Larry E. Davis
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Fundamentals of Neurologic Disease

Second Edition

Springer

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Preface

After the publication of this book in 2005, medical students in neurology clerkships, psychiatry residents rotating through neurology ward services, as well as many students in allied health fields found this textbook to be a valuable resource in learning the complicated field of neurology. The book continues its original purpose of being short enough to be easily read during a 3–4-week clerkship, having many clear 2-color illustrations, focusing on the most common and important neurologic diseases, and emphasizing the pathophysiology of the disorders. The glossary of medical terms is updated enabling the students to quickly understand the various complex medical terms they encounter.

We have updated and expanded the scope of this textbook to include increasingly prominent neurologic diseases with a new chapter on sleep disorders and a new section on paraneoplastic neurologic syndromes. New information has been added about the phenomenology and pathophysiology of neurologic disease that has been learned in the intervening decade. Although we made every effort to include new information, we were careful to keep the text concise and clear—a hallmark that made the first edition very useful to students and trainees.

Important improvements to the first edition of the textbook are the addition of video clips that provide examples ranging from how to perform the normal neurologic exam to abnormal exam findings common in the diseases discussed. In addition, we begin each chapter with an illustrative case. This helps to provide the patient context for the information in the chapter and remind the reader why this knowledge is important. We hope this will supplement the learning experience and put a "face to a name" when learning about neurologic disease.

We have maintained the order of the original text beginning with a discussion of the approach to the neurologic patient and introductions to the neurologic exam and tests commonly ordered to evaluate patients. Just as in performing the neurologic exam, the text follows a neuroanatomical organization. Within each chapter, key representative diseases that manifest in the particular region of the neuroaxis are reviewed. We continue to cover both adult and pediatric neurologic diseases.

We hope this edition will continue to be valuable to all those who seek to learn the fundamentals of neurology.

Larry Davis, M.D. and Sarah Pirio Richardson, M.D.

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We both thank Dr. Kathy Haaland for writing an excellent chapter on Disorders of Higher Cortical Function and to Erin Milligan, PhD, Department of Neuroscience, University of New Mexico School of Medicine for her advice to improve the clarity of the section on neuropathic pain. We are indebted to Drs. Molly King and Jessica Schultz for their enormous work on the first edition and their encouragement in writing a second edition in which they decided not to participate. Without the success of their early efforts, the second edition would never have happened.

Finally, we thank again all those who helped in the second edition to update the illustrations and radiologic examples. We are grateful to Yvonne Walston, CMI, of Creative Imagery, Inc. who again has provided clear, easy to understand illustrations to improve each chapter. We appreciate the hard work of Meg Radigan, Colleen Frangos, and Ashley Wegele who contributed greatly to this edition with their video and editing expertise. Dr. Blaine Hart again contributed neuroimaging examples to accompany the discussion of radiologic findings in almost all chapters. Thanks also to Drs. Mark Becher and Mario Kornfeld for contributing the neuropathologic illustrations contained within. We also appreciate the encouragement and enthusiasm for this project from Greg Sutorius and Richard Lansing, Springer US.

Contents

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Essential Neurologic Exam

(Minimum exam performed on every patient. Depending on history and abnormal findings, the neurologic exam is usually expanded)

Mental Status: Key elements: (1) alertness (2) orientation to person, place and time, (3) cooperation, (4) estimated cognition and judgment relative to socioeconomic background and education, (5) recent memory, (6) mood and affect (depressed, euphoric, psychotic), (7) speech (articulation and aphasia)

Cranial nerves

II Visual acuity: Use near card with reading glasses, newsprint = 20/40
Visual fields: Finger counting or movement with one eye closed
Fundoscopic exam of retina and optic disk
III, IV, VI: Look for full range of eye movement and palpebral fissures for ptosis Pupils: look for unequal size in mm and light reflex and accommodation
V: Facial sensation (touch and cold sensation in all 3 divisions)
VII: Eye closure, wrinkling forehead and smile
VIII: Auditory- hears whispers in each ear with opposite ear masking Vestibular- nystagmus, balance problems
IX, X: Midline elevation of uvula, no hoarse voice
XI: Sternocleidomastoid and trapezius strength
XII: Tongue protrudes midline without atrophy

Motor

Strength: always test proximal muscles (deltoid, biceps, iliopsoas, quadriceps), arm drift and distal muscles (grip, fingers spread apart, foot and great toe dorsiflexion and plantar flexion). Scoring system: 0/5 no movement, 1/5 flicker, 2/5 moves if gravity eliminated, 3/5 moves against gravity, 4/5 against moderate resistance, 5/5 normal for age and sex
Fine motor coordination of hands (rapid, smooth finger tapping)
Muscle tone (spastic, rigid, flaccid) and bulk (focal or generalized atrophy)
Involuntary movements (tremor at rest, static position of outstretched arms, and intention when moving toward a target), chorea, dystonia

Sensory

Sensation loss in dermatome, sensory nerve distribution or distally in feet
Small unmyelinated fiber loss (diminished cold temperature or pin prick)
Large myelinated fiber loss (diminished vibration to 128cps tuning fork or position sense of toes)

Cerebellum

Finger to nose
Heel to shin
Tandem gait (heel to toe walking)
Romberg test (standing with eyes closed)

Reflexes

Biceps (C5&6), Triceps (C7&8), Knee (L3&4), Ankle (S1)
Babinski response

Spine exam

Straight leg raise
Neck flexion

Gait

Station (width of feet to stand), smoothness of walking forward, backward and turning, presence of normal arm swing

Approach to the Patient With a Neurologic Problem

1

Key Steps in Neurologic Diagnosis and Treatment

Expert neurologists use knowledge both of basic neuroscience (anatomy, biochemistry, physiology, pathology) and of clinical disease (characteristics of specific diseases) to formulate the best possible diagnosis when a patient presents with a neurologic concern (Fig. 1.1). To develop into an expert clinician, students must hone their critical reasoning skills in order to incorporate clinical skills (taking the history, conducting the physical and neurologic examination, and ordering of appropriate tests), basic science knowledge, and an understanding of disease pathogenesis.

Achieving an accurate diagnosis is crucial in reaching the goals of neurologic care: to alleviate signs and symptoms; to restore function; and to keep the patient in the best possible health. To achieve these goals, the doctor's clinical reasoning must establish the correct hypotheses or differential diagnosis, arrive at the correct diagnosis, and initiate appropriate treatment. Studies have shown that errors in clinical reasoning are not rare. They usually stem from three factors: (1) inadequate basic science and medical disease knowledge; (2) incomplete and inaccurate data collection; and (3) incorrect integration and interpretation of the data collected. *Acquisition of medical knowledge* comes from reading medical articles, attending lectures, and experience from seeing many patients. *Incomplete and inaccurate data collection* may come from patient factors (poor historian, altered mental status, unavailable significant others for history, complex illness involving several organs, and multiple chronic illnesses with overlapping symptoms) or clinician factors (poor history taking skills with failure to ask key questions, poor listening to the patient's answers, incomplete clinical exam, missing medical records, inaccurate laboratory data, and lack of appropriate laboratory tests). *Incorrect integration and interpretation of data* collected is complex and stems from ignoring key pieces or history, clinical or lab data, incorrect emphasis of pieces of the acquired data, failure to order key laboratory tests or neuroimaging, and failure to consider the correct differential diagnosis.

The expert clinician often is able to establish the correct diagnosis by listening to the history, forming key hypotheses, narrowing the hypotheses based on the neurologic exam, and ordering the key laboratory and neuroimaging tests. Forming the key hypotheses comes from clinical experience with pattern recognition, knowledge of the more likely (highest probability) diagnoses in that clinical situation, and the ability to order the appropriate tests to confirm the diagnosis. The challenge facing the medical student is to make an accurate diagnosis without the years of experience and extensive reading, which they do not possess

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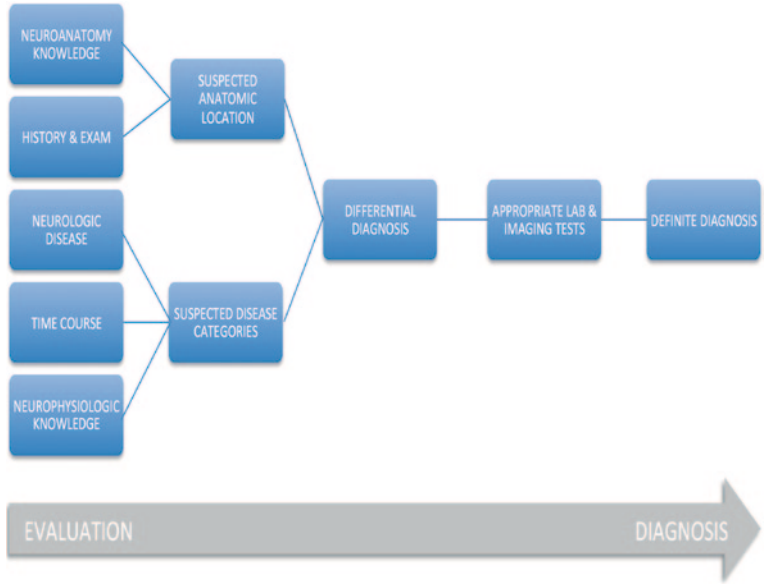


Fig. 1.1 Approach to the neurologic patient

at their level of education. Fortunately, there are methods to help a student narrow a differential diagnosis and increase their accuracy. The following eight steps in diagnosing neurologic conditions can be followed by a junior medical student to help them focus their diagnostic attention. This avoids costly mistakes due to ordering inappropriate laboratory tests, establishing an incorrect diagnosis, and prescribing the wrong treatment.

