection	Recovery	Lower motor neuron paralysis	Recovery
Death	Residual disability	Complete	Late deterioration

Anterior horn cell infection Recovery Lower motor neuron paralysis Recovery Death Residual disability Complete Late deterioration

1124 • NEUROLOGY Parenchymal bacterial infections Cerebral abscess Bacteria may enter the cerebral substance through penetrating injury, by direct spread from paranasal sinuses or the middle ear, or secondary to sepsis. Untreated congenital heart disease is a recognised risk factor. The site of abscess formation and the likely causative organism are both related to the source of infection (Box 25.69). Initial infection leads to local suppuration followed by loculation of pus within a surrounding wall of gliosis, which in a chronic abscess may form a tough capsule.

Haematogenous spread may lead to multiple abscesses. Clinical features A cerebral abscess may present acutely with fever, headache, meningism and drowsiness, but more commonly presents over days or weeks as a cerebral mass lesion with little or no evidence of infection. Seizures, raised intracranial pressure and focal hemisphere signs occur alone or in combination. Distinction from a cerebral tumour may be impossible on clinical grounds. Investigations Lumbar puncture is potentially hazardous in the presence of raised intracranial pressure and CT should always precede it. CT reveals single or multiple low-density areas, which show ring enhancement with contrast and surrounding cerebral oedema (Fig. 25.36). There may be an elevated white blood cell count and ESR in patients with active local infection. The possibility of cerebral toxoplasmosis or tuberculous disease secondary to HIV infection (p. 320) should always be considered. Management and prognosis Antimicrobial therapy is indicated once the diagnosis is made. The likely source of infection should guide the choice of antibiotic (see Box 25.69). In neurosurgical patients, the addition of vancomycin should be considered. Surgical drainage by burr-hole aspiration or excision may be necessary, especially where the presence of a capsule may lead to a persistent focus of infection. Epilepsy frequently develops and is often resistant to treatment. Despite advances in therapy, mortality remains 10–20% and may partly relate to delay in diagnosis and treatment.

25.69 Aetiology and treatment of bacterial cerebral abscess

Site of abscess	Source of infection	Likely organisms	Recommended treatment
Frontal lobe	Paranasal sinuses	Teeth	Streptococci
Anaerobes	Cefotaxime 2–3 g IV 4 times daily plus Metronidazole 500 mg IV 3 times daily	Temporal lobe	Middle ear
Streptococci	Enterobacteriaceae	Ampicillin 2–3 g IV 3 times daily plus Metronidazole 500 mg IV 3 times daily plus either Cerebellum	Sphenoid sinus
Mastoid/middle ear	Pseudomonas spp.	Anaerobes	Ceftazidime 2 g IV 3 times daily or Gentamicin* 5 mg/kg IV daily
Any site	Penetrating trauma	Staphylococci	Flucloxacillin 2–3 g IV 4 times daily or Cefuroxime 1.5 g IV 3 times daily
Multiple	Metastatic and cryptogenic	Streptococci	Anaerobes
Benzyllpenicillin 1.8–2.4 g IV 4 times daily if endocarditis or cyanotic heart disease	Otherwise	cefotaxime 2–3 g IV 4 times daily plus Metronidazole 500 mg IV 3 times daily	*Monitor gentamicin levels.

Fig. 25.36 Right temporal cerebral abscess (arrows), with surrounding oedema and midline shift to the left. A Unenhanced computed tomography (CT) image. B Contrast-enhanced CT image. A B

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involvement is suspected. Active disease is suggested by an elevated cell count, usually lymphocytic, and the protein content may be elevated to 0.5–1.0 g/L with an increased gamma globulin fraction. Serological tests in CSF are usually positive but progressive disease can occur with negative CSF serology. Management The injection of procaine benzylpenicillin (procaine penicillin) and probenecid for 17 days is essential in the treatment of neurosyphilis of all types (p. 338). Further courses of penicillin must be given if symptoms are not relieved, if the condition continues to advance or if the CSF continues to show signs of active disease. The cell count returns to normal within 3 months of completion of treatment, but the elevated protein takes longer to subside and some serological tests may never revert to normal. Evidence of clinical progression at

any time is an indication for renewed treatment. Diseases caused by bacterial toxins

Tetanus

This disease results from infection with *Clostridium tetani*, a commensal in the gut of humans and domestic animals that is found in soil. Infection enters the body through wounds, which may be trivial. It is rare in the UK, occurring mostly in gardeners and farmers, but a recent increase has been seen in intravenous drug misusers. By contrast, the disease is common in many developing countries, where dust contains spores derived from animal and human excreta. Unhygienic practices soon after birth may lead to infection of the umbilical stump or site of circumcision, causing tetanus neonatorum. Tetanus is still one of the major killers of adults, children and neonates in developing countries, where the mortality rate can be nearly 100% in the newborn and around 40% in others. In circumstances unfavourable to growth of the organism, spores are formed and these may remain dormant for years in the soil. Spores germinate and bacilli multiply only in the anaerobic conditions that occur in areas of tissue necrosis or if the oxygen tension is lowered by the presence of other organisms, particularly if aerobic. The bacilli remain localised but produce an exotoxin with an affinity for motor nerve endings and motor nerve cells. Subdural empyema This is a rare complication of frontal sinusitis, osteomyelitis of the skull vault or middle ear disease. A collection of pus in the subdural space spreads over the surface of the hemisphere, causing underlying cortical oedema or thrombophlebitis. Patients present with severe pain in the face or head and pyrexia, often with a history of preceding paranasal sinus or ear infection. The patient then becomes drowsy, with seizures and focal signs such as a progressive hemiparesis. The diagnosis rests on a strong clinical suspicion in patients with a local focus of infection. Careful assessment with contrast-enhanced CT or MRI may show a subdural collection with underlying cerebral oedema. Management requires aspiration of pus via a burr hole and appropriate parenteral antibiotics. Any local source of infection must be treated to prevent re-infection.

Spinal epidural abscess

The characteristic clinical features are pain in a root distribution and progressive transverse spinal cord syndrome with paraparesis, sensory impairment and sphincter dysfunction. Features of the primary focus of infection may be less obvious and thus can be overlooked. The resurgence of resistant staphylococcal infection and intravenous drug misuse has contributed to a recent marked rise in incidence. X-ray changes occur late, if present, so MRI or myelography should precede urgent neurosurgical intervention. Decompressive laminectomy with abscess drainage relieves the pressure on the dura. Organisms may be grown from the pus or blood. Surgery, together with appropriate antibiotics, may prevent complete and irreversible paraplegia.

Lyme disease

Infection with *Borrelia burgdorferi* can cause numerous neurological problems, including polyradiculopathy, meningitis, encephalitis and mononeuritis multiplex (p. 255).

Neurosyphilis

Neurosyphilis may present as an acute or chronic process and may involve the meninges, blood vessels and/or parenchyma of the brain and spinal cord. The decade to 2008 saw a 10-fold increase in the incidence of syphilis, mostly as a result of misguided relaxation of safe sex measures with the advent of effective antiretroviral treatments for AIDS. Paralleled future increases in neurosyphilis are inevitable. The clinical manifestations are diverse and early diagnosis and treatment are essential.

Clinical features

The clinical and pathological features of the three most common presentations are summarised in Box 25.70. Neurological examination reveals signs indicative of the anatomical localisation of lesions. Delusions of grandeur suggest general paresis of the insane, but more commonly there is simply progressive dementia. Small and irregular pupils that react to convergence but not light, as described by Argyll Robertson (see Box 25.22, p. 1092), may accompany any neurosyphilitic syndrome but most commonly tabes dorsalis. Investigations

Routine screening for syphilis

is warranted in many neurological patients. Treponemal antibodies (p. 338) are positive in the serum in most patients, but CSF examination is essential if neurological

25.70 Clinical and pathological features of neurosyphilis Type and interval from primary infection
 Pathology Clinical features Meningovascular (5 years)* Endarteritis obliterans Meningeal exudate
 Granuloma (gumma) Stroke Cranial nerve palsies Seizures/mass lesion General paralysis of the
 insane (5–15 years)* Degeneration in cerebral cortex/ cerebral atrophy Thickened meninges
 Dementia Tremor Bilateral upper motor signs Tabes dorsalis (5–20 years)* Degeneration of sensory
 neurons Wasting of dorsal columns Optic atrophy Lightning pains Sensory ataxia Visual failure
 Abdominal crises Incontinence Trophic changes Any of the above Argyll Robertson pupils (p. 1092)

1126 • NEUROLOGY Prevention Tetanus can be prevented by immunisation and prompt treatment of contaminated wounds by débridement and antibiotics. In patients with a contaminated wound, the immediate danger of tetanus can be greatly reduced by the injection of 1200 mg of penicillin followed by a 7-day course of oral penicillin. For those allergic to penicillin, erythromycin should be used. When the risk of tetanus is judged to be present, an intramuscular injection of 250 IU of human tetanus antitoxin should be given, along with toxoid, which should be repeated 1 month and 6 months later. For those already immunised, only a booster dose of toxoid is required.

Botulism Botulism is caused by the neurotoxins of *Clostridium botulinum*, which are extremely potent and cause disease after ingestion of even picogram amounts. Its classical form is an acute onset of bilateral cranial neuropathies associated with symmetric descending weakness. Anaerobic conditions are necessary for the organism's growth. It may contaminate and thrive in many foodstuffs, where sealing and preserving provide the requisite conditions. Contaminated honey has been implicated in infant botulism, in which the organism colonises the gastrointestinal tract. Wound botulism is a growing problem in injection drug-users. The toxin causes predominantly bulbar and ocular palsies (difficulty in swallowing, blurred or double vision, ptosis), progressing to limb weakness and respiratory paralysis. Criteria for the clinical diagnosis are shown in Box 25.72. The anterior horn cells are affected after the exotoxin has passed into the blood stream and their involvement results in rigidity and convulsions. Symptoms first appear from 2 days to several weeks after injury: the shorter the incubation period, the more severe the attack and the worse the prognosis. Clinical features By far the most important early symptom is trismus – spasm of the masseter muscles, which causes difficulty in opening the mouth and in masticating; hence the name 'lockjaw'. Lockjaw in tetanus is painless, unlike the spasm of the masseters due to dental abscess, septic throat or other causes. Conditions that can mimic tetanus include hysteria and phenothiazine overdosage, or overdose in intravenous drug misusers. In tetanus, the tonic rigidity spreads to involve the muscles of the face, neck and trunk. Contraction of the frontalis and the muscles at the angles of the mouth leads to the so-called 'risus sardonicus'. There is rigidity of the muscles at the neck and trunk of varying degree. The back is usually slightly arched ('opisthotonus') and there is a board-like abdominal wall. In the more severe cases, violent spasms lasting for a few seconds to 3–4 minutes occur spontaneously, or may be induced by stimuli such as movement or noise. These episodes are painful and exhausting, and suggest a grave outlook, especially if they appear soon after the onset of symptoms. They gradually increase in frequency and severity for about 1 week and the patient may die from exhaustion, asphyxia or aspiration pneumonia. In less severe illness, periods of spasm may not commence until a week or so after the first sign of rigidity, and in very mild infections they may never appear. Autonomic involvement may cause cardiovascular complications, such as hypertension. Rarely, the only manifestation of the disease may be 'local tetanus' – stiffness or spasm of the muscles near the infected wound – and the prognosis is good if treatment is commenced at this stage. Investigations The diagnosis is made on clinical grounds. It is rarely possible to isolate the infecting organism from the original

locus of entry. Management Established disease Management of established disease should begin as soon as possible, as shown in Box 25.71. 25.71 Treatment of tetanus Neutralise absorbed toxin