Steps in diagnosing neurologic conditions

1. Determine that the patient's complaint is a neurologic problem
2. Localize the origin of the neurologic symptom or sign within the nervous system
3. Establish a time course of symptoms
4. Determine most likely disease category
5. Form differential diagnoses
6. Order appropriate laboratory or neuroimaging tests, if needed
7. Establish definite diagnosis
8. Begin appropriate etiologic and symptomatic treatment

Determine the Condition Involves the Nervous System

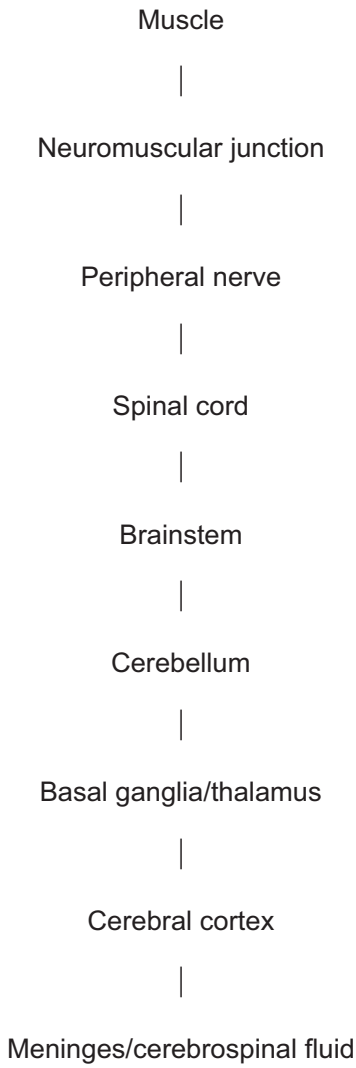
The first step is to determine whether the patient's signs and symptoms are due to an illness involving the nervous system. This decision is based on the history and physical exam coupled with knowledge of general medical diseases. For example, syncope causes loss of consciousness but the etiology is usually from cardiovascular disease.

Make an Anatomic Localization

Another important step based on the history and physical examination is to establish the most likely neuroanatomic site that could cause the patient's problem. While experts may bypass this step, it is helpful to the beginning clinician. Knowledge of the site enables the clinician to narrow the list of differential diagnoses and to determine which laboratory and neuroimaging tests will yield the most useful information.

Neurologic localization is possible because the nervous system is organized such that each major neuroanatomic location gives rise to specific signs and symptoms. The nervous system differs from many other organs such as the liver in which damage to any lobe produces similar symptoms.

The nervous system can be divided into discrete anatomic compartments that give rise to a specific constellation of signs and symptoms. The organization of this book echoes the neuroanatomic organization of the nervous system.



In defining the neuroanatomic site, it is helpful to establish the highest and lowest levels of the nervous system that can give rise to the patient's signs and symptoms. Helpful keys in determining the most likely site include

1. Find the earliest signs and symptoms of the illness, which usually denotes anatomically where the disease began.
2. Determine the anatomic site where weakness and/or sensory changes likely are produced. Motor and sensory systems are multisynaptic long tract systems commonly involved in many diseases. For example, weakness from motor system dysfunction can occur at the motor cortex, brainstem, spinal cord, peripheral nerves, neuromuscular junctions, and/or muscle level—and each site has unique characteristics that help localize the problem.
3. Identify accompanying non-neurologic signs and symptoms that may help localize site.

Although there are many neurologic signs and symptoms that point to a given neuroanatomic site, below are some of the more common clinical features—keeping in mind that there can be exceptions to these rules in certain diseases.

Muscle

- Weakness without sensory loss
- Proximal muscles weaker than distal muscles
- Weakness often slowly progressive
- Muscle atrophy

Neuromuscular Junction

- Fatigue (especially in chewing and in proximal limb muscles)
- Weakness without sensory loss
- Ptosis with episodic diplopia
- No muscle atrophy

Peripheral Nerve

- Mixture of motor and sensory findings
- Distribution of signs may be in a single nerve or multiple nerves
- Distal limb signs more pronounced than proximal signs
- Trunk uncommonly involved
- Pain in feet or along a single nerve distribution

- Sensory loss may be to pain and temperature, vibration and position sense, or multiple modalities
- Muscle atrophy and occasionally fasciculations correspond to involved nerve

Nerve Root
- Dermatomal distribution of sensory loss
- Neck or back pain common that may extend into limb
- Loss of deep tendon reflex associated with that root
- Weakness only in muscles supplied by that root

Spinal Cord
- Sensory level
- Weakness may involve both legs or all limbs
- Bowel and bladder signs
- Autonomic nervous system dysfunction
- Loss of reflexes at the injury level with hyperactivity below level
- Babinski signs
- Leg spasticity

Brainstem
- Cranial nerve involvement (especially face weakness, face sensory loss, dysphagia, dysarthria, hoarseness, and diplopia)
- Vertigo
- Tetraparesis with four limb weakness and spasticity
- Coma or depressed level of consciousness
- Changes in blood pressure, heart rate, and respiratory rate

Cerebellum
- Ataxia of limbs and/or gait
- Vertigo
- Nystagmus
- Slurred speech

Basal Ganglia
- Extrapyramidal signs (bradykinesia, shuffling gait, masked facies, etc.)
- Movement disorder (chorea, athetosis, dystonia, or tremor which may be unilateral or bilateral)

Cerebral Cortex
- Unilateral focal neurologic signs such as hemiparesis, hemihypesthesia, homonymous hemianopia
- Aphasia
- Memory loss
- Apraxia
- Dementia
- Seizures

Meninges and Cerebrospinal Fluid
- Headache—usually diffuse
- Meningismus
- Cranial nerve signs—often multiple nerves involved

Establish time course of symptoms

The time course of the patient's symptoms is an important part of the history and can be difficult to obtain. The patient often may not have recognized early symptoms or attributes them to other causes. Determination of the time course helps to identify the urgency of the work-up, disease category classification, and prognosis. In children, it is often difficult to determine whether the disease is progressive or static. Static lesions may be misinterpreted as progressive when children fail to reach their expected age-related milestones.

Determine most likely disease etiology

Most neurologic diseases fall into one disease category, and each category has common clinical features that allow selection of the category. Below are useful questions to establish the most likely disease category:
- Is the problem new or has it occurred in the past?
- Was there a trigger for the onset or episode?
- What aggravates and alleviates the symptom?
- Was onset acute, subacute, or gradual?
- Are signs rapidly progressive (over hours to 2 days), subacute (over days to a few weeks),

slowly progressive (over months to years) or static and not progressive?
- Are signs unilateral or bilateral?
- Is pain a feature, what are its characteristics, and where is it located?
- Is there a family history of similar problems?
- Is lesion likely a mass or non-mass?
- Is the location focal, multifocal, or diffuse?

The acronym VINDICATES is one way to classify etiological groups. Below are common clinical features seen in each group. Again, diseases in each category may not express all the features listed.

Vascular
- Sudden onset
- Asymmetrical signs
- Symptoms worse at beginning and then improve
- Hemiparesis and hemihypesthesia (but not anesthesia) common

Inflammatory/Infectious
- Fairly rapid onset and progression
- Fever common
- Signs usually involve meninges or cerebral cortex
- White blood cell count and erythrocyte sedimentation rate elevated

Neoplastic
- Slowly progressive
- In adults mainly involves cerebral cortex while in children mainly involve the cerebellum and brainstem
- Unilateral focal signs common early in disease

Degenerative/Hereditary
- Slowly progressive
- Symmetrical signs
- Diffuse signs
- Pain seldom prominent
- Family history of similar illness may be present
- Clinical features vary but often include dementia, parkinsonism, and weakness
- In genetic diseases, the age of clinical onset is helpful

Intoxication or Withdrawal
- Gradual onset of symptoms over hours to weeks
- History of drug or substance use
- Altered mentation (confusion, delirium, stupor, or coma)
- Distal symmetrical polyneuropathy common (alcohol)
- Focal neurologic signs less common

Congenital/Developmental
- Present at birth or early childhood
- Family history of similar disease common
- Mainly static but can appear progressive in childhood as child fails to gain developmental milestones
- Mental retardation, seizures, and spasticity common

Autoimmune/Demyelinating
- Onset over days
- Prominent motor, sensory, visual, and/or cerebellar signs common
- Symmetric or diffuse clinical features

Trauma
- Abrupt onset
- History of trauma present
- Coma or loss of consciousness common
- May cause motor and sensory dysfunction of one peripheral nerve
- Clinical improvement often occurs

Endocrine/Metabolic
- Gradual onset
- Slowly progressive
- Systemic disease common (liver, lung, adrenal, or kidney)
- Symmetric signs
- Abnormal lactation common

Social/Psychological
- Past or present history of psychiatric illness, especially depression
- History of abuse
- Waxing and waning of symptoms
- Non-physiological exam

- Secondary gain
- Positive review of systems with multiple somatic complaints

Form Differential Diagnoses

At this point, the clinician uses the information gained from the history and neurologic examination, most likely disease category, and knowledge of neuroanatomy and neurophysiology to establish a clinical diagnosis or list of relevant differential diagnoses. In essence, the clinical diagnosis is a working diagnosis that allows the clinician to determine which laboratory or neuroimaging tests, if any, are necessary to establish a definite diagnosis. While this book gives the reader considerable basic information about common neurologic diseases, the reader should refer to journal articles and comprehensive neurology textbooks for complete information on specific diseases and details about up-to-date therapy.

The differential diagnosis should focus on diagnoses considered most likely. The adage, "Think of horses, not zebras, when you hear hoof beats, unless you are in Africa" is true in neurology. Common diagnoses are common even if they do not present with all features described in a textbook. The differential diagnosis should contain diseases that you intend to rule in or out by appropriate laboratory tests. One can always add more diseases to the differential diagnosis list as the work-up proceeds. However, it is important to remember when your patient has atypical features for your common diagnosis to also consider alternative uncommon diagnoses.

Order Appropriate Laboratory and/or Neuroimaging Tests, if Needed

Neurologic tests should serve to (1) establish the etiologic diagnosis when several likely diagnoses exist, (2) help make therapeutic decisions, and (3) aid in following the results of treatment. Knowledge of the approximate neuroanatomic location and the most likely category of disease process enables the clinician to order appropriate tests. As neurologic tests are expensive, time-consuming, and occasionally dangerous or uncomfortable to the patient, thought must be given before ordering. The overall goal should be to establish the diagnosis efficiently in both time and money. The shotgun approach (where many tests are ordered in hopes of finding the diagnosis) is both expensive and often unhelpful.

Establish Definite Diagnosis

The definite or etiologic diagnosis implies that the diagnosis is firm and no further diagnostic tests are indicated. Combining information gained from the history and physical exam, the results of appropriate laboratory and neuroimaging tests, and knowledge of the anatomy and pathophysiology of the disease in question, the physician (or student physician) arrives at the *definite* diagnosis. For some diseases, there may be a single diagnostic test that establishes the etiology. For example, growth of *Streptococcus pneumonia*e from the cerebrospinal fluid of a patient with meningeal symptoms establishes the definite diagnosis of pneumococcal bacterial meningitis. For other diseases, classic migraine headache for example, there may be no diagnostic test that establishes the etiology and definite diagnosis must rest on the history, physical exam, and knowledge of the disease in question.

Begin Appropriate Etiologic and Symptomatic Treatment

Treatment of neurologic disease differs from treatment of diseases of other organs in several aspects. First, neurons rarely divide after birth. Thus, the brain cannot replace loss of neurons. Second, damaged central nervous system (CNS) myelin or oligodendrocytes have limited ability to remyelinate the naked axon segments. Third, surgical removal of a brain lesion may not be

possible because the lesion is inaccessible due to its deep anatomic location or because the lesion is surrounded by critical brain areas (*eloquent brain*). Fourth, any drugs given systemically to the patient must be capable of crossing the blood–brain barrier. This barrier severely limits many otherwise effective medications that could be given to the patient. Even if the drugs were given intrathecally into the CSF space to bypass the blood–brain barrier, they would have difficulty diffusing any distance into the cerebral cortex.

Management of the patient with a neurologic disease can be divided into four categories: prevention, etiologic treatment, symptomatic treatment, and rehabilitation. The key to success is to work with the patient to manage their concerns—not just to respond to abnormal laboratory results.

Prevention "An ounce of prevention is worth a pound of cure" is particularly pertinent in neurologic disease. A major effort in neurology focuses on early disease detection and prompt treatment to minimize later complications. For example, the treatment of hypertension markedly reduces the incidence of subsequent strokes. Treatment of the patient with a transient ischemic attack with aspirin reduces future strokes by 20%. Immunization of children with poliovirus vaccine prevents subsequent paralytic poliomyelitis.

Etiologic Treatment Treatment of the etiology should be the goal in the care of every patient. Often it is possible to reverse or halt the underlying disease process. This may cure the patient, such as by surgical removal of a meningioma. Once the etiology is established, current treatment options are easily found in standard medical or neurologic textbooks or recent review articles in journals. Unfortunately, for many neurologic diseases, the etiologies are unknown or partially known and hence treatment options may not exist for certain diseases or be focused at the nervous system in general—causing treatment-limiting side effects.

Symptomatic Treatment Treatment should be aimed not only at the etiology but also at relieving the patient's signs and symptoms—they are, after all, why the patient sought care. Symptomatic treatment often brings considerable improvement in the quality of the patient's life. For example, administration of L-dopa greatly improves the motor features of Parkinson's disease. However, symptomatic treatment is not etiologic treatment. While L-dopa improves the symptoms of Parkinson's disease, it does not halt disease progression. Similarly, narcotics relieve the pain of the brain tumor but do not cure the tumor. When treating the patient, it is important to observe for side effects.

Symptomatic treatment should also address the psychological aspects of the illness. Fear or worry about the disease frequently causes anxiety or depression that may incapacitate the patient. Even if the disease cannot be cured and is fatal, the patient should know that the physician cares and will do everything possible to minimize suffering.

Neurorehabilitation Neurorehabilitation should not be overlooked as an important therapeutic tool in the care of the neurologic patient. We are becoming increasingly aware that the brain has considerable capacity for recovery from damage. There are many factors involved in recovery. An important one is neuroplasticity. The term "neuroplasticity" means that other neuronal populations take over the function of the damaged part of the brain. At present, we have little understanding of how the brain can alter synaptic pathways to accomplish this. In general, children have a greater capacity than adults for neuroplasticity. Increasing evidence suggests that it can be enhanced through active stimulation, motivation, and rehabilitation of the patient. In addition, rehabilitation can help the patient new methods to compensate.

Neurologic Examination

2

Overview

Observations made during the interview begin the neurologic exam. You should note the patient's speech pattern, mentation, behavior, and even presence of abnormal motor movements. The neurologic exam is divided into specific components that are documented in the record. Doing the exam in an organized, stereotyped way will help to ensure that no component is missed. Below is a recommended order for the neurologic exam as it is commonly performed. For each area, there are additional tests that can be done (see comprehensive neurology textbooks for details). A video demonstrating the normal neurologic exam can also be viewed.

Mental Status Examination

The mental status exam can be more or less thorough depending on the presenting problem and your observations while taking the history. Areas to examine include alertness, attention, cooperation, memory, cognition, affect, speech, and language.

Alertness, attention, and cooperation are evaluated during the history. If the patient fails to demonstrate the ability to attend, to stay awake, or to cooperate, the remainder of the mental status exam should be interpreted cautiously. For example, problems with memory may be due to the fact that the patient never paid attention to the information presented.

Memory problems are suggested by a vague imprecise history, inability to recall current events, or not remembering the events of the day. One can ask the patient to repeat three objects (like apple, table, and penny) immediately and then after 5 min. Normal subjects usually can repeat at least two of the objects at 5 min, especially with prompting.

Cognition should be evaluated relative to the patient's education and socioeconomic background. As an estimate of the patient's general mental capability, cognition includes reasoning, planning, solving problems, thinking abstractly, comprehending complex ideas, learning quickly, and learning from experience. If a deficit is detected, critical questions include the timing of the onset and whether it is progressive or static in course.

One useful screening test of mental status is called the *Folstein Mini-mental Status Exam* (Table 2.1). The test is not sensitive for mild cognitive impairment as scores as low as 22/30 may be normal depending on education and socioeconomic background.

Mood and *affect* are assessed during the mental status exam as psychiatric disease such as depression can present with memory complaints. When evaluating affect, it is important to note inappropriate tearful or jocular behavior that may not be congruous with the subject matter being discussed.

Speech and language abnormalities are divided into dysarthria and dysphasia. *Dysarthria* results

Electronic supplementary material The online version of this chapter (doi: 10.1007/978-1-4939-2359-5_2) contains videos as supplementary material and can be accessed at http://link.springer.com/book/10.1007/978-1-4939-2359-5.

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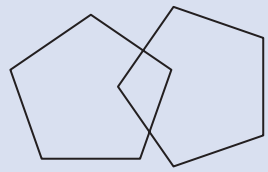
Table 2.1 Folstein mini-mental status examination. (Adapted from [1])

Task	Instructions	Scoring	
Date orientation	"Tell me the date?" Ask for omitted items	One point each for year, season, date, day of week, and month	5
Place orientation	"Where are you?" Ask for omitted items	One point each for state, county, town, building, and floor or room	5
Register three objects	Name three objects slowly and clearly. Ask the patient to repeat them	One point for each item correctly repeated	3
Serial sevens	Ask the patient to count backwards from 100 by 7. Stop after five answers (Or ask them to spell "world" backwards)	One point for each correct answer (or letter)	5
Recall three objects	Ask the patient to recall the objects mentioned above	One point for each item correctly remembered	3
Naming	Point to your watch and ask the patient "what is this?" Repeat with a pencil	One point for each correct answer	2
Repeating a phrase	Ask the patient to say "no ifs, ands, or buts"	One point if successful on first try	1
Verbal commands	Give the patient a plain piece of paper and say "Take this paper in your right hand, fold it in half, and put it on the floor"	One point for each correct action	3
Written commands	Show the patient a piece of paper with "CLOSE YOUR EYES" printed on it	One point if the patient's eyes close	1
Writing	Ask the patient to write a sentence	One point if sentence has a subject, a verb, and makes sense	1
Drawing	Ask the patient to copy a pair of intersecting pentagons onto a piece of paper 	One point if the figure has ten corners and two intersecting lines	1
Scoring	A score of 24 or above is considered normal		***30***

from poor articulation—like talking with rocks in your mouth. The sentence makes sense but the sound is garbled. Abnormalities of the mouth (poor dentition) or CN IX, X, and XII dysfunction are common causes. Dysarthria does not affect the ability to read or write. *Dysphasia* implies dysfunction in constructing or understanding language. In expressive aphasia, the patient often speaks short truncated sentences without adjectives or adverbs but understanding is relatively preserved. Receptive aphasia usually has normal sounding speech but the content does not make sense relative to the question. In both dysphasias, there is difficulty in repeating phrases such as "No ifs ands or buts." Dysphasia also affects the ability to read and write. Language abnormalities and apraxias are fully covered in the chapter on higher cortical function

Cranial Nerves

I. Olfaction is seldom routinely tested unless the patient has a complaint of poor taste or smell or history suggesting problems with frontal lobes or facial bones. First, ensure that there are no obstructions in the nasal passages by inspection with otoscope. Smell cannot be tested on each side separately since both sides of the nose communicate. Ask the patient to close their eyes and to identify the odor when presented and then identify the odor's name. Common substances such as coffee grounds, unlit cigarettes, and perfumed soap are convenient to test. Use of alcohol or ammonia should not be used as those odors stimulate CN V fibers located in the anterior nose and give a false-positive test.

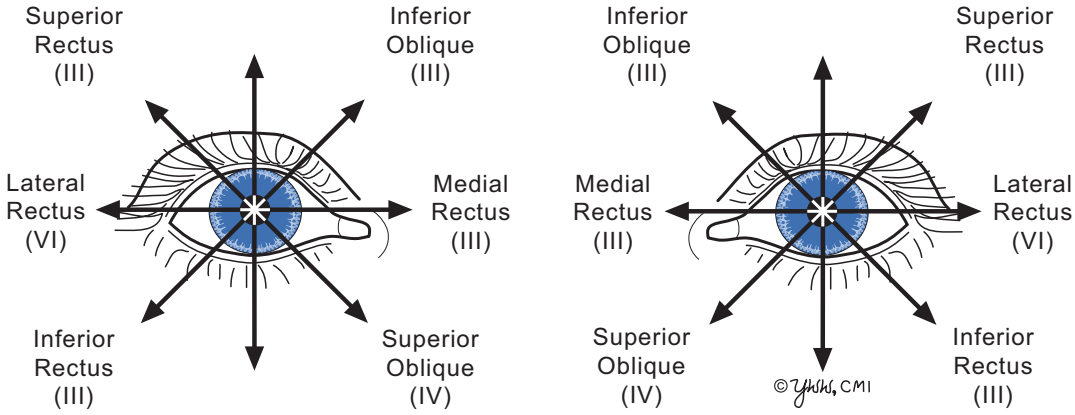


Fig. 2.1 Directions of gaze

II. Optic nerve function is usually divided into visual acuity, visual fields, and fundoscopic exam. To test *visual acuity* in each eye with their glasses, one can use a Snellen eye chart or a near-vision card. Ability to read standard newsprint suggests 20/40 or better acuity. If their glasses are not available, a pinhole card (paper with pin pushed through the center) can improve their vision. If visual acuity is 20/50 or better, the problem is usually ocular and not neurologic.