- Give IV injection of 3000 IU of human tetanus antitoxin Prevent further toxin production
- Débride wound
- Give benzylpenicillin 600 mg IV 4 times daily (metronidazole if patient is allergic to penicillin)
- Control spasms
- Nurse in a quiet room
- Avoid unnecessary stimuli
- Give IV diazepam
- If spasms continue, paralyse patient and ventilate

General measures

- Maintain hydration and nutrition
- Treat secondary infections

25.72 US Centers for Disease Control (CDC) definition of botulism Three main syndromes

- Infantile
- Food-borne
- Wound infection

Clinical features

- Absence of fever
- Symmetrical neurological deficits
- Patient remains responsive
- Normal or slow heart rate and normal blood pressure
- No sensory deficits with the exception of blurred vision

Management includes assisted ventilation and general supportive measures until the toxin eventually dissociates from nerve endings 6–8 weeks following ingestion. A polyvalent antitoxin is available for post-exposure prophylaxis and for the treatment of suspected botulism. It specifically neutralises toxin types A, B and E and is not effective against infantile botulism (in which active growth of the organism allows continued toxin production). Prion diseases Prions are unique amongst infectious agents in that they are devoid of any nucleic acid. They appear to be transmitted by acquisition of a normal mammalian protein (prion protein, PrPC) that is in an abnormal conformation (PrPSC, containing an excess of beta-sheet protein); the abnormal protein inhibits the 26S

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earlier. Patients affected by vCJD are typically younger than those with sporadic CJD and present with neuropsychiatric changes and sensory symptoms in the limbs, followed by ataxia, dementia and death. Progression is slightly slower than in patients with sporadic CJD (mean time to death is over a year). Characteristic EEG changes are not present, but MRI brain scans show characteristic high-signal changes in the pulvinar thalami in a high proportion of cases (Fig. 25.37). Brain histology is distinct, with very florid plaques containing the prion proteins. Abnormal prion protein has been identified in tonsil specimens from patients with vCJD, leading to the suggestion that the disease could be transmitted by reticulo-endothelial tissue (like TSEs in animals but unlike sporadic CJD in humans). It was the emergence of this form of the disorder that led to the changes in public health and farming policy in the UK; while the incidence of vCJD has declined dramatically, surveillance and research continue. Intracranial mass lesions and raised intracranial pressure Many different types of mass lesion may arise within the intracranial cavity (Box 25.74). In developing countries tuberculoma and other infections are frequent causes, but in the West intracranial haemorrhage and brain tumours are more common. The clinical features depend on the site of the mass, its nature and its rate of expansion. Symptoms and signs (see Box 25.75) are produced by a number of mechanisms. Raised intracranial pressure Raised intracranial pressure (RICP) may be caused by mass lesions, cerebral oedema, obstruction to CSF circulation leading proteasome, which can degrade misfolded proteins, leading to accumulation of the abnormally configured PrPSC protein instead of normal PrPC. The result is accumulation of protein that forms amyloid in the CNS, causing a transmissible spongiform encephalopathy (TSE) across several species. Human prion diseases (Box 25.73) are characterised by the histopathological triad of cortical spongiform change, neuronal cell loss and gliosis. Associated with these changes there is deposition of amyloid, made up of an altered form of a normally occurring protein, the prion protein. Prion proteins are not inactivated by cooking or conventional sterilisation, and transmission is thought to

occur by consumption of infected CNS tissue or by inoculation (e.g. via depth EEG electrodes, corneal grafts, cadaveric dura mater grafts and pooled cadaveric growth hormone preparations). The same diseases can occur in an inherited form, due to mutations in the PrP gene. The apparent transmission of bovine spongiform encephalopathy (BSE) to humans was thought to be responsible for the emergence of a new variant of CJD (vCJD) in the UK (see below). This outbreak led to nationwide precautionary measures, such as leucodepletion of all blood used for transfusion, and the mandatory use of disposable surgical instruments wherever possible for tonsillectomy, appendicectomy and ophthalmological procedures.

Creutzfeldt-Jakob disease Creutzfeldt-Jakob disease (CJD) is the best-characterised human TSE. Some 10% of cases arise from a mutation in the gene coding for the prion protein. The sporadic form is the most common, occurring in middle-aged to elderly patients. Clinical features usually involve a rapidly progressive dementia, with myoclonus and a characteristic EEG pattern (repetitive slow-wave complexes), although a number of other features, such as visual disturbance or ataxia, may also be seen. These are particularly common in CJD transmitted by inoculation (e.g. by infected dura mater grafts). Death occurs after a mean of 4–6 months. There is no effective treatment.

Variant Creutzfeldt-Jakob disease This type of CJD (vCJD) emerged in the late 1990s, affecting a small number of patients in the UK. The causative agent appears to be identical to that causing BSE in cows, and the disease may have been a result of the epidemic of BSE in the UK a decade.

25.73 Prion diseases affecting humans

Disease	Mechanism
Creutzfeldt-Jakob disease	Sporadic Unknown: spontaneous PrPC to PrPSC conversion or somatic mutation
Familial	Genetic: mutations in the PrP gene
Variant	Dietary ingestion: infection from bovine spongiform encephalopathy
Gerstmann-Sträussler-Scheinker disease	Genetic: mutations in the PrP gene
Fatal familial insomnia	Genetic: mutations in the PrP gene
Sporadic fatal insomnia	Genetic: spontaneous PrPC to PrPSC conversion or somatic mutation
Kuru	Dietary: ingestion of affected human brain

Fig. 25.37 Magnetic resonance imaging in variant Creutzfeldt-Jakob disease. Arrows indicate bilateral pulvinar hyperintensity.

1128 • NEUROLOGY a large hemisphere mass may cause ‘temporal coning’ (Fig. 25.38). This may stretch the 3rd and/or 6th cranial nerves or cause pressure on the contralateral cerebral peduncle (giving rise to ipsilateral upper motor neuron signs), and is usually accompanied by progressive coma. Downward movement of the cerebellar tonsils through the foramen magnum may compress the medulla – ‘tonsillar coning’ (Fig. 25.39). This may result in brainstem haemorrhage and/or acute obstruction of the CSF pathways. As coning progresses, coma and death occur unless the condition is rapidly treated.

Management Primary management of RICP should be targeted at relieving the cause (e.g. surgical decompression of mass lesion, glucocorticoids to reduce vasogenic oedema or shunt procedure to relieve hydrocephalus). Supportive treatment includes maintenance of CSF pressure, impaired CSF absorption and cerebral venous obstruction (see Box 25.74). Clinical features In adults, intracranial pressure is less than 10–15 mmHg. The features of RICP are listed in Box 25.75. The speed of pressure increase influences presentation. If slow, compensatory mechanisms may occur, including alteration in the volume of fluid in CSF spaces and venous sinuses, minimising symptoms. Rapid pressure increase (as in aggressive tumours) does not permit these compensatory mechanisms to take place, leading to early symptoms, including sudden death. Papilloedema is not always present, either because the pressure rise has been too rapid or because of anatomical anomalies of the meningeal sheath of the optic nerve. A false localising sign is one in which the pathology is remote from the site of the expected lesion; in RICP, the 6th cranial nerve (unilateral or bilateral) is most commonly affected but the 3rd, 5th and 7th nerves may also be involved. Sixth nerve palsies are thought to be due either to stretching of the

long slender nerve or to compression against the petrous temporal bone ridge. Transtentorial herniation of the uncus may compress the ipsilateral 3rd nerve and usually involves the pupillary fibres first, causing a dilated pupil; however, a false localising contralateral 3rd nerve palsy may also occur, perhaps due to extrinsic compression by the tentorial margin. Vomiting, coma, bradycardia and arterial hypertension are later features of RICP. The rise in intracranial pressure from a mass lesion may cause displacement of the brain. Downward displacement of the medial temporal lobe (uncus) through the tentorium due to 25.74 Common causes of raised intracranial pressure

Mass lesions • Intracranial haemorrhage (traumatic or spontaneous): Extradural haematoma Subdural haematoma Intracerebral haemorrhage • Cerebral tumour (particularly posterior fossa lesions or high-grade gliomas: see Box 25.76) • Infective: Cerebral abscess Tuberculoma Cysticercosis (p. 298) Hydatid cyst (p. 299) • Colloid cyst (in ventricles) Disturbance of cerebrospinal fluid circulation • Obstructive (non-communicating) hydrocephalus: obstruction within ventricular system • Communicating hydrocephalus: site of obstruction outside ventricular system Obstruction to venous sinuses • Cerebral venous thrombosis • Trauma (depressed fractures overlying sinuses) Diffuse brain oedema or swelling • Meningo-encephalitis • Trauma (diffuse head injury, near-drowning) • Subarachnoid haemorrhage • Metabolic (e.g. water intoxication) • Idiopathic intracranial hypertension 25.75 Clinical features of intracranial mass lesions

Presentation Features Seizures Focal onset $\pm$ generalised spread Focal symptoms Progressive loss of function Weakness Numbness Dysphasia Cranial neuropathy False localising signs Unilateral/bilateral 6th nerve palsies Contralateral 3rd nerve (usually pupil first) Raised intracranial pressure (usually aggressive tumours causing vasogenic oedema or obstructive hydrocephalus) Headache worse on lying/straining Vomiting Diplopia (6th nerve involvement) Papilloedema Bradycardia, raised blood pressure Impaired conscious level Stroke/TIA-like symptoms Acute haemorrhage into tumour Paroxysmal 'tumour attacks' Cognitive/behavioural change Usually frontal mass lesions Endocrine abnormalities Pituitary tumours Incidental finding Asymptomatic but identified on imaging (meningiomas commonly) (TIA = transient ischaemic attack) Fig. 25.38 Cerebral tumour displacing medial temporal lobe and causing pressure on the mid-brain and 3rd cranial nerve. 3rd nerve deformed Cerebral tumour Mid-brain distorted Tentorial margin