Visual fields are evaluated by confrontation testing each eye separately. Standing about 4 feet away with one eye closed and the patient looking at your nose, the patient is asked to count the number of fingers (1, 2 or 5) presented in the four visual quadrants. Confrontational testing can detect a homonymous hemianopia or quadranopia but not constriction of visual fields from glaucoma.

On fundoscopic examination, carefully observe the retinal vessels for hemorrhages and exudates and then follow them into the optic disc itself. Color and size of the disc and the presence of papilledema are particularly important. Papilledema is suggested by swollen optic disc heads with the margins appearing blurred/raised.

Pupil size and the light reflex involve CN II and autonomic eye nerves. Observe the pupils in dim light with illumination from below. The pupils should be round and be within 1 mm of each other in size and constrict equally when the patient attempts to look at their nose (*accommodation*). Anisocoria or unequal pupil sizes signifies dysfunction of sympathetic nerve (small pupil or miosis) or parasympathetic nerve (large pupil or mydriasis). In the *light reflex*, one tests a direct light reflex (the pupil constricts when a light is shined into it) and then a consensual reflex (the opposite pupil constricts when a light is shined into the other). Both pupils should constrict briskly and equally to light. Shining the light into one eye and failing to see both pupils to constrict imply ipsilateral retina or CN II dysfunction, failure of ipsilateral iris to constrict implies dysfunction of ipsilateral sympathetic nerve, and failure of contralateral pupil to constrict suggests dysfunction of contralateral sympathetic nerve.

III, IV, VI. Oculomotor, trochlear, and abducens nerves innervate the extraocular eye muscles. They are evaluated by observing the eye move correctly when the patient is asked to follow your finger in all nine directions of gaze (Fig. 2.1). Observe whether the eye movements are conjugate (move together), move the entire range, and are smooth. Presence of double vision in one gaze direction suggests dysfunction of a given nerve or eye muscle. In Fig. 2.2, a patient with a right CN VI palsy is unable to move his right eye laterally. *Nystagmus* can be seen in healthy people at the far end of horizontal gaze, but is an abnormal sign at rest, near mid position or is sustained.

The size of the palpebral fissure (distance between upper and lower eyelid) depends on CN III and sympathetic nerves. Marked drooping of the upper eyelid (ptosis) that interferes with vision implies CN III dysfunction or prior eye trauma. Mild ptosis without obstructing vision implies sympathetic nerve dysfunction. When mild ptosis is

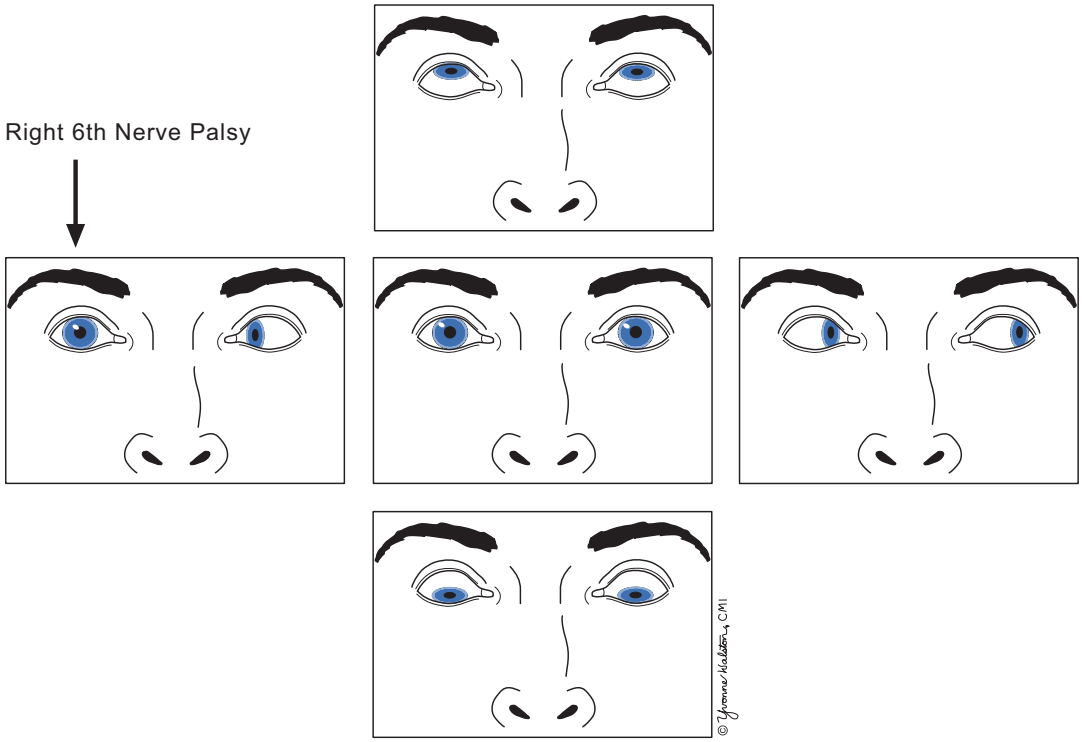


Fig. 2.2 Right 6th nerve palsy

accompanied by ipsilateral miosis (pupillary constriction), the lesion is called Horner's syndrome.

V. Trigeminal nerve function is tested by evaluating face sensation. Lightly touch the 3 divisions of the CN 5 with a cotton tip, your fingers or a cool tuning fork. The patient should perceive these as equal on both sides. The corneal reflex (touching the edge of the cornea over the outside of the iris with a wisp of cotton or a soft facial tissue) should produce prompt blinking of both eyes. Failure to blink in either eye suggests an afferent problem in the stimulated CN V, failure of ipsilateral eye but not contralateral eye to blink suggests dysfunction of ipsilateral CN VII, and failure of contralateral eye to blink but not ipsilateral eye suggests dysfunction of contralateral CN VII. Having the patient open her jaw and attempt to move the jaw laterally against resistance test motor fibers of CN V.

VII. Facial nerve function is evaluated by testing facial muscles. Ask the patient to open her eyes wide, close them shut tightly and pull back her lips. The muscles of facial expression, innervated by CN VII, should show equal and symmetrical movement on both sides of the face.

A lower motor neuron lesion (facial nerve or nucleus) produces weakness of both the upper and lower face. An upper motor neuron lesion (corticobulbar tract above the level of CN VII nucleus) causes weakness only of the lower face because forehead muscles receive bilateral innervation.

The chorda tympani nerve branch can be tested by determining whether the patient can detect the taste of sugar or salt placed on the anterior two-thirds of one side of the tongue.

VIII. Auditory nerve hearing evaluation is tested by masking the opposite ear with finger or sounds and determining whether the patient can hear whispers (mid sound frequencies) or rubbing fingers (higher sound frequencies) in the other ear. If there is hearing loss, the external auditory canal should be inspected with an otoscope. *Vestibular* nerve testing is described in the chapter on dizziness and vertigo.

IX. Glossopharyngeal nerve function is tested by asking patient to say, "aah" and observing the soft palate and uvula rising symmetrically. Deviation of the uvula and soft palate to one side indicates a lesion on the contralateral nerve. Touching the pharynx with a cotton Q-tip should elicit a gag reflex from CN IX and X.

X. Vagus nerve function is tested by listening for hoarseness in the patient's voice. If present, vocal cord movements can be visualized by otolaryngology to confirm paralysis.

XI. Accessory nerve function is tested by shoulder shrug and head turn. Ask the patient to shrug her shoulders to her ears and then push down. Strength should be symmetric. Then ask her to turn her head to either side while you apply resistance with your entire hand on her lower jaw. Again, strength should be symmetric. Remember that the right sternocleidomastoid muscle turns the head to the left.

XII. Hypoglossal nerve function is evaluated by asking a patient to protrude the tongue straight out and moving it from side to side. Deviation of the tongue to one side with atrophy and fasciculations in that side of the tongue suggests an ipsilateral lower motor neuron lesion.

Neck: The patient should be able to smoothly flex her neck to touch her chin on the chest and rotate the head fully towards the shoulders. In meningitis, the patient cannot flex or resists flexing the neck while in cervical arthritis, there is restricted rotation of the neck, called meningismus.

Motor Examination

A complete motor examination includes the evaluation of muscle bulk, tone, strength, and gait. In addition, any involuntary movements should be noted.

Muscle bulk compares the size of muscles on each side. In particular observe the hands for atrophy of small intrinsic muscles and feet for atrophy of intrinsic foot muscles seen by permanent elevation of toes at the second metatarsal joints (hammer toes). Atrophy from lower motor neuron lesions (denervation) shrinks a muscle by two-thirds its normal size. If the denervation is active, fasciculations are seen. Upper motor neuron lesions, disuse, or deconditioning reduces bulk by only one-third without fasciculations.

Table 2.2 British Medical Research Council method of scoring muscle strength

Score	Strength finding
0	No movement
1	Flicker movements
2	Movement with gravity eliminated
3	Movement against gravity only
4	Full movement against some resistance
5	Full movement against full resistance

In evaluating *muscle tone*, the patient is asked to relax like being a "rag doll" while you move the limbs through extension, flexion, and rotation. Think of the tone as a rubber band and decide if she is floppy (hypotonic), normal, or too tight (spasticity or rigidity). Hypotonia suggests a cerebellar or lower motor neuron lesion. Spasticity is increased tone that depends on how quickly you move the limb—with faster movement, there is more spasticity and with slow movement, less increase in tone. Rigidity is resistance to limb movement that is consistent through the entire range (like bending a lead pipe) as seen in Parkinson's disease.

Muscle strength is commonly evaluated using the British Medical Research Council method where strength is graded on a relative scale of 0 to 5 (Table 2.2). In this relative system, the muscle strength of both a healthy grandmother and a young male weightlifter would both be scored at 5. The value of this scoring system is that it is highly reproducible between examiners. The disadvantage is that it is insensitive to slight worsening of mild weakness since both would be scored 4.

Since there are over 400 muscles in the human body, it is useful to group muscles into proximal and distal muscles (Table 2.3). It is helpful to ask the patient to flex or extend the limb and hold it there against your force. Start with minimal pressure and then increase until maximal or the limb gives way. True weakness tends to be gradually overcome as pressure increases. Give-way or suddenly "letting go" of a position by a patient may indicate pain in a limb or reluctance to give "full effort".