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isolated stable headache is almost never due to intracranial tumour. The size of the primary tumour is of far less prognostic significance than its location within the brain. Tumours within the brainstem will result in early neurological deficits, while those in the frontal region may be quite large before symptoms occur. fluid balance, blood pressure control, head elevation, and use of diuretics such as mannitol. Intensive care support may be needed (p. 208). Brain tumours Primary brain tumours are a heterogeneous collection of neoplasms arising from the brain tissue or meninges, and vary from benign to highly malignant. Primary malignant brain tumours (Box 25.76) are rare, accounting for 1% of all adult tumours but a higher proportion in children. The most common benign brain tumour is a meningioma. Primary brain tumours do not metastasise due to the absence of lymphatic drainage in the brain. There are rare pathological subtypes, however, such as medulloblastoma, which do have a propensity to metastasise; the reasons for this are not clear. Most cerebral tumours are sporadic but may be associated with genetic syndromes such as neurofibromatosis or tuberous sclerosis. Brain tumours are not classified by the usual TNM system but by the World Health Organisation (WHO) grading I-IV; this is based on histology (e.g. nuclear

pleomorphism, presence of mitoses and presence of necrosis), with grade I the most benign and grade IV the most malignant. Gliomas account for 60% of brain tumours, with the aggressive glioblastoma multiforme (WHO grade IV) the most common glioma, followed by meningiomas (20%) and pituitary tumours (10%). Although the lower-grade gliomas (I and II) may be very indolent, with prognosis measured in terms of many years, these may transform to higher-grade disease at any time, with a resultant sharp decline in life expectancy. Most malignant brain tumours are due to metastases, with intracranial metastases complicating about 20% of extracranial malignancies. The rate is higher with primaries in the bronchus, breast and gastrointestinal tract (Fig. 25.40). Metastases usually occur in the white matter of the cerebral or cerebellar hemispheres but there are diffuse leptomeningeal types. Clinical features The presentation is variable and usually influenced by the rate of growth. High-grade disease (WHO grades III and IV) tends to present with a short (weeks) history of mass effect (headache, nausea secondary to RICP), while more indolent tumours can present with slowly progressive focal neurological deficits, depending on their location (see Box 25.75); generalised or focal seizures are common in either. Headache, if present, is usually accompanied by focal deficits or seizures, and Fig. 25.39 Tonsillar cone. Downward displacement of the cerebellar tonsils below the level of the foramen magnum. Cerebellar tonsil Level of foramen magnum Fourth ventricle Atlas Axis 25.76 Primary brain tumours Histological type Common site Age Malignant Glioma (astrocytoma) Cerebral hemisphere Cerebellum Brainstem Adulthood Childhood/adulthood Childhood/young adulthood Oligodendroglioma Cerebral hemisphere Adulthood Medulloblastoma Posterior fossa Childhood Ependymoma Posterior fossa Childhood/adolescence Cerebral lymphoma Cerebral hemisphere Adulthood Benign Meningioma Cortical dura Parasagittal Sphenoid ridge Suprasellar Olfactory groove Adulthood (often incidental finding) Neurofibroma Acoustic neuroma Adulthood Craniopharyngioma Suprasellar Childhood/adolescence Pituitary adenoma Pituitary fossa Adulthood Colloid cyst Third ventricle Any age Pineal tumours Quadrigeminal cistern Childhood (teratomas) Young adulthood (germ cell) Fig. 25.40 Contrast-enhanced computed tomogram of the head showing a large metastasis within the left hemisphere (large arrow). There is surrounding cerebral oedema, and a smaller metastasis (small arrow) within the wall of the right lateral ventricle. The primary lesion was a lung carcinoma.

1130 • NEUROLOGY the sphenoid ridge, when partial excision is often all that is possible. Thereafter, post-operative surveillance may be required, as radiotherapy is effective at preventing further growth of residual tumour. Pituitary adenomas may be removed by a trans-sphenoidal route, avoiding the need for a craniotomy. Unfortunately, gliomas, which account for the majority of brain tumours, cannot be completely excised, since infiltration spreads well beyond the apparent radiological boundaries of the intracranial mass. Recurrence is therefore the rule, even if the mass of the tumour is apparently removed completely; partial excision ('debulking') may be useful in alleviating symptoms caused by RICP, but although there is increasing evidence that the degree of surgical excision may have a positive influence on survival, this has not yet been convincingly demonstrated. Radiotherapy and chemotherapy In the majority of primary CNS tumours, radiation and chemotherapy are used to control disease and extend survival rather than for cure. Meningioma and pituitary adenoma offer the Investigations Diagnosis is by neuroimaging (Figs 25.41 and 25.42) and pathological grading following biopsy or resection where possible. The more malignant tumours are more likely to demonstrate contrast enhancement on imaging. If the tumour appears metastatic, further investigation to find the primary is required. Management Brain tumours are treated with a combination of surgery, radiotherapy and chemotherapy, depending on

the type of tumour and the patient. Advancing age is the most powerful negative prognostic factor in CNS tumours, so best supportive care (including glucocorticoid therapy) may be most appropriate in older patients with metastases or high-grade disease. Treatment may not always be indicated in low-grade gliomas and watchful waiting may be appropriate, although a more aggressive approach is increasingly favoured. Dexamethasone given orally (or intravenously where RICP is acutely or severely raised) may reduce the vasogenic oedema typically associated with metastases and high-grade gliomas. Prolactin- or growth hormone-secreting pituitary adenomas (p. 683) may respond well to treatment with dopamine agonists (such as bromocriptine, cabergoline or quinagolide); in this situation, imaging and hormone levels may be all that is required to establish a formal diagnosis, precluding the need for surgery. Surgical The mainstay of primary treatment is surgery, either resection (full or partial debulking) or biopsy, depending on the site and likely radiological diagnosis. Clearly, if a tumour occurs in an area of brain that is highly important for normal function (e.g. motor strip), then biopsy may be the only safe surgical intervention but, in general, maximal safe resection is the optimal surgical management. Meningiomas and acoustic neuromas offer the best prospects for complete removal and thus cure. Some meningiomas can recur, however, particularly those of Fig. 25.41 Magnetic resonance image showing a meningioma in the frontal lobe (arrow A) with associated oedema (arrow B). A B Fig. 25.42 Magnetic resonance image of an acoustic neuroma (arrows) in the posterior fossa compressing the brainstem. A Axial image. B Coronal image. A B

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2 (see below). When sporadic, acoustic neuroma occurs after the third decade and is more frequent in females. The tumour commonly arises near the nerve's entry point into the medulla or in the internal auditory meatus, usually on the vestibular division. Acoustic neuromas account for 80–90% of tumours at the cerebellopontine angle. Clinical features Acoustic neuroma typically presents with unilateral progressive hearing loss, sometimes with tinnitus. Vertigo is an unusual symptom, as slow growth allows compensatory brainstem mechanisms to develop. In some cases, progressive enlargement leads to distortion of the brainstem and/or cerebellar peduncle, causing ataxia and/or cerebellar signs in the limbs. Distortion of the fourth ventricle and cerebral aqueduct may cause hydrocephalus (see below), which may be the presenting feature. Facial weakness is unusual at presentation but facial palsy may follow surgical removal of the tumour. The tumour may be identified incidentally on cranial imaging. Investigations MRI is the investigation of choice (see Fig. 25.42). Management Surgery is the treatment of choice. If the tumour can be completely removed, the prognosis is excellent, although deafness is a common complication of surgery. Stereotactic radiosurgery (radiotherapy) may be appropriate for some lesions. Neurofibromatosis Neurofibromatosis encompasses two clinically and genetically separate conditions, with an autosomal dominant pattern of inheritance. The more common neurofibromatosis type 1 (NF1) is caused by mutations in the NF1 gene on chromosome 17, half of which are new mutations. NF1 is characterised by neurofibromas (benign peripheral nerve sheath tumours) and skin involvement (Fig. 25.43), and may affect numerous systems (Box 25.77). best chance of life-long remission. The gliomas are incurable; high-grade, WHO grade IV disease still carries a median survival of just over 1 year. In this situation, patient and family should always be involved in decisions regarding treatment. The diagnosis, and often the symptoms, are devastating, and support from palliative care and social work is crucial at an early stage. In WHO grade III disease, prognosis is a little better (2–4 years), and in rarer, more indolent tumours very prolonged survival is possible.

Advances have been made recently in terms of therapeutic outcome. Standard care for WHO grade IV glioblastoma multiforme is now combination radiotherapy with temozolomide chemotherapy; although this improves median survival of the population from only 12 to 14.5 months, up to 25% of patients survive for more than 2 years (compared to approximately 10% with radiotherapy alone). Ten percent will survive more than 5 years with temozolomide (virtually unheard of with radiotherapy alone). Benefits are more likely in well-debulked patients who are younger and fitter. Implantation of chemotherapy gives a small survival benefit. Understanding of the molecular biology of brain tumours has allowed the use of biomarkers to guide therapy and prognostic discussions. In patients with methylation of the promoter region of the MGMT (methyl guanine methyl transferase) gene (about 30% of the population), 2-year survival is almost 50%. MGMT reduces the cytotoxicity of temozolomide and this mutation also reduces the enzyme's activity, rendering the tumour more sensitive to chemotherapy. In grade II and III gliomas, the presence of the loss of heterozygosity (LOH) 1p19q chromosomal abnormality confers chemosensitivity and thus improves prognosis. The presence of a rare mutation in the IDH-1 (isocitrate dehydrogenase) gene confers a more favourable prognosis in patients with glioblastoma. There is a small group of highly malignant grade IV tumours that can be cured with aggressive therapy. Medulloblastomas have a good chance of long-term remission with maximal surgery followed by irradiation of the whole brain and spine; younger patients may also benefit from concomitant and adjuvant chemotherapy. Older patients do not tolerate this, however. Once tumours relapse, chemotherapy response rates are low and survival is short in high-grade disease. In the more uncommon low-grade tumours, repeated courses of chemotherapy can result in much more prolonged survival. In metastatic disease, radiotherapy offers a modest improvement in survival but with costs in terms of quality of life; treatment therefore needs careful discussion with the patient. Benefits may be superior in breast cancer but there is little to separate other pathologies. Occasional chemosensitive cancers, such as small-cell lung cancer, may benefit from systemic chemotherapy but intracerebral metastases represent a late stage of disease and have a short prognosis.

Prognosis The WHO histological grading system is a powerful predictor of prognosis in primary CNS tumours, though it does not yet take account of individual biomarkers. For each tumour type and grade, advancing age and deteriorating functional status are the next most important negative prognostic features. The overall 5-year survival rate of about 14% in adults masks a wide variation that depends on tumour type.

Acoustic neuroma This is a benign tumour of Schwann cells of the 8th cranial nerve, which may arise in isolation or as part of neurofibromatosis type 1. Fig. 25.43 A café au lait spot (arrow A) and subcutaneous nodules (arrows B) on the forearm of a patient with neurofibromatosis type 1. B B A

1132 • **NEUROLOGY** Neurofibromatosis type 2 (NF2) is caused by mutations of the NF2 gene on chromosome 22, and is characterised by schwannomas (benign peripheral nerve sheath tumours comprising Schwann cells only) with little skin involvement; the clinical manifestations are more restricted to the eye and nervous system (Box 25.77). Malignant change may occur in NF1 neurofibromas but is rare in NF2 schwannomas. The prevalence of NF1 and NF2 is about 20–50 per 100 000 and 1.5 per 100 000, respectively.

Von Hippel–Lindau disease This rare autosomal dominant disease is caused by mutations of the VHL tumour suppressor gene on chromosome 3. It promotes development of tumours affecting the kidney, adrenal gland, CNS, eye, inner ear, epididymis and pancreas, which may undergo malignant change. Benign haemangiomas and haemangioblastomas affect about 80% of patients, and are mostly cerebellar and retinal.

25.77 Neurofibromatosis types 1 and 2: clinical features Neurofibromatosis 1 Neurofibromatosis 2 Skin

Cutaneous/subcutaneous neurofibromas Angiomas Café au lait patches (> 6) Axillary/groin freckling Hypopigmented patches Much less commonly affected than in NF1 Café au lait patches (usually < 6) Cutaneous schwannomas: plaque lesions Subcutaneous schwannomas Eyes Lisch nodules (iris fibromas) Glaucoma Congenital ptosis Cataracts Retinal hamartoma Optic nerve meningioma Nervous system Plexiform neurofibromas Malignant peripheral nerve sheath tumours Aqueduct stenosis Slight tonsillar descent Cognitive impairment Epilepsy Vestibular schwannomas Cranial nerve schwannomas (not 1 and 2) Spinal schwannomas Peripheral nerve schwannomas Cranial meningiomas Spinal meningiomas Spinal/brainstem ependymomas Spinal/cranial astrocytoma Bone Scoliosis Osteoporosis Pseudoarthrosis Cardiorespiratory systems Pulmonary stenosis Hypertension Renal artery stenosis Compression from neurofibroma causing restrictive lung defect Gastrointestinal system Gastrointestinal stromal tumour (GIST) Duodenal/ampullary neuroendocrine tumour Fig. 25.44 The circulation of cerebrospinal fluid (CSF). (1) CSF is synthesised in the choroid plexus of the ventricles and flows from the lateral and third ventricles through the aqueduct to the fourth ventricle. (2) At the foramina of Luschka and Magendie it exits the brain, flowing over the hemispheres (3) and down around the spinal cord and roots in the subarachnoid space. (4) It is then absorbed into the dural venous sinuses via the arachnoid villi. Choroid plexus

25.78 Causes of hydrocephalus Congenital malformations • Aqueduct stenosis • Chiari malformations • Dandy-Walker syndrome • Benign intracranial cysts • Vein of Galen aneurysms • Congenital central nervous system infections • Craniofacial anomalies Acquired causes • Mass lesions (especially those in the posterior fossa) • Tumour • Colloid cyst of third ventricle • Abscess • Haematoma • Absorption blockages due to: Inflammation (e.g. meningitis, sarcoidosis) Intracranial haemorrhage Paraneoplastic neurological disease Paraneoplastic neurological syndromes often present before the underlying tumour declares itself and cause considerable disability. They are discussed in full on page 1110. Hydrocephalus Hydrocephalus is the excessive accumulation of CSF within the brain, and may be caused either by increased CSF production, by reduced CSF absorption, or by obstruction of the circulation (Fig. 25.44). Symptoms range from none to sudden death, depending on the speed at which and degree to which hydrocephalus develops. The causes are listed in Box 25.78. The terms 'communicating' and 'non-communicating' (also known as obstructive) hydrocephalus refer to blockage either outside or within the ventricular system, respectively (Fig. 25.45). Normal pressure hydrocephalus Normal pressure hydrocephalus (NPH) is a controversial entity, said to involve intermittent rises in CSF pressure, particularly at night. It is described in old age as being associated with a triad of gait apraxia, dementia and urinary incontinence.

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villi. A number of drugs may be associated, including tetracycline, vitamin A and retinoid derivatives. Clinical features The usual presentation is with headache, sometimes accompanied by diplopia and visual disturbance (most commonly, transient obscurations of vision associated with changes in posture). Clinical examination reveals papilloedema but little else. False localising cranial nerve palsies (usually of the 6th nerve) may be present. It is important to record visual fields accurately for future monitoring. Investigations Brain imaging is required to exclude a structural or other cause (e.g. cerebral venous sinus thrombosis, p. 1162). The ventricles are typically normal in size or small ('slit' ventricles). The diagnosis may be confirmed by lumbar

puncture, which shows raised normal CSF constituents at increased pressure (usually

30 cmH₂O CSF). Management Management can be difficult and there is no evidence to support any specific treatment. Weight loss in overweight patients may be helpful if it can be achieved. Acetazolamide or topiramate may help to lower intracranial pressure, the latter perhaps aiding weight loss in some patients. Repeated lumbar puncture is an effective treatment for headache but may be technically difficult in obese individuals and is often poorly tolerated. Patients failing to respond, in whom chronic papilloedema threatens vision, may require optic nerve sheath fenestration or a lumbo-peritoneal shunt. Head injury Diagnosis of head trauma is usually clear – either from the history or from signs of external trauma to the head. Brain injury is more likely with skull fracture but can occur without. Individual cranial nerves may be damaged in fractures of the facial bones or skull base. Intracranial effects can be substantial and take several forms: extradural haematoma (collection of blood between the skull and dura); subdural haematoma (collection of blood between the dura and the surface of the brain); intracerebral haematoma; or diffuse axonal injury. Whatever pathology occurs, the resultant RICP may lead to coning (see Figs 25.38 and 25.39). Haematomas are identified by CT and management is by surgical drainage, usually via a burr hole. Penetrating skull fractures lead to increased infection risk. Long-term sequelae include headache, cognitive decline and depression, all contributing to significant social, work, personality and family difficulties. Subdural haematoma may occur spontaneously, particularly in patients on anticoagulants, in old age, and with alcohol misuse. There may or may not be a history of trauma. Patients present with subacute impairment of brain function, both globally (obtundation and coma) and focally (hemiparesis, seizures). Headache may not be present. The diagnosis should always be considered in those who present with reduced conscious level. Beyond the immediate consequences of brain injury, there is increasing suspicion of long-term consequences, including dementia, postulated after either single (moderate or severe) injuries or even after multiple mild injuries, such as in boxers. If substantiated, this would encourage more effort to go into prevention of repeated brain injury in sporting contexts. Fig. 25.45 Magnetic resonance image of hydrocephalus due to aqueduct stenosis. A Axial T2-weighted image (cerebrospinal fluid appears white): note the dilated lateral ventricles. B Sagittal T1-weighted image (cerebrospinal fluid appears black): note the dilated ventricles (top arrow) and narrowed aqueduct (bottom arrow). A B Management Diversion of the CSF by means of a shunt placed between the ventricular system and the peritoneal cavity or right atrium may result in rapid relief of symptoms in obstructive hydrocephalus. The outcome of shunting in NPH is much less predictable and, until a good response can be predicted, the management of individual cases will remain uncertain. Idiopathic intracranial hypertension This usually occurs in obese young women. The annual incidence is about 3 per 100 000. RICP occurs in the absence of a structural lesion, hydrocephalus or other

identifiable cause. The aetiology is uncertain but there is an association with obesity in females, perhaps inducing a defect of CSF reabsorption by the arachnoid

1134 • NEUROLOGY may be lower motor neuron signs, including weakness, wasting and reflex impairment (Fig. 25.47). Investigations Where there is no trauma, imaging should not be carried out for isolated cervical pain. MRI is the investigation of choice in those with radicular symptoms. X-rays offer limited benefit, except in excluding destructive lesions, and electrophysiological studies rarely add to clinical examination with MRI. Management Conservative treatment with analgesics and physiotherapy results in resolution of symptoms in the great majority of patients, but a few require surgery in the form of discectomy or radicular decompression. Cervical myelopathy Dorsomedial herniation of a disc and the development of transverse bony bars or posterior osteophytes may result in pressure on the spinal cord or the anterior spinal artery, which supplies the anterior two-thirds of the cord (see Fig. 25.46). Disorders of cerebellar function Cerebellar dysfunction can manifest as incoordination of limb function, gait ataxia (p. 1087), speech or eye movements. Acute dysfunction may be caused by alcohol or prescription drugs (especially the sodium channel-blocking antiepileptic drugs phenytoin and carbamazepine). Inflammatory changes in the cerebellum may cause symptoms in the aftermath of some infections (especially herpes zoster) or as a paraneoplastic phenomenon. The hereditary spinocerebellar ataxias are described on page 1115; they manifest as progressive ataxias in middle and old age, often with other neurological features that aid specific diagnosis. Disorders of the spine and spinal cord The spinal cord and spinal roots may be affected by intrinsic disease or by disorders of the surrounding meninges and bones. The clinical presentation of these conditions depends on the anatomical level at which the cord or roots are affected, as well as the nature of the pathological process involved. It is important to recognise when the spinal cord is at risk of compression (p. 1136) so that urgent action can be taken. Cervical spondylosis Cervical spondylosis is the result of osteoarthritis in the cervical spine. It is characterised by degeneration of the intervertebral discs and osteophyte formation. Such 'wear and tear' is extremely common and radiological changes are frequently found in asymptomatic individuals over the age of 50. Spondylosis may be associated with neurological dysfunction. In order of frequency, the C5/6, C6/7 and C4/5 vertebral levels affect C6, C7 and C5 roots, respectively (Fig. 25.46). Cervical radiculopathy Acute onset of compression of a nerve root occurs when a disc prolapses laterally. More gradual onset may be due to osteophytic encroachment of the intervertebral foramina. Clinical features The patient complains of pain in the neck that may radiate in the distribution of the affected nerve root. The neck is held rigidly and neck movements may exacerbate pain. Paraesthesia and sensory loss may be found in the affected segment and there Fig. 25.46 Magnetic resonance image showing cervical cord compression (arrow) in cervical spondylosis. Fig. 25.47 Findings in cervical nerve root compression. Biceps, deltoid and spinati Biceps C5 Brachioradialis Supinator C6 Triceps, fingers and wrist extensors Triceps C7 Reflex loss Muscle weakness Sensory loss (see Fig 25.10, p. 1071) Root