Table 2.3 Muscles commonly tested and their nerve root and peripheral nerve

	Muscle and (function)	Nerve root	Peripheral nerve
Proximal arm	Deltoid (adducts shoulder)	C5	Axillary
	Biceps (flexes elbow)	C5	Musculocutaneous
	Triceps (extends elbow)	C7	Radial
Distal arm	Flexor carpi radialis and ulnaris (wrist flexors)	C6–7	Median and ulnar
	Extensor carpi radialis and ulnaris (wrist extensors)	C6–8	Radial
	Abductor pollicis brevis (abducts thumb)	C8	Median
	Abductor digiti minimi (abducts little finger)	T1	Ulnar
Proximal leg	Iliopsoas (hip flexion)	L2-4	Femoral
	Quadriceps (knee extension)	L2-4	Femoral
	Hamstrings (Knee flexion)	L4-S1	Sciatic
Distal leg	Tibialis anterior (ankle dorsiflexion)	L4-5	Peroneal
	Gastrocnemius (ankle flexor)	S1-2	Tibial
	Tibialis posterior (ankle inversion)	L5	Tibial
	Extensor hallucis longus (dorsiflexes great toe)	L5-S1	Peroneal
	Foot flexors (dorsiflexion of all toes)	L5-S1	Tibial

Weakness comes from many anatomic locations. Figure 2.3 gives the key anatomy of the corticospinal tract that produces upper motor neuron lesions. Chapters on the approach to the patient and disorders of muscle, neuromuscular junction, peripheral nerve, spinal cord, brainstem, and cerebrovascular disease give additional ways to evaluate the motor system.

Gait evaluation is the most useful screening test of the motor system. Ask the patient to get out of chair and walk normally, on toes and heels, and turn. One can also ask a patient to hop or walk backwards. Observe for smoothness of the gait, posture of the trunk and arms, unsteadiness during turns, appropriate armswing, and any balance abnormalities. The presence of an asymmetrical gait or limp can be caused by many processes such as hemiparesis, leg joint arthritis, old fractures, balance problems, or even leg pain that must be sorted out during the rest of the neurologic exam.

Balance can be evaluated by using the Romberg position and tandem gait. In the Romberg test, the individual is asked to put her feet together and balance with her eyes open. If the balance is normal, the patient is asked to close her eyes, thus assuming the Romberg position. Marked sway or loss of balance with eyes closed, but not when open, is the Romberg sign. This sign is usually due to poor position sense in the feet. In tandem walking, the patient attempts to walk heel to toe in a straight line. Abnormal tandem gait implies dysfunction of inner ear, position sensors in the feet, vestibular brainstem/cerebellar nuclei or tracts, or orthopedic leg problems.

Involuntary movements should be noticed during the history and exam. In general, the movements should be characterized by: (1) location (bilateral vs. unilateral, upper extremities vs. lower extremities); (2) duration (continuous vs. intermittent); (3) provoking factors (at rest vs. posture vs. action); and (4) alleviating factors (change of position vs. voluntary suppression). Types of involuntary movements include tremor, dystonia, chorea, ballismus, tics, and myoclonus. Most involuntary movements are due to disorders of the basal ganglia and that chapter describes these involuntary movements.

Coordination

For coordination to be tested accurately, the patient must have normal or near-normal muscle strength of their limbs. The finger–nose–finger test asks the patient to touch the tip of the index finger to her nose, then to the examiner's finger, and back to the nose again. Cerebellar dysfunction causes a tremor perpendicular to the direction of movement that intensifies as the finger nears the target and is especially worse coming

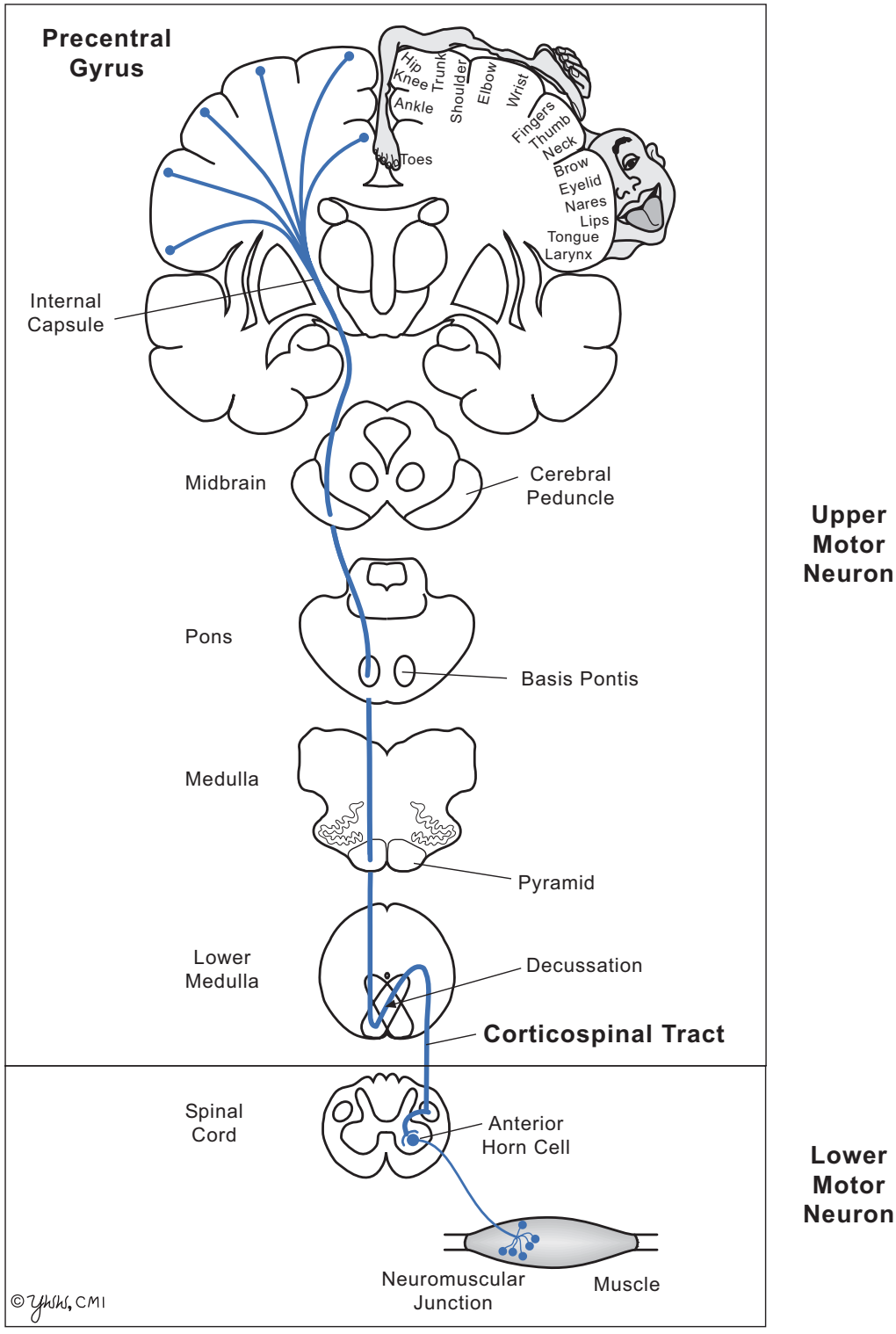


Fig. 2.3 Anatomy of the corticospinal tract

in to the nose. The heel-to-shin test asks the patient to place a heel on the opposite knee with the ankle dorsiflexed and then slide the heel down the front of the shin to the great toe. Again cerebellar dysfunction causes the heel to move perpendicular to the line of heel movement. Rapid alternating movement test asks the patient to pat the knee with the palm and then the back of the hand as she gradually increases the speed.

Sensation

The evaluation of sensation is often divided into small unmyelinated nerve fiber peripheral nerve functions (pain, temperature), larger thinly myelinated nerve fiber functions (vibration, position sense) and cortical sensory functions (stereognosis, graphesthesia, two-point discrimination). Normally, the tests are performed on the hands and feet unless the history or exam suggests damage to particular nerves or roots (Fig. 2.4a, b).

Pain is usually tested with a new safety pin and the patient is asked to determine whether the gentle prick was "sharp" from pin edge or "dull" from clip edge. One compares the sides and other areas in the limb. Pain stimulates both unmyelinated and thinly myelinated sensory fibers. Always discard the safety pin when finished.

Temperature is usually tested with a cool metal object such as a tuning fork. The control temperature for comparison is the face or upper arm. The patient is asked whether the test skin area is as cool as the control skin area. The test is usually done on the dorsum of the foot and moves up the leg until the temperature is perceived as cool.

Vibration is tested with a 128 cps tuning fork by pressing the stem over the great toe and placing your finger beneath the toe. The patient is asked to say when the vibration disappears, which should be when you can no longer feel it vibrate in your finger. The tuning fork is moved up the leg proximally until the patient perceives the vibration well. If the toes have normal vibration sensation, testing the fingers is seldom necessary.

Position sense is determined by grasping the great toe on the sides and instructing the patient to respond "up or down" from where the toe was last time. Move the toe only a millimeter or two. If the patient has trouble distinguishing up or down, you can move the toe in a larger arc until you are satisfied they can detect movement. If the toes are normal, testing the fingers is seldom necessary.

Stereognosis is tested with the eyes closed and asking the patient to identify simple objects placed in the hand, such as coins or a key. *Graphesthesia* is tested with the eyes closed and asking the patient to identify numbers or letters written on the palm of each hand. These tests require normal primary sensation and abnormalities imply dysfunction in the contralateral sensory cortex or parietal lobe (see chapter on higher cortical function).

Reflexes

Deep tendon reflexes (DTRs) or stretch reflexes evaluate a local circuit from muscle spindles to spinal cord level and back to appropriate muscles. The most common reflexes tested are biceps jerk (TJ), triceps jerk (TJ), knee jerk (KJ), and ankle jerk (AJ) (Fig. 2.5). Position the patient comfortably, usually with arm resting on the thigh and feet just touching the exam step or the floor. Using a long well-balanced hammer with a soft percussion tip, tap the tendon to deliver the stimulus. The key is to be consistent in the application of force. If the reflex is difficult to attain, it can be augmented by asking the patient to grit her teeth or make a fist with the other hand. Children and young adults, especially if anxious or cold, tend to have brisk reflexes while the elderly often have diminished reflexes. DTR are scored per Table 2.4.

The extensor *plantar reflex* or *Babinski sign* suggests damage to the corticospinal tract (upper motor lesion) in children older than 2 years and adults. It is elicited by scratching the sole of the foot from the heel, along the lateral aspect of the foot, and finally arching across the ball of the foot to the great toe. The Babinski sign is present if the great toe extends—often with fanning of the other toes accompanying the great toe exten-

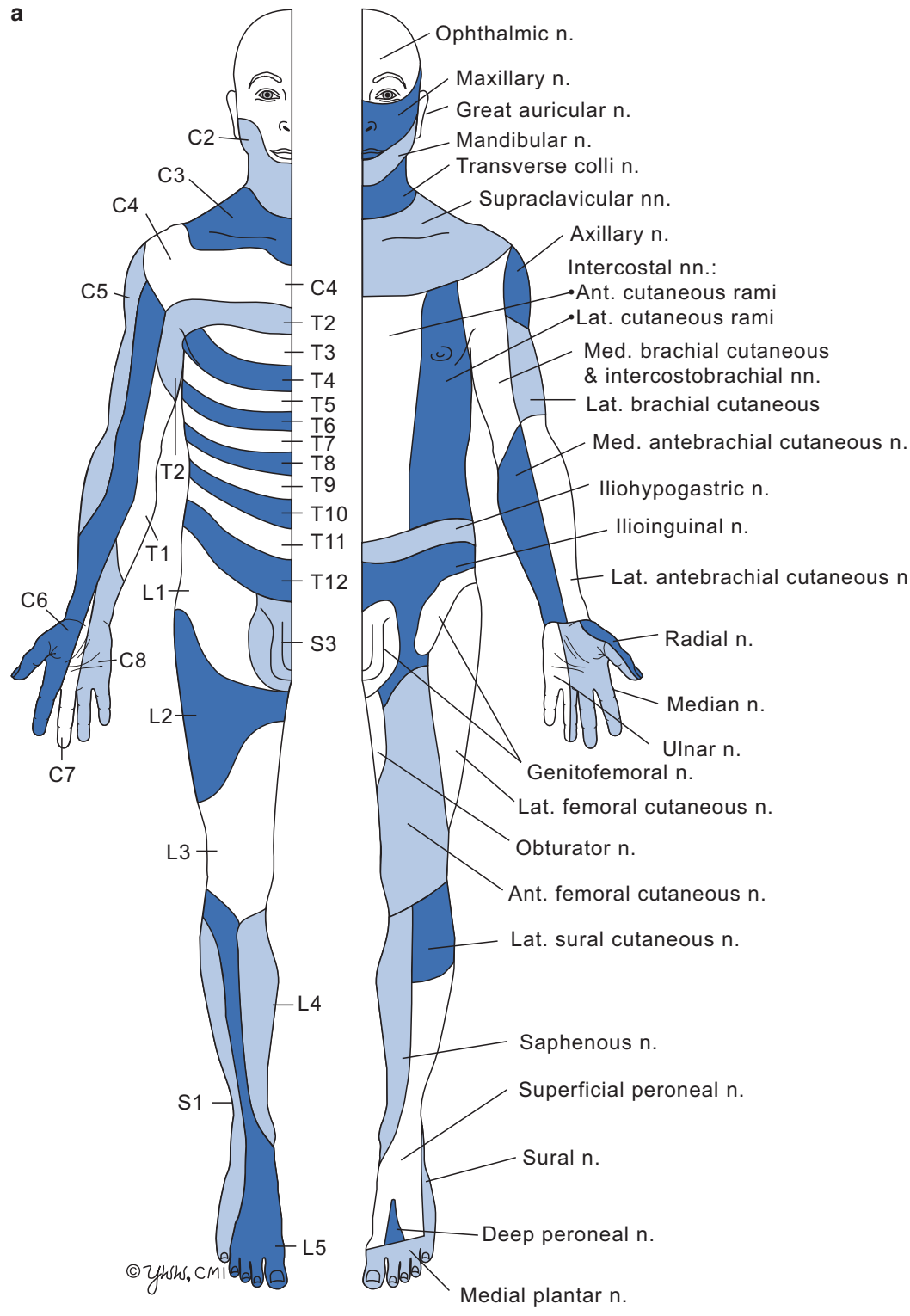


Fig. 2.4 Dermatomes and peripheral nerve distributions. **a** Anterior view.

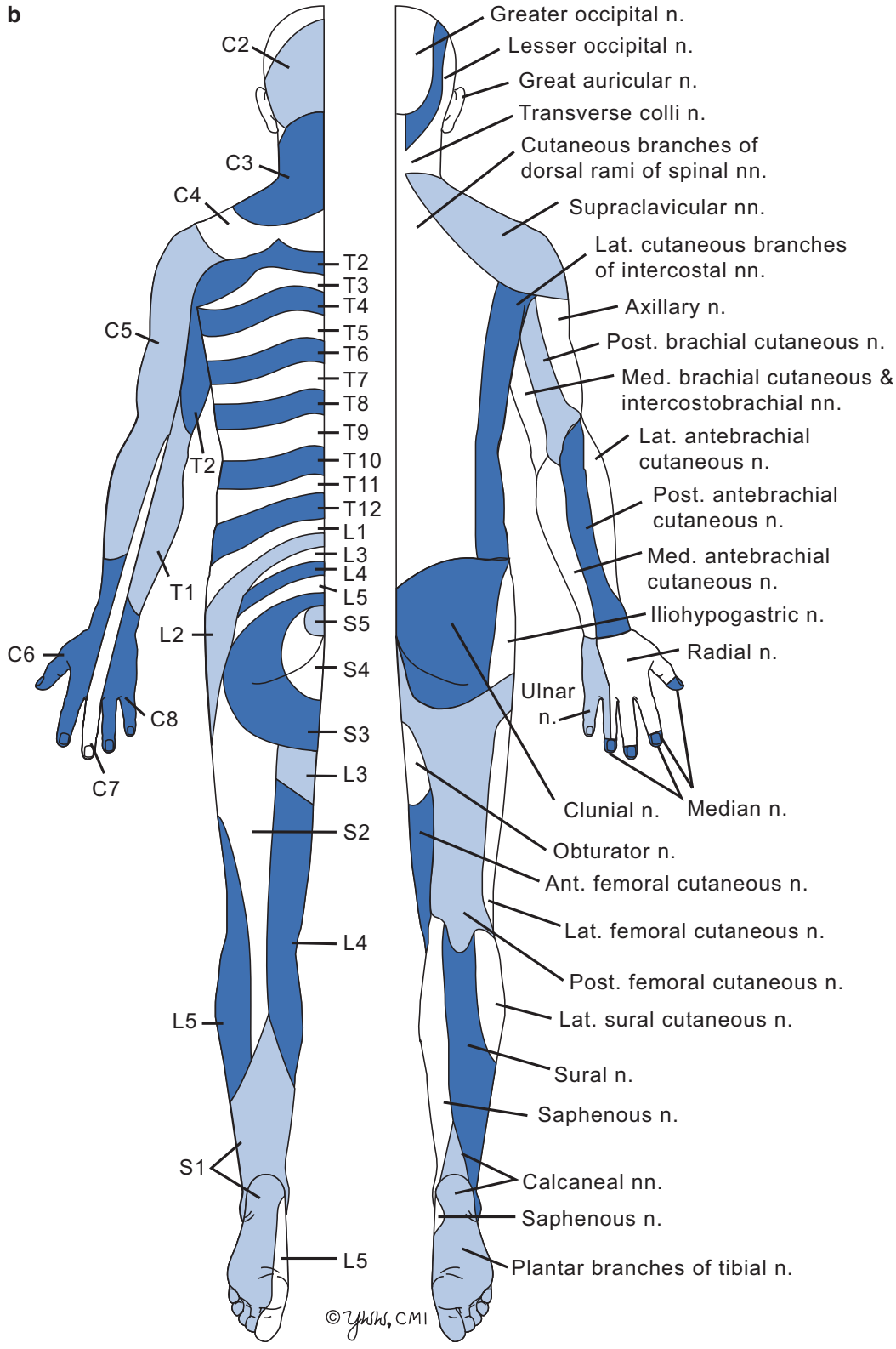


Fig. 2.4 (continued) **b** Posterior view

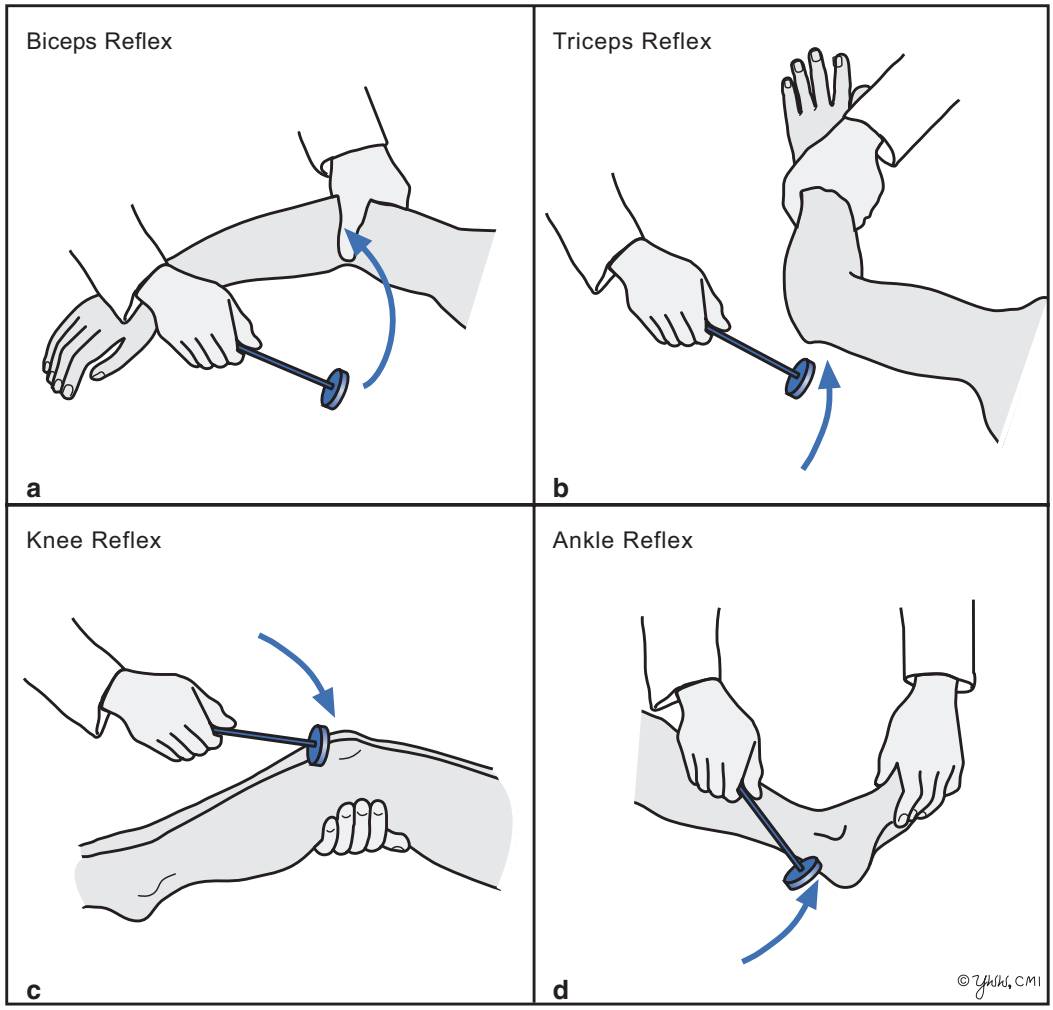


Fig. 2.5 Deep tendon reflexes

sion. A Babinski sign is stereotypic each time you perform the maneuver. Withdrawal from "tickling" tends to be erratic, does not look the same way each time, and often triggered by touching the sole of the foot anywhere.