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Pathophysiology The altered mechanics of the lumbar spine result in loss of lumbar lordosis and there may be spasm of the paraspinal musculature. Root pressure is suggested by limitation of flexion of the hip on the affected side if the straight leg is raised (Lasègue's sign). If the third or

fourth lumbar root is involved, Lasègue's sign may be negative, but pain in the back may be induced by hyperextension of the hip (femoral nerve stretch test). The roots most frequently affected are S1, L5 and L4; the signs of root pressure at these levels are summarised in Figure 25.48. Clinical features The onset may be sudden or gradual. Alternatively, repeated episodes of low back pain may precede sciatica by months or years. Constant aching pain is felt in the lumbar region and may radiate to the buttock, thigh, calf and foot. Pain is exacerbated by coughing or straining but may be relieved by lying flat. Investigations MRI is the investigation of choice if available, since soft tissues are well imaged. Plain X-rays of the lumbar spine are of little value in the diagnosis of disc disease, although they may demonstrate conditions affecting the vertebral body. CT can provide helpful images of the disc protrusion and/or narrowing of exit foramina. Management Some 90% of patients with sciatica recover following conservative treatment with analgesia and early mobilisation; bed rest does not help recovery. The patient should be instructed in backstrengthening exercises and advised to avoid physical manoeuvres likely to strain the lumbar spine. Injections of local anaesthetic or glucocorticoids may be useful adjunctive treatment if symptoms are due to ligamentous injury or joint dysfunction. Surgery may have to be considered if there is no response to conservative treatment or if progressive neurological deficits develop. Central disc prolapse with bilateral symptoms and signs and disturbance of sphincter function requires urgent surgical decompression. Lumbar canal stenosis This occurs with a congenitally narrowed lumbar spinal canal, exacerbated by the degenerative changes that commonly occur with age. Pathophysiology The symptoms of spinal stenosis are thought to be due to local vascular compromise secondary to the canal stenosis, rendering Clinical features The onset is usually insidious and painless but acute deterioration may occur after trauma, especially hyperextension injury. Upper motor neuron signs develop in the limbs, with spasticity of the legs usually appearing before the arms are involved. Sensory loss in the upper limbs is common, producing tingling, numbness and proprioception loss in the hands, with progressive clumsiness. Sensory manifestations in the legs are much less common. Neurological deficit usually progresses gradually and disturbance of micturition is a very late feature. Investigations MRI (see Fig. 25.46) (or rarely myelography) will direct surgical intervention. The former provides information on the state of the spinal cord at the level of compression. Management Surgical procedures, including laminectomy and anterior discectomy, may arrest progression of disability but neurological improvement is not the rule. The decision as to whether surgery should be undertaken may be difficult. Manual manipulation of the cervical spine is of no proven benefit and may precipitate acute neurological deterioration. Prognosis The prognosis of cervical myelopathy is variable. In many patients, the condition stabilises or even improves without intervention. If progression results in sphincter dysfunction or pyramidal signs, surgical decompression should be considered. Lumbar spondylosis This term covers degenerative disc disease and osteoarthritic change in the lumbar spine. Pain in the distribution of the lumbar or sacral roots ('sciatica') is almost always due to disc protrusion but can be a feature of other rare but important disorders, including spinal tumour, malignant disease in the pelvis and tuberculosis of the vertebral bodies. Lumbar disc herniation While acute lumbar disc herniation is often precipitated by trauma (usually lifting heavy weights while the spine is flexed), genetic factors may also be important. The nucleus pulposus may bulge or rupture through the annulus fibrosus, giving rise to pressure on nerve endings in the spinal ligaments, changes in the vertebral joints or pressure on nerve roots. Fig. 25.48 Findings in lumbar nerve root compression. Knee extension Knee Femoral nerve L4 Ankle dorsiflexion Ankle inversion None L5 Plantar flexion Ankle S1 Reflex loss Muscle weakness Sensory loss (see Fig 25.10, p. 1071) Root L3/L4 L4/L5 L5/S1 Disc level

1136 • NEUROLOGY the nerve roots ischaemic and intolerant of the increased demand that occurs on exercise. Clinical features Patients, who are usually elderly, develop exercise-induced weakness and paraesthesia in the legs ('spinal claudication'). These symptoms progress with continued exertion, often to the point that the patient can no longer walk, but are quickly relieved by a short period of rest. Physical examination at rest shows preservation of peripheral pulses with absent ankle reflexes. Weakness or sensory loss may only be apparent if the patient is examined immediately after exercise. Investigations The investigation of first choice is MRI, but contraindications (body habitus, metallic implants) may make CT or myelography necessary. Management Lumbar laminectomy may provide relief of symptoms and recovery of normal exercise tolerance. Spinal cord compression Spinal cord compression is one of the more common neurological emergencies encountered in clinical practice and the usual causes are listed in Box 25.79. A space-occupying lesion within the spinal canal may damage nerve tissue either directly by pressure or indirectly by interference with blood supply. Oedema from venous obstruction impairs neuronal function, and ischaemia from arterial obstruction may lead to necrosis of the spinal cord. The early stages of damage are reversible but severely damaged neurons do not recover; hence the importance of early diagnosis and treatment. Clinical features The onset of symptoms of spinal cord compression is usually slow (over weeks) but can be acute as a result of trauma or metastases (see Figs 25.46, 25.49 and 25.50), especially if there is associated arterial occlusion. The symptoms are shown in Box 25.80. Pain and sensory symptoms occur early, while weakness and sphincter dysfunction are usually late manifestations. The signs vary according to the level of the cord compression and the 25.79 Causes of spinal cord compression Site Frequency Causes Vertebral 80% Trauma (extradural) Intervertebral disc prolapse Metastatic carcinoma (e.g. breast, prostate, bronchus) Myeloma Tuberculosis Meninges (intradural, extramedullary) 15% Tumours (e.g. meningioma, neurofibroma, ependymoma, metastasis, lymphoma, leukaemia) Epidural abscess Spinal cord (intradural, intramedullary) 5% Tumours (e.g. glioma, ependymoma, metastasis) 25.80 Symptoms of spinal cord compression Pain • Localised over the spine or in a root distribution, which may be aggravated by coughing, sneezing or straining Sensory • Paraesthesia, numbness or cold sensations, especially in the lower limbs, which spread proximally, often to a level on the trunk Motor • Weakness, heaviness or stiffness of the limbs, most commonly the legs Sphincters • Urgency or hesitancy of micturition, leading eventually to urinary retention 25.82 Investigation of acute spinal cord syndrome • Magnetic resonance imaging of spine or myelography • Plain X-rays of spine • Chest X-ray • Cerebrospinal fluid • Serum vitamin B12 25.81 Signs of spinal cord compression Cervical, above C5 • Upper motor neuron signs and sensory loss in all four limbs • Diaphragm weakness (phrenic nerve) Cervical, C5–T1 • Lower motor neuron signs and segmental sensory loss in the arms; upper motor neuron signs in the legs • Respiratory (intercostal) muscle weakness Thoracic cord • Spastic paraplegia with a sensory level on the trunk • Weakness of legs, sacral loss of sensation and extensor plantar responses Cauda equina • Spinal cord ends approximately at the T12/L1 spinal level and spinal lesions below this level can cause lower motor neuron signs only by affecting the cauda equina structures involved. There may be tenderness to percussion over the spine if there is vertebral disease and this may be associated with a local kyphosis. Involvement of the roots at the level of the compression may cause dermatomal sensory impairment and corresponding lower motor signs. Interruption of fibres in the spinal cord causes sensory loss (p. 1083) and upper motor neuron signs below the level of the lesion, and there is often disturbance of sphincter function. The distribution of these signs varies with the level of the lesion (Box 25.81). The Brown–Séquard syndrome (see Fig. 25.18E, p. 1084) results if damage is confined to one side of the cord; the findings are explained by the anatomy of

the sensory tracts (see Fig. 25.11, p. 1072). With compressive lesions, there is usually a band of pain at the level of the lesion in the distribution of the nerve roots subject to compression. Investigations Patients with a history of acute or subacute spinal cord syndrome should be investigated urgently, as listed in Box 25.82. The

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good functional recovery can be expected unless a marked neurological deficit has developed before diagnosis. Extradural compression due to malignancy is the most common cause of spinal cord compression in developed countries and has a poor prognosis. Useful function can be regained if treatment, such as radiotherapy, is initiated within 24 hours of the onset of severe weakness or sphincter dysfunction; management should involve close cooperation with both oncologists and neurosurgeons. Spinal cord compression due to tuberculosis is common in some areas of the world and may require surgical treatment. This should be followed by appropriate antituberculous chemotherapy (p. 592) for an extended period. Traumatic lesions of the vertebral column require specialised neurosurgical treatment. Intrinsic diseases of the spinal cord There are many disorders that interfere with spinal cord function due to non-compressive involvement of the spinal cord itself. A list of these disorders is given in Box 25.83. The symptoms and signs are generally similar to those that would occur with extrinsic compression (see Boxes 25.80 and 25.81), although a suspended sensory loss (see Fig. 25.18F, p. 1084) can occur only with intrinsic disease such as syringomyelia. Urinary symptoms usually occur earlier in the course of an intrinsic cord disorder than with compressive disorders. Investigation of intrinsic disease starts with imaging to exclude a compressive lesion. MRI provides most information about structural lesions, such as diastematomyelia, syringomyelia (Fig. 25.51) or intrinsic tumours. Non-specific signal change may be seen in the spinal cord in inflammatory (see Fig. 25.30, p. 1109) or infective conditions and metabolic disorders such as vitamin B12 deficiency. Lumbar puncture or blood tests may be required to make a specific diagnosis. investigation of choice is MRI (Fig. 25.49), as it can define the extent of compression and associated soft-tissue abnormality (Fig. 25.50). Plain X-rays may show bony destruction and soft-tissue abnormalities. Routine investigations, including chest X-ray, may provide evidence of systemic disease. If myelography is performed, CSF should be taken for analysis; in cases of complete spinal block, this shows a normal cell count with a very elevated protein causing yellow discoloration of the fluid (Froin's syndrome). The risk of acute deterioration after myelography in spinal cord compression means that the neurosurgeons should be alerted before it is undertaken. Where a secondary tumour is causing the compression, needle biopsy may be required to establish a tissue diagnosis. Management Treatment and prognosis depend on the nature of the underlying lesion. Benign tumours should be surgically excised, and a Fig. 25.49 Axial magnetic resonance image of thoracic spine. A neurofibroma (N) is compressing the spinal cord (SC) and emerging in a 'dumbbell' fashion through the vertebral foramen into the paraspinal space. SC N Fig. 25.50 Computed tomographic myelogram of cervical spine at the level of C2 showing bony erosion of vertebra by a metastasis (arrow). Fig. 25.51 Sagittal magnetic resonance image showing descent of cerebellar tonsils and central syrinx. The MRI shows descent of the cerebellar tonsils (top arrow), with a large central cord syrinx extending down from the cervical cord (middle arrow) to the thoracic cord (bottom arrow).

1138 • NEUROLOGY studies and EMG, p. 1076). Neuropathies can occur in association with many systemic diseases, toxins and drugs (Box 25.85). Clinical features Motor nerve involvement

produces features of a lower motor neuron lesion (p. 1082). Symptoms and signs of sensory nerve involvement depend on the type of sensory nerve involved (p. 1083); small-fibre neuropathies are often painful. Autonomic involvement may cause postural hypotension, disturbance of sweating, cardiac rhythm and gastrointestinal, bladder and sexual functions; isolated autonomic neuropathies are rare and more commonly complicate other neuropathies. Investigations The investigations required reflect the wide spectrum of causes (Box 25.86). Neurophysiological tests are key in discriminating between demyelinating and axonal neuropathies, and in identifying entrapment neuropathies. Most neuropathies are of the chronic axonal type. Diseases of peripheral nerves Disorders of the peripheral nervous system are common and may affect the motor, sensory or autonomic components, either in isolation or in combination. The site of pathology may be nerve root (radiculopathy), nerve plexus (plexopathy) or nerve (neuropathy). Neuropathies may present as mononeuropathy (single nerve affected), multiple mononeuropathies ('mononeuritis multiplex') or a symmetrical polyneuropathy (Box 25.84). Cranial nerves 3–12 share the same tissue characteristics as peripheral nerves elsewhere and are subject to the same range of diseases. Pathophysiology Damage may occur to the nerve cell body (axon) or the myelin sheath (Schwann cell), leading to axonal or demyelinating neuropathies. The distinction is important, as only demyelinating neuropathies are usually susceptible to treatment. Making the distinction requires neurophysiology (nerve conduction 25.83)

Intrinsic diseases of the spinal cord

Type of disorder	Condition	Clinical features
Congenital	Diastematomyelia (spina bifida)	Features variably present at birth and deteriorate thereafter LMN features, deformity and sensory loss of legs Impaired sphincter function Hairy patch or pit over low back Incidence reduced by increased maternal intake of folic acid during pregnancy
Hereditary	spastic paraplegia	Onset usually in adult life Autosomal dominant inheritance usual Slowly progressive UMN features affecting legs > arms Little or no sensory loss
Infective/inflammatory	Transverse myelitis due to viruses (HZV), schistosomiasis, HIV, MS, sarcoidosis	Weakness and sensory loss, often with pain, developing over hours to days UMN features below lesion Impaired sphincter function
Paraneoplastic		May predate tumour diagnosis
Vascular	Anterior spinal artery infarct due to atherosclerosis, aortic dissection, embolus	Abrupt onset Anterior horn cell loss (LMN) at level of lesion UMN features below it Spinothalamic sensory loss below lesion but dorsal column sensation spared
Spinal AVM/dural fistula		Onset variable (acute to slowly progressive) Variable LMN, UMN, sensory and sphincter disturbance Symptoms and signs often not well localised to site of AVM
Neoplastic	Glioma, ependymoma	Weakness and sensory loss often with pain, developing over months to years UMN features below lesion in cord; additional LMN features in conus Impaired sphincter function
Metabolic	Vitamin B12 deficiency (subacute combined degeneration)	Progressive spastic paraparesis with proprioception loss Absent reflexes due to peripheral neuropathy ± Optic nerve and cerebral involvement (p. 715) Copper deficiency Excess dietary zinc Nitrous oxide toxicity Modifies vitamin B12 metabolism
Degenerative	Motor neuron disease	Relentlessly progressive LMN and UMN features, associated bulbar weakness No sensory involvement (p. 1116)
Syringomyelia		Gradual onset over months or years, pain in cervical segments Anterior horn cell loss (LMN) at level of lesion, UMN features below it Suspended spinothalamic sensory loss at level of lesion, dorsal columns preserved (see Figs 25.18F (p. 1084) and 25.51) (AVM = arteriovenous malformation; HIV = human immunodeficiency virus; HZV = herpes zoster virus; LMN = lower motor neuron; MS = multiple sclerosis; UMN = upper motor neuron)

25.84 Causes of polyneuropathy Genetic • Charcot-Marie-Tooth disease (CMT) • Hereditary neuropathy with liability to pressure palsies (HNPP) • Hereditary sensory ± autonomic neuropathies (HSN, HSAN) • Familial amyloid polyneuropathy • Hereditary neuralgic amyotrophy Drugs • Amiodarone • Antibiotics (dapsone, isoniazid, metronidazole, ethambutol) • Antiretrovirals • Chemotherapy (cisplatin, vincristine, thalidomide) • Phenytoin Toxins • Alcohol • Nitrous oxide (recreational use) • Rarely: lead, arsenic, mercury, organophosphates, solvents Vitamin deficiencies • Thiamin • Pyridoxine • Vitamin B12 • Vitamin E Infections • HIV • Leprosy • Brucellosis Inflammatory • Guillain-Barré syndrome • Chronic inflammatory demyelinating polyradiculoneuropathy • Vasculitis (polyarteritis nodosa, granulomatosis with polyangiitis (also known as Wegener's granulomatosis), rheumatoid arthritis, systemic lupus erythematosus) • Paraneoplastic (antibody-mediated) Systemic medical conditions • Diabetes • Renal failure • Sarcoidosis Malignant disease • Infiltration Others • Paraproteinaemias • Amyloidosis • Critical illness polyneuropathy/ myopathy 25.85 Common causes of axonal and demyelinating chronic polyneuropathies Axonal • Diabetes mellitus • Alcohol • Uraemia • Cirrhosis • Amyloid • Myxoedema • Acromegaly • Paraneoplasm • Drugs and toxins (see Box 25.84) • Deficiency states (see Box 25.84) • Hereditary factors • Infection (see Box 25.84) • Idiopathic factors Demyelinating • Chronic inflammatory demyelinating polyradiculoneuropathy • Multifocal motor neuropathy • Paraprotein-associated demyelinating neuropathy • Charcot-Marie-Tooth disease type I and type X 25.86 Investigation of peripheral neuropathy Initial tests • Glucose (fasting) • Erythrocyte sedimentation rate, C-reactive protein • Full blood count • Urea and electrolytes • Liver function tests • Serum protein electrophoresis • Vitamin B12, folate • ANA, ANCA • Chest X-ray • HIV testing If initial tests are negative • Nerve conduction studies • Vitamins E and A • Genetic testing (see Box 25.84) • Lyme serology (p. 256) • Serum angiotensin-converting enzyme • Serum amyloid (ANCA = antineutrophil cytoplasmic antibody; ANA = antineutrophil antibody) 25.87 Symptoms and signs in common entrapment neuropathies Nerve Symptoms Muscle weakness/ muscle-wasting Area of sensory loss Median (at wrist) (carpal tunnel syndrome) Pain and paraesthesia on palmar aspect of hands and fingers, waking patient from sleep. Pain may extend to arm and shoulder Abductor pollicis brevis Lateral palm and thumb, index, middle and lateral half fourth finger Ulnar (at elbow) Paraesthesia on medial border of hand, wasting and weakness of hand muscles All small hand muscles, excluding abductor pollicis brevis Medial palm and little finger, and medial half fourth finger Radial Weakness of extension of wrist and fingers, often precipitated by sleeping in abnormal posture, e.g. arm over back of chair Wrist and finger extensors, supinator Dorsum of thumb Common peroneal Foot drop, trauma to head of fibula Dorsiflexion and eversion of foot Nil or dorsum of foot Lateral cutaneous nerve of the thigh (meralgia paraesthetica) Tingling and dysaesthesia on lateral border of thigh Nil Lateral border of thigh Entrapment neuropathy Focal compression or entrapment is the usual cause of a mononeuropathy. Symptoms and signs of entrapment neuropathy are listed in Box 25.87. Entrapment neuropathies may affect anyone but diabetes, excess alcohol or toxins, or genetic syndromes may be predisposing causes. Unless axonal loss

1140 • NEUROLOGY Clinical features Distal paraesthesia and pain precede muscle weakness that ascends rapidly from lower to upper limbs and is more marked proximally than distally. Facial and bulbar weakness commonly develops, and respiratory weakness requiring ventilatory support occurs in 20% of cases. Weakness progresses over a maximum of 4 weeks (usually less). Rapid deterioration to respiratory failure can develop within hours. Examination shows diffuse weakness with loss of reflexes. Miller Fisher syndrome presents with internal and external ophthalmoplegia,

ataxia and areflexia. Investigations The CSF protein is raised, but may be normal in the first 10 days. There is usually no increase in CSF white cell count ($> 10 \times 10^6$ cells/L suggests an alternative diagnosis). Electrophysiological changes may emerge after a week or so, with conduction block and multifocal motor slowing, sometimes most evident proximally as delayed F waves (p. 1076). Antibodies to the ganglioside GM1 are found in about 25%, usually the motor axonal form. Other causes of an acute neuromuscular paralysis should be excluded (e.g. poliomyelitis, botulism, diphtheria, spinal cord syndromes or myasthenia), via the history and examination rather than investigations. Management Active treatment with plasma exchange or intravenous immunoglobulin therapy shortens the duration of ventilation and improves prognosis. In severe GBS, both intravenous immunoglobulin (IVIg) and plasma exchange started within 2 weeks of onset hasten recovery with similar rates of adverse effects but IVIg treatment is significantly more likely to be completed than plasma exchange. Overall, 80% of patients recover completely within 3–6 months, 4% die and the remainder suffer residual neurological disability, which can be severe. Adverse prognostic features include older age, rapid deterioration to ventilation and evidence of axonal loss on EMG. Supportive measures to prevent pressure sores and deep venous thrombosis are essential. Regular monitoring of respiratory function (vital capacity) is needed in the acute phase, as respiratory failure may develop with little warning.

Chronic polyneuropathy The most common axonal and demyelinating causes of polyneuropathy are shown in Box 25.85. A chronic symmetrical axonal polyneuropathy, evolving over months or years, is the most common form of chronic neuropathy. Diabetes mellitus is the most common cause but in about 25–50% no cause can be found. Hereditary neuropathy Charcot-Marie-Tooth disease (CMT) is an umbrella term for the inherited neuropathies. The members of this group of syndromes have different clinical and genetic features. The most common CMT is the autosomal dominantly inherited CMT type 1, usually caused by a mutation in the PMP-22 gene. Common signs are distal wasting ('inverted champagne bottle' legs), often with pes cavus, and predominantly motor involvement. X-linked and recessively inherited forms of CMT, causing demyelinating or axonal neuropathies, also occur. has occurred, entrapment neuropathies will recover, provided the primary cause is removed, either by avoiding the precipitation of activity or by surgical decompression. Multifocal neuropathy Multifocal neuropathy (mononeuritis multiplex) is characterised by lesions of multiple nerve roots, peripheral nerves or cranial nerves (Box 25.88). Vasculitis is a common cause, either as part of a systemic disease or isolated to the nerves, or it may arise on a background of a polyneuropathy (e.g. diabetes). Multifocal motor neuropathy (MMN) with conduction block is a rare pure motor neuropathy, typically affecting the arms; it is associated with anti-GM1 antibodies in about 50% and responds to intravenous immunoglobulin.

Polyneuropathy A polyneuropathy is typically associated with a 'length-dependent' pattern, occurring in the longest peripheral nerves first and affecting the distal lower limbs before the upper limbs. Sensory symptoms and signs develop in an ascending 'glove and stocking' distribution (p. 1083). In inflammatory demyelinating neuropathies, the pathology may be more patchy, affecting the upper rather than lower limbs. Guillain-Barré syndrome Guillain-Barré syndrome (GBS) is a heterogeneous group of immune-mediated conditions with an incidence of 1–2/100 000/ year. In Europe and North America, the most common variant is an acute inflammatory demyelinating polyneuropathy (AIDP). Axonal variants, either motor (acute motor axonal neuropathy, AMAN) or sensorimotor (acute motor and sensory axonal neuropathy, AMSAN), are more common in China and Japan, and account for 10% of GBS in Western countries (often associated with *Campylobacter jejuni*). The hallmark is an acute paralysis evolving over days or weeks with loss of tendon reflexes. About twothirds of those with AIDP have a prior history of infection, and an autoimmune response

triggered by the preceding infection causes demyelination. A number of GBS variants have been described, associated with specific anti-ganglioside antibodies; the best recognised is Miller Fisher syndrome, which involves anti-GQ1b antibodies.