Table 2.4 Scoring deep tendon reflexes

Score	Reflex finding
0	Absent
1+	Diminished, often requiring reinforcement
2+	Normal or physiologic
3+	Brisk without clonus
4+	Abnormally brisk, usually with clonus

Frontal lobe release signs imply bilateral frontal lobe damage. The *grasp reflex* is elicited by nonvoluntarily persistently grasping of your fingers when placed or lightly stroked across the patient's palm. Other frontal lobe release signs are discussed in the chapter on higher cortical function.

Pediatric Neurologic Exam

The most striking difference in the pediatric and adult neurologic exams is that the age of the patient results in very different exam techniques and elements. The key portions of the exam are testing the same systems, albeit in different ways. As

a child gets older, you can incorporate more and more of the adult exam into the pediatric exam. Therefore, the infant exam will be presented as it is the most disparate of the pediatric stages as compared to the adult.

General

Observe the baby. How does she act? Is she irritable, easily consoled, sleeping and easy to arouse or somnolent. Encephalopathy in the infant often presents as hyperirritability. Does the face or other features appear dysmorphic? Note the spacing of the eyes and ears.

Skin

Always get the clothes off the infant. Look for hyper- or hypo-pigmentation. Check the base of the spine for dimpling or hair tufts. Examine the diaper area; note the morphology of the genitalia.

Head

Head circumference: Always measure the head and the circumference measured compared to a standard age circumference chart. This should be compared to all previously obtained measures if possible. The parents can be measured as well. Bigheaded parents can produce bigheaded children.

Fontanel: The anterior fontanel should be soft, not tense or sunken. Some pulsation is normal. The posterior fontanel should not be palpable after birth.

Eyes

Check eye movements by giving the child something to observe. In infants, faces work well at a distance of about 6 in. In older babies round, red objects can catch their attention. Check for smooth movements and the extent of tracking. Tracking past midline begins around age 2 months. Vertical tracking begins around 3–4 months.

Fundoscopic exam is important to identify the red reflex. To do this, while looking through the ophthalmoscope, aim at the child's eye. If you see the red of the retina, you have a red reflex. This screens for congenital cataracts and retinoblastoma. If you have a cooperative infant you may be able to actually examine the back of the eye. Also using the ophthalmoscope or a penlight, check for the pupillary light response.

Mouth

Using your gloved little finger, check for the *suck reflex*. Infants should latch on and your finger should not slip from her mouth during suck. While your finger is in her mouth, also check for palate height. At some point during the exam, the baby will probably cry. Use this opportunity to assess palate elevation.

Tone

Always assess tone when the head is midline. When the head is turned, you trigger the asymmetric tonic neck reflex (*fencer posture*) giving increased tone on the side opposite the head turn. Passively move the arms and legs. The child should move some in response to you and not be totally limp. Pick up the baby, with your hands around her chest. Does she slip through your fingers or can she stay between your hands without you holding onto her chest? The former demonstrates hypotonia. Hypertonia is evident when the child's legs scissor when you vertically suspend her. For further tone assessment, turn the baby on her belly with your hand and support her stomach and chest. Does she flop over your hand (hypotonia), arch her back and neck slightly (normal tone) or stay rigidly extended (hypertonia)? Now place the infant on his back. A normal posture in the infant is flexion of all four extremities. As a baby gets older, the limbs assume a more extended posture. Take the baby's hands and pull her to a seated position. Resist the urge to support the head. Even at birth, the full-term infant will flex the extremities and pull the head up.

Table 2.5 Primitive reflexes with expected time of appearance and disappearance

Reflex	Appears by (wk gestation)	Gone by (approximate) (mo)
Suck	34	4
Root	34	4
Palmar grasp	34	6
Plantar grasp	34	10
Tonic neck	34	4–6
Moro	34	3–6
Automatic step	35	2

Reflexes

Always assess reflexes when the head is midline for the same reasons as above. Check the deep tendon reflexes as in the adult; however, these can usually be tapped with the fingers in infants. Ankle clonus is usually present in infants. Three to four beats bilaterally are normal. Sustained clonus or asymmetries should be noted.

Primitive Reflexes

After checking for the suck reflex, one should also check Moro, grasp and step reflexes.

Moro: With the infant on his back, grab his hands, lift him slightly off the bed and then allow him to drop back onto the bed. The response should be a symmetric brisk extension of arm and legs and drawing of the arms back to midline.

Grasp: Place your finger into the baby's palm. She should firmly grasp it, equally on both sides.

Step: Lift the infant so he is standing on the examining surface (with you supporting his weight). He should take automatic steps on the table or bed.

Root: Brush the side of the child's cheek. The head will turn towards the check you touched.

Table 2.5 gives the timing of appearance and disappearance of these primitive reflexes. Always remember to redress and swaddle the baby after you are done.

Video Legend

This video shows an example of the Neurologic Examination on a 30 year-old healthy woman

Segment 1: Mental Status Examination
- Folstein Mini-mental status exam
- Language testing

Segment 2: Cranial Nerve Examination
- CN I Olfaction
- CN II Optic nerve
- CN III, IV, VI Oculomotor, trochlear and abducens
- CN V Trigeminal
- CN VII Facial nerve
- CN VIII Auditory nerve
- CN IX, X, XII Glossopharyngeal, Vagus, Hypoglossal
- CN XI Accessory nerve

Segment 3: Motor Examination
- Muscle bulk
- Muscle strength
- Muscle tone
- Gait exam
- Romberg test

Segment 4: Coordination Examination
- Finger-to-nose
- Heel-to-shin

Segment 5: Sensation Examination
- Light touch
- Pain
- Temperature
- Vibration
- Proprioception

Segment 6: Reflexes Examination

Reference

1. Folstein MF, et al. Mini mental state. J Psychiatr Res. 1975;12:196–198.

Recommended Reading

O'Brien M. Aids to the examination of the peripheral nervous system. 5th edn. London: Saunders; 2010. (Superb booklet that outlines how to test each muscle, describes areas of sensation for all peripheral nerves, and is easily kept in a doctor's bag)

Common Neurologic Tests

3

Overview

Neurologic tests can establish a diagnosis when several possible diagnoses exist, help make therapeutic decisions, and assess the results of treatment. These tests are divided into the evaluation of *function, structure*, or underlying *molecular/genetic* abnormalities. Often these tests can be complimentary in establishing a diagnosis. For example, a neurologist performs the neurologic examination and narrows the general location of the disease process. Brain imaging through either magnetic resonance imaging (MRI) or computed tomography (CT) can then precisely locate abnormal brain tissue; however, the etiologic process may not be known simply from the imaging signal abnormalities and further metabolic/genetic testing may be required to understand the disease process and to guide treatment.

Major neurologic tests are briefly discussed below in terms of their basic principles, indications, cost, and side effects.

Function

Neurologic Examination

As the entry point into the diagnostic and therapeutic process, the neurologic examination yields information about normal and abnormal neurologic functioning as well as the likely anatomic location producing the abnormal findings. In some diseases (e.g., migraine headache and trigeminal neuralgia), the neurologic history and exam is the only diagnostic test. To detect abnormalities most sensitively, this test requires the patient to be alert, cooperative, and not aphasic or demented. The test is safe, inexpensive, comfortable, and can be repeated frequently—but testing does take some time with a complete history and physical examination requiring 30 min–1 h (see The Neurologic Examination Chap. 2 for full details).

Neuropsychological Tests

Neuropsychological tests evaluate higher cortical function and do so with a higher degree of precision and certainty than usual bedside testing. A neuropsychologist usually administers these tests, which have been developed and standardized to enable better evaluation of different aspects of cortical function (Table 3.1). While neuropsychological tests are sensitive indicators of a cognitive disorder, they are not highly localizing to the part of the cerebral cortex that is dysfunctional. Although the tests are quantitative, the score does not highly correlate with the size of the lesion.

These tests are used to (1) divide cognitive abnormalities into specific subtypes that may assist in establishing a diagnosis, (2) determine a

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Table 3.1 Neuropsychological tests organized by brain area/function

Frontal lobe
Wechsler memory scale
Milan sorting test
Porteus maze test
Parietal lobe
Wechsler block design
Benton figure copying test
Temporal lobe
Halstead–Reitan battery (parts)
Milner's maze learning task
Intelligence and personality
Wechsler adult intelligence scale-III
Wechsler adult intelligence scale for children-III
Minnesota multiphasic personality inventory
Rorschach test

quantitative score on specific tests so repeated tests can measure disease progression or improvement, (3) distinguish dementia from psychological illnesses such as depression, and (4) determine an IQ score for legal or medico-social reasons. For the typical patient with marked dementia from Alzheimer's disease, neuropsychological tests add little information. When ordering this testing, clearly state the concern so the neuropsychologist can construct the most useful battery of tests.

Neuropsychological tests are safe, inexpensive, and comfortable to the patient. Testing takes 1–4 h depending on the extent of the battery. These tests can be repeated occasionally but cannot be administered frequently as repeated testing at short intervals would produce a "learning effect" that could falsely improve the score.

Electroencephalogram (EEG)

The EEG is a tracing of electronically amplified and summated electrical activity of the superficial layers of the cerebral cortex adjacent to the calvarium. This electrical activity comes primarily from inhibitory and excitatory postsynaptic potentials of pyramidal cells. Electrodes are placed over the scalp in precise locations to record the brain's electrical activity when awake and often during sleep. Differences in voltage between two selected electrodes plotted over time are produced as continuous digital waveforms on a computer screen. The complete EEG tracing is made up of waveforms from several different source electrodes. A trained technician performs the EEG and a neurologist with special training interprets the tracing.

Information derived from an EEG is divided into waveforms that suggest epileptiform brain activity and those that suggest an encephalopathy (metabolic or structural in origin). Epileptiform brain waves (spikes and sharp waves) are paroxysmal, repetitive, brief, and often of higher voltage than background activity. Background activity is divided into 4 different frequencies (cycles per second or hertz [Hz]): (>12 Hz), α (8–12 Hz), θ (4–7 Hz) and δ (0–3 Hz) that range from fast to slow. The frequency is the dominant EEG frequency seen in occipital leads when an awake individual has their eyes closed.

Most encephalopathies produce slowing of background activity often into the δ range. EEG electrical activity comes from intact responding neuronal populations and does not emanate from brain tumors or dead neurons in infarcted brain. However, localized brain masses (tumor or abscess) produce a localized slowing (δ waves) from dysfunctional neurons located around the mass. Some drugs (especially barbiturates) increase background activity into the β range.

While an EEG gives considerable information about abnormal brain function, it gives limited information as to the precise location of the brain dysfunction. Since electrical currents flow by path of least resistance, the actual source of the electrical activity may not be directly beneath the recording electrode. In general, conventional methods localize the EEG source to a 2-cm cube. Under some circumstances, the EEG is coupled with a video monitor so the patient's behavior can be correlated with EEG findings. The EEG is often performed during wakefulness and sleeping as epileptiform discharges are usually more

frequent during sleep. The EEG can also study patients during sleep to evaluate sleep abnormalities, such as narcolepsy and sleep apnea syndromes. Under special circumstances, electrodes can be surgically placed over the cortical surface or within the brain to search for specific foci of seizure genesis.

Present indications for ordering a routine EEG include to (1) evaluate unwitnessed episodes of loss of consciousness for likelihood of seizures, (2) characterize interictal (between seizures) brain activity to better determine the type of seizure disorder, (3) distinguish encephalopathy from frequent seizures (status epilepticus) in a stuporous or comatose patient, (4) distinguish nonepileptic events from epileptic seizures, and (5) determine brain death.

The routine EEG is safe, inexpensive, comfortable to the patient, and takes about 2 h to complete. An EEG can be repeated as often as necessary. Figure 3.1 demonstrates typical EEG changes.

Electromyogram (EMG)

The EMG is the evaluation of the electrical function of individual muscle motor unit potentials at rest and during muscle contraction. The EMG is performed by inserting a recording needle electrode into the belly of a muscle. The needle tip is the recording electrode and the needle shaft is the reference electrode in a concentric needle while a monopolar needle compares the electrical signal of fibers to that of a reference electrode on the skin surface. Electrical activity from muscle fibers is recorded and amplified to appear on an oscilloscope as a tracing of voltage versus time with accompanying sound. Physicians need special training to perform and to interpret the EMG.

Abnormal motor units or individual muscle fibers demonstrate changes in duration, amplitude, and pattern of the waveform that occur during needle insertion, rest, and voluntary contraction. An EMG distinguishes normal muscle from disease due to nerve damage or muscle disease. An EMG is safe, somewhat uncomfortable to the patient, inexpensive, and requires 30–60 min. To minimize patient discomfort, the patient should receive a clear description of what will happen and frequent reassurance.

Normal Muscle Insertion of a needle into a normal muscle injures and mechanically stimulates many muscle fibers, producing a burst of action potentials of short duration (< 300 msec). At rest normal muscle is electrically silent as normal muscle tone is not the result of electrical contraction of muscle fibers. As an electrical impulse travels along the surface of a single muscle fiber toward the recording electrode, the impulse becomes positive (downward deflection shown on the computer screen by convention) relative to the reference electrode. As the impulse comes beneath the electrode, the waveform becomes negative (upward deflection) and then becomes slightly positive and returns to baseline as the impulse travels past the electrode (Fig. 3.2). A single muscle fiber contraction lasts about 2–4 msec and is less than 300 volt in amplitude. The firing of a single muscle fiber (called fibrillation which does not cause visible muscle movement) does not occur normally and is a sign of muscle membrane instability either from denervation or myopathy. In normal muscle, an electrical impulse travels from a spinal cord anterior horn neuron (lower motor neuron) along its axon to eventually innervate 10–1000 muscle fibers (called a motor unit). The number of muscle fibers innervated depends on the muscle with proximal limb muscles having the highest number of innervated muscle fibers. During mild voluntary muscle contraction, an entire motor unit fires almost simultaneously producing a motor unit action potential (MUAP). A typical MUAP has 3–4 excursions across the baseline (phases) and a maximum amplitude of 0.5–5 mV (Fig. 3.2). The shape and duration of a given MUAP remain quite constant on repeat firings and generally appear different from other nearby MUAPs.

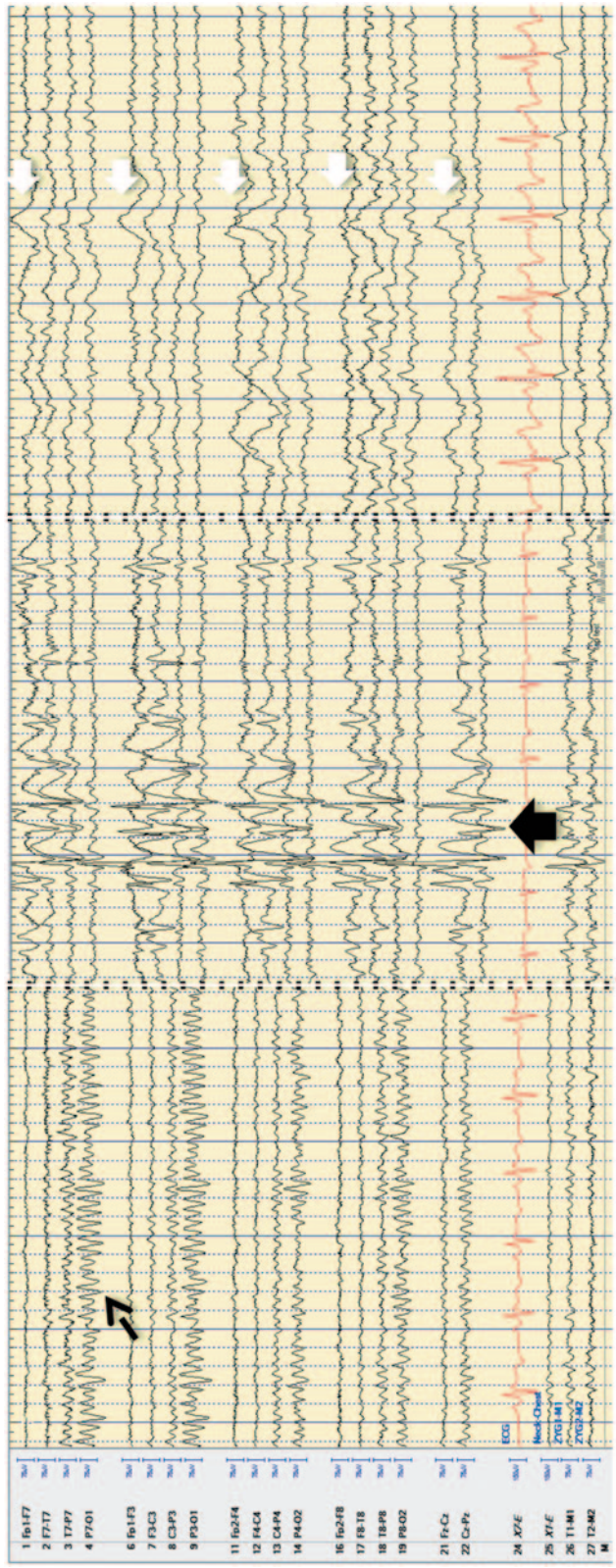

Fig 3.1 **a** Normal EEG tracing with dashed arrow indicating alpha rhythm of 8–9 Hz posteriorly. **b** Abnormal EEG tracing with epileptiform abnormalities with black block arrow showing a series of spike-and-wave complexes. **c** Abnormal EEG tracing showing slowing of brain rhythms with a right-sided predominance (white *block arrows* indicating a slow wave). (Courtesy of Dr. Glen Fenton)

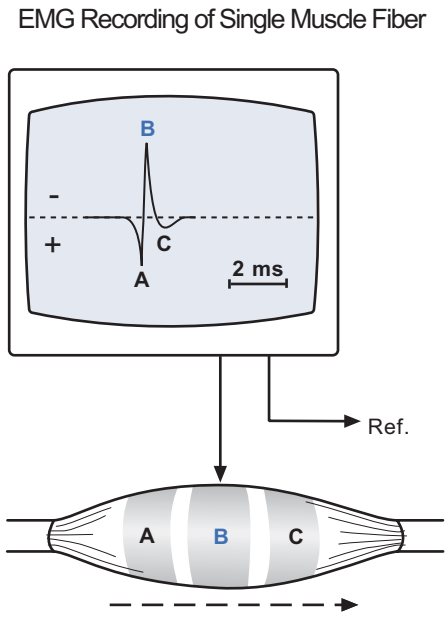

Fig 3.2 Single MUP on EMG

Denervated Muscle Immediately after complete nerve transection, the muscle is paralyzed, unexcitable by nerve stimulation, and electrically silent by EMG except for insertion potentials. Beginning 2–3 weeks after a muscle loses its innervation, spontaneous individual muscle fiber contractions may appear. The EMG demonstrates fibrillations and positive sharp waves (brief monophasic positive spikes). Until the motor unit completely degenerates, spontaneous firing of the MUAP also occurs (called a fasciculation which produces a visible muscle twitch). If the nerve damage is incomplete and occurred several months earlier, the denervated muscle fiber induces adjacent motor nerves to branch or sprout and send a nerve branch to reinnervate the denervated muscle fiber