25.88 Causes of multifocal mononeuropathy

Axonal (defined on nerve conduction studies) • Vasculitis (systemic or non-systemic) • Diabetes mellitus • Sarcoidosis • Infection (HIV, hepatitis C, Lyme disease, leprosy, diphtheria) Focal demyelination with/without conduction block • Multifocal motor neuropathy • Multiple compression neuropathies (usually in association with underlying disease, such as diabetes or alcoholism) • Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) • Hereditary neuropathy with a predisposition to pressure palsy (autosomal dominant, peripheral myelin protein 22 gene) • Lymphoma

Diseases of the neuromuscular junction • 1141

Chronic demyelinating polyneuropathy The acquired chronic demyelinating neuropathies include chronic inflammatory demyelinating peripheral neuropathy (CIDP), multifocal motor neuropathy (see above) and paraprotein-associated demyelinating neuropathy. CIDP typically presents with relapsing or progressive motor and sensory changes, evolving over more than 8 weeks (in distinction to the more acute GBS). It is important to recognise, as it usually responds to glucocorticoids, plasma exchange or intravenous immunoglobulin. Some 10% of patients with acquired demyelinating polyneuropathy have an abnormal serum paraprotein, sometimes associated with a lymphoproliferative malignancy. They may also demonstrate positive antibodies to myelin-associated glycoprotein (anti-MAG antibodies).

Brachial plexopathy Trauma usually damages either the upper or the lower parts of the brachial plexus, according to the mechanics of the injury. The clinical features depend on the anatomical site of the damage (Box 25.89). Lower parts of the brachial plexus are vulnerable to infiltration from breast or apical lung tumours (Pancoast tumour, p. 600) or damage by therapeutic irradiation. The lower plexus may also be compressed by a cervical rib or fibrous band between C7 and the first rib at the thoracic outlet. Neuralgic amyotrophy (also known as brachial neuritis) presents as an acute brachial plexopathy of probable inflammatory origin. Severe shoulder pain precedes the appearance of a patchy upper brachial plexus lesion, with motor and/or sensory involvement. There is no specific treatment and recovery is often incomplete; it may recur in about 25% and there is a rare autosomal dominant hereditary form. The appearance of vesicles should indicate the alternative diagnosis of motor zoster.

25.89 Physical signs in brachial plexus lesions

Site	Affected muscles	Sensory loss
Upper plexus (Erb–Duchenne)	Biceps, deltoid, spinati, rhomboids, brachioradialis (triceps, serratus anterior)	Patch over deltoid
Lower plexus (Déjerine–Klumpke)	All small hand muscles, claw hand (ulnar wrist flexors)	Ulnar border of hand/forearm
Thoracic outlet syndrome	Small hand muscles, ulnar forearm	Ulnar border of hand/forearm/ upper arm

Spinal root lesions Spinal root lesions (radiculopathy) are described above. Clinical features include muscle weakness and wasting and dermatomal sensory and reflex loss, which reflect the pattern of the roots involved. Pain in the muscles innervated by the affected roots may be prominent.

Diseases of the neuromuscular junction Myasthenia gravis This is the most common cause of acutely evolving, fatigable weakness and preferentially affects ocular, facial and bulbar muscles.

Pathophysiology Myasthenia gravis is an autoimmune disease, most commonly (80% of cases) caused by antibodies to acetylcholine receptors in the post-junctional membrane of the neuromuscular junction. The resultant blockage of neuromuscular transmission and complement-mediated inflammatory response reduces the number of acetylcholine receptors and damages the end plate (Fig. 25.52). Other antibodies can

produce a similar clinical picture, most notably autoantibodies to muscle-specific kinase (MuSK), which is involved in the regulation and maintenance of acetylcholine receptors. About 15% of patients (mainly those with late onset) have a thymoma, most of the remainder displaying thymic follicular hyperplasia. Myasthenic patients are more likely to have associated organ-specific autoimmune diseases. Triggers are not always evident but some drugs (e.g. penicillamine) can precipitate an antibody-mediated myasthenic syndrome that may persist after drug withdrawal. Other drugs, especially aminoglycosides and quinolones, may exacerbate the neuromuscular blockade and should be avoided in patients with myasthenia. Clinical features Myasthenia gravis usually presents between the ages of 15 and 50 years and there is a female preponderance in younger patients. In older patients, males are more commonly affected. It tends to run a relapsing and remitting course. The most evident symptom is fatigable muscle weakness; movement is initially strong but rapidly weakens as muscle use continues. Worsening of symptoms towards the end of the day or following exercise is characteristic. There are no sensory signs or signs of involvement of the CNS, although weakness of the oculomotor muscles may mimic a central eye movement disorder. The first symptoms are usually intermittent ptosis or diplopia but weakness of chewing, swallowing, speaking or limb movement also occurs. Resting of the eyelids (looking downwards) may be followed by increased reflex elevation with up-gaze (so-called Cogan's lid twitch sign). Any limb muscle may be affected, most commonly those of the shoulder girdle; the patient is unable to undertake tasks above shoulder level, such as combing the hair, without frequent rests. Respiratory muscles may be involved and respiratory failure is an avoidable cause of death. Aspiration may occur if the cough is ineffectual. Ventilatory support is required where weakness is severe or of abrupt onset. Lumbosacral plexopathy Lumbosacral plexus lesions may be caused by neoplastic infiltration or compression by retroperitoneal haematomas. A small-vessel vasculopathy can produce a unilateral or bilateral lumbar plexopathy in association with diabetes mellitus ('diabetic amyotrophy') or an idiopathic form in nondiabetic patients. This presents with painful wasting of the quadriceps with weakness of knee extension and an absent knee reflex.

1142 • NEUROLOGY Fig. 25.52 Myasthenia gravis and Lambert-Eaton myasthenic syndrome (LEMS). In myasthenia there are antibodies to the acetylcholine receptors on the post-synaptic membrane, which block conduction across the neuromuscular junction (NMJ). Myasthenic symptoms can be transiently improved by inhibition of acetylcholinesterase (e.g. with Tensilon – edrophonium bromide), which normally removes the acetylcholine. A cell-mediated immune response produces simplification of the post-synaptic membrane, further impairing the 'safety factor' of neuromuscular conduction. In LEMS, antibodies to the pre-synaptic voltage calcium channels impair release of acetylcholine from the motor nerve ending; calcium is required for the acetylcholine-containing vesicle to fuse with the pre-synaptic membrane for release into the NMJ. Motor neuron Lambert-Eaton syndrome Antibodies to pre-synaptic calcium channels Acetylcholine packets released by calcium influx Acetylcholine Ca^{2+} Voltage-gated calcium channel Acetylcholine receptor Acetylcholinesterase removes acetylcholine from neuromuscular junction Sodium channels in clefts amplify potential change Depolarisation of muscle membrane In myasthenia end plate is subject to cell-mediated immune assault (end plate simplified) Myasthenia gravis Antibodies to acetylcholine receptors Investigations Intravenous injection of the short-acting anticholinesterase edrophonium bromide (the Tensilon test) is less widely used than before. Improvement in muscle function occurs within 30 seconds and usually persists for 2–3 minutes but the test is not entirely specific or sensitive. Cover with intravenous atropine is necessary to avoid bradycardia. Planning assessment beforehand (e.g. speech or limb movements) allows some

objectivity in gauging the effect. Repetitive stimulation during nerve conduction studies may show a characteristic decremental response (p. 1076) if the muscle has been clinically affected. Anti-MuSK antibodies are more common in acetylcholine receptor antibody-negative patients with prominent bulbar involvement. All patients should have a thoracic CT to exclude thymoma, especially those without anti-acetylcholine receptor antibodies. Screening for associated autoimmune disorders, particularly thyroid disease, is important. Management The goals of treatment are to maximise the activity of acetylcholine at remaining receptors in the neuromuscular junctions and to limit or abolish the immunological attack on motor end plates. The duration of action of acetylcholine is prolonged by inhibiting acetylcholinesterase. The most commonly used anticholinesterase drug is pyridostigmine. Muscarinic side-effects, including diarrhoea and colic, may be controlled by propantheline. Overdosage of anticholinesterase drugs may cause a 'cholinergic crisis' due to depolarisation block of motor end plates, with muscle 25.90

Immunological treatment of myasthenia

Acute treatments

- Intravenous immunoglobulin • Lowers production of antibodies and rapidly reduces weakness
- Plasma exchange • Removing antibody from the blood may produce marked improvement; this is usually brief, so is normally reserved for myasthenic crisis or for pre-operative preparation

Long-term treatments

- Glucocorticoid treatment • Improvement is commonly preceded by marked exacerbation of myasthenic symptoms, so treatment should be initiated in hospital • Usually necessary to continue treatment for months or years, risking adverse effects
- Pharmacological immunosuppression treatment • Azathioprine 2.5 mg/kg daily reduces the necessary dosage of glucocorticoids and may allow their withdrawal. Effect on clinical features may be delayed for months • Mycophenolate mofetil: less commonly used
- Thymectomy • Should be considered in any antibody-positive patient under 45 years with symptoms not confined to extraocular muscles, unless the disease has been established for more than 7 years • Likely to be required for thymoma

Diseases of muscle • 1143

Diseases of muscle Muscle disease, either hereditary or acquired, is rare. Most typically, it presents with a proximal symmetrical weakness. Diagnosis is dependent on recognition of clinical clues, such as cardiorespiratory involvement, evolution, family history, exposure to drugs, the presence of contractures, myotonia and other systemic features, and on investigation findings, most importantly EMG and muscle biopsy. Hereditary syndromes include the muscular dystrophies, muscle channelopathies, metabolic myopathies (including mitochondrial diseases) and congenital myopathies. Muscular dystrophies These are inherited disorders with progressive muscle destruction and may be associated with cardiac and/or respiratory involvement and sometimes non-myopathic features (Box 25.91). Myotonic dystrophy is the most common, with a prevalence of about 12/100 000. Clinical features The pattern of the clinical features is defined by the specific syndromes. Onset is often in childhood, although some patients, especially those with myotonic dystrophy, may present as adults. Wasting and weakness are usually symmetrical, without fasciculation or sensory loss, and tendon reflexes are usually preserved until a late stage. Weakness is usually proximal, except in myotonic dystrophy type 1, when it is distal. Investigations The diagnosis can be confirmed by specific molecular genetic testing, supplemented with EMG and muscle biopsy if necessary. Creatine kinase is markedly elevated in the dystrophinopathies 25.91

The muscular dystrophies

Type	Genetics	Age of onset	Muscles affected	Other features
Myotonic dystrophy (DM1)	Autosomal dominant; expanded triplet repeat chromosome 19q	Any	Face (including ptosis), sternomastoids, distal limb, generalised	later Myotonia, cognitive impairment,

cardiac conduction abnormalities, lens opacities, frontal balding, hypogonadism Proximal myotonic myopathy (PROMM; DM2) Autosomal dominant; quadruplet repeat expansion in Zn finger protein 9 gene chromosome 3q 8–50 years Proximal, especially thigh, sometimes muscle hypertrophy As for DM1 but cognition not affected Muscle pain Duchenne X-linked; deletions in dystrophin gene Xp21 < 5 years Proximal and limb girdle Cardiomyopathy and respiratory failure Becker X-linked; deletions in dystrophin gene Xp21 Childhood/early adulthood Proximal and limb girdle Cardiomyopathy common but respiratory failure uncommon Limb girdle Many mutations on different chromosomes Childhood/early adulthood Limb girdle Very variable depending on genetic subtype, some involve cardiac and respiratory systems Facioscapulohumeral (FSH) Autosomal dominant; tandem repeat deletion chromosome 4q35 7–30 years Face and upper limb girdle, distal lower limb weakness Pain in shoulder girdle common, deafness Cardiorespiratory involvement rare Oculopharyngeal Autosomal dominant and recessive; triplet repeat expansion in PABP2 gene chromosome 14q 30–60 years Ptosis, external ophthalmoplegia, dysphagia, tongue weakness Mild lower limb weakness Emery–Dreifuss X-linked recessive; mutations in emerin gene 4–5 years Humero-peroneal, proximal limb girdle later Contractures develop early Cardiac involvement leads to sudden death fasciculation, paralysis, pallor, sweating, excessive salivation and small pupils. This may be distinguished from severe weakness due to exacerbation of myasthenia ('myasthenic crisis') by the clinical features and, if necessary, by the injection of a small dose of edrophonium. Immunological treatment of myasthenia is outlined in Box 25.90. Thymectomy may improve overall prognosis but awaits clinical trial confirmation. Prognosis is variable and remissions may occur spontaneously. When myasthenia is entirely ocular, prognosis is excellent and disability slight. Young female patients with generalised disease may benefit from thymectomy, while older patients are less likely to have a remission despite treatment. Rapid progression of the disease more than 5 years after onset is uncommon. Lambert–Eaton myasthenic syndrome Other rarer conditions can present with muscle weakness due to impaired transmission across the neuromuscular junction. The most common of these is the Lambert–Eaton myasthenic syndrome (LEMS), which can occur as an inflammatory or paraneoplastic phenomenon. Antibodies to pre-synaptic voltage-gated calcium channels (see Fig. 25.52) impair transmitter release. Patients may have autonomic dysfunction (e.g. dry mouth) in addition to muscle weakness but the cardinal clinical sign is absence of tendon reflexes, which return after sustained contraction of the relevant muscle. The condition is associated with underlying malignancy in a high percentage of cases and investigation must be directed towards identifying any neoplasm. Diagnosis is made electrophysiologically on the presence of post-tetanic potentiation of motor response to nerve stimulation at a frequency of 20–50/sec. Treatment is with 3,4-diaminopyridine, or pyridostigmine and immunosuppression.

1144 • NEUROLOGY Mitochondrial dysfunction can be caused by alterations in either mitochondrial DNA or genes encoding for oxidative processes. Genetic abnormalities or mutations in mitochondrial DNA may affect single individuals and single tissues (most commonly muscle). Thus, patients with exercise intolerance, myalgia and sometimes recurrent myoglobinuria may have isolated pathogenic mutations in genes encoding for oxidation pathways. Inherited disorders of the oxidative pathways of the respiratory chain in mitochondria cause a group of disorders, either restricted to the muscle or associated with non-myopathic features (Box 25.93). Many of these mitochondrial disorders are inherited via the mitochondrial genome, down the maternal line (p. 49). Diagnosis is based on clinical appearances, supported by muscle biopsy appearance (usually with 'ragged red' and/or cytochrome oxidase-negative fibres), and specific mutations either on blood or, more reliably, muscle testing. Mutations may be due either to point mutations or to

deletions of mitochondrial DNA. A disorder called Leber hereditary optic neuropathy (LHON) is characterised by acute or subacute loss of vision, most frequently in males, due to bilateral optic atrophy. Three point mutations account for more than 90% of LHON cases. Channelopathies Inherited abnormalities of the sodium, calcium and chloride ion channels in striated muscle produce various syndromes of familial periodic paralysis, myotonia and malignant hyperthermia, which may be recognised by their clinical characteristics and potassium abnormalities (Box 25.94). Genetic testing is available. Acquired myopathies These include the inflammatory myopathies, or myopathy associated with a range of metabolic and endocrine disorders or drug and toxin exposure (Fig. 25.53). (Duchenne and Becker) but is normal or moderately elevated in the other dystrophies. Screening for an associated cardiac abnormality (cardiomyopathy or dysrhythmia) is important. Management There is no specific therapy for most of these conditions but physiotherapy and occupational therapy help patients cope with their disability. Glucocorticoids can be used in Duchenne muscular dystrophy but side-effects should be anticipated and avoided by dose modification. Ataluren is a compound given by infusion to affected individuals that may 'override' the stop sign in Duchenne, theoretically leading to normalisation of muscle proteins and potentially reducing or arresting functional deteriorations. Treatment of associated cardiac failure or arrhythmia (with pacemaker insertion if necessary) may be required; similarly, management of respiratory complications (including nocturnal hypoventilation) can improve quality of life. Improvements in non-invasive ventilation have led to significant improvements in survival for patients with Duchenne muscular dystrophy. Genetic counselling is important. Inherited metabolic myopathies There are a large number of rare inherited disorders that interfere with the biochemical pathways that maintain the energy supply (adenosine triphosphate, ATP) to muscles. These are mostly recessively inherited deficiencies in the enzymes necessary for glycogen or fatty acid (β -oxidation) metabolism (Box 25.92). They typically present with muscle weakness and pain. Mitochondrial disorders Mitochondrial diseases are discussed on page 49. Mitochondria are present in all tissues and dysfunction causes widespread effects on vision (optic atrophy, retinitis pigmentosa, cataracts), hearing (sensorineural deafness) and the endocrine, cardiovascular, gastrointestinal and renal systems. Any combination of these should raise the suspicion of a mitochondrial disorder, especially if there is evidence of maternal transmission. 25.92 Inherited disorders of muscle metabolism Disease Clinical features Diagnosis Carbohydrate (glycogen) metabolism Myophosphorylase deficiency (McArdle's disease): autosomal recessive Exercise-induced myalgia, stiffness, weakness (with 'second wind' phenomenon), myoglobinuria Creatine kinase (CK) elevated Muscle biopsy Enzyme assay Acid maltase deficiency (Pompe's disease): autosomal recessive Infantile form: death within 2 years Childhood: death in twenties or thirties Adult: progressive proximal myopathy with respiratory failure CK elevated Blood lymphocyte analysis for glycogen granules Muscle biopsy Enzyme assay Lipid metabolism (β -oxidation) Carnitine-palmitoyl transferase (CPT) deficiency Myalgia after exercise, myoglobinuria, weakness CK normal between attacks Urinary organic acids Enzyme assays Muscle biopsy 25.93 Mitochondrial syndromes Syndrome Clinical features Myoclonic epilepsy with ragged red fibres (MERRF) Myoclonic epilepsy, cerebellar ataxia, dementia, sensorineural deafness $\pm$ peripheral neuropathy, optic atrophy and multiple lipomas Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) Episodic encephalopathy, stroke-like episodes often preceded by migraine-like headache, nausea and vomiting Chronic progressive external ophthalmoplegia (CPEO) Progressive ptosis and external oculomotor palsy, proximal myopathy $\pm$ deafness, ataxia and cardiac conduction defects Kearns-Sayre syndrome Like CPEO but early age of onset (< 20 years), heart block, pigmentary retinopathy Mitochondrial neurogastrointestinal

encephalomyopathy (MNGIE) Progressive ptosis, external oculomotor palsy, gastrointestinal dysmotility (often pseudo-obstruction), diffuse leucoencephalopathy, thin body habitus, peripheral neuropathy and myopathy Neuropathy, ataxia and retinitis pigmentosa (NARP) Weakness, ataxia and progressive loss of vision, along with dementia, seizures and proximal weakness

Diseases of muscle • 1145

25.94 Muscle channelopathies Channel Muscle disease Gene and inheritance Clinical features Sodium Paramyotonia congenita SCN4A (17q35) Autosomal dominant Cold-evoked myotonia with episodic weakness provoked by exercise and cold Potassium-aggravated myotonia SCN4A Pure myotonia without weakness provoked by potassium Hyperkalaemic periodic paralysis SCN4A Autosomal dominant Brief (mins to hours), frequent episodes of weakness provoked by rest, cold, potassium, fasting, pregnancy, stress Less common than hypokalaemic periodic paralysis Hypokalaemic periodic paralysis SCN4A Autosomal dominant (one-third new mutations) Longer (hours to days) episodic weakness triggered by rest, carbohydrate loading, cold Chloride Myotonia congenita: Thomsen's disease CLCN1 Autosomal dominant Myotonia usually mild, little weakness Becker's disease CLCN1 Autosomal recessive Myotonia often severe, transient weakness Calcium Hypokalaemic periodic paralysis CACNA1S Autosomal dominant Episodic weakness triggered by carbohydrate meal Malignant hyperthermia CACNA1S, CACNL2A Autosomal dominant Hyperpyrexia due to excess muscle activity, precipitated by drugs, usually anaesthetic agents; most common cause of death during general anaesthetic Potassium Andersen-Tawil syndrome KCNJ2 Autosomal dominant Similar to hypokalaemic periodic paralysis, associated with cardiac and non-myopathic features (skeletal and facial) Ryanodine receptor Malignant hyperthermia Central core and multicore disease RYR1 (19q13) RYR1 Mostly autosomal dominant As malignant hyperthermia above Present in infancy with mild progressive weakness Fig. 25.53 Causes of acquired proximal myopathy. Inflammatory • Polymyositis • Dermatomyositis • Inclusion body myositis (predominantly distal effects) Drugs • Glucocorticoids • Statins • Amiodarone • β -blockers • Opiates • Chloroquine • Ciclosporin • Vincristine • Clofibrate • Zidovudine Paraneoplastic • Carcinomatous neuromyopathy • Dermatomyositis Toxic • Alcohol (chronic and acute syndromes) • Amphetamines/cocaine/heroin • Vitamin E • Organophosphates • Snake venoms Endocrine/metabolic • Hypothyroidism • Hyperthyroidism • Acromegaly • Cushing's syndrome (including iatrogenic) • Addison's disease • Conn's syndrome • Osteomalacia • Hypokalaemia (liquorice, diuretic and purgative abuse) • Hypercalcaemia (disseminated bony metastases)

1146 • NEUROLOGY epilepsydiagnosis.org International League Against Epilepsy: free access to videos of different seizure types and clinical summaries of the epilepsies. headinjurysymptoms.org Symptoms and management of mild and moderate head injury. ihs-classification.org/en/ International Headache Society: full access to 3rd edition of International Classification of Headache Disorders. neurosymptoms.org Advice on managing functional neurological symptoms. ninds.nih.gov National Institute of Neurological Disorders and Stroke. sign.ac.uk Scottish Intercollegiate Guidelines network: SIGN 107 Diagnosis and management of headache in adults; SIGN 110 Early management of patients with a head injury; SIGN 113 Diagnosis and pharmacological management of Parkinson's disease; SIGN 143 Diagnosis and management of epilepsy in adults. wfneurology.org World Federation of Neurology. Further information Journal articles Scolding N, Barnes D, Cader S, et al. Association of British Neurologists: revised (2015) guidelines for prescribing diseasemodifying treatments in multiple sclerosis. Pract Neurol 2015; 0:1-7. Websites aneuroa.org/ American Neurological Association. brainandspine.org.uk and

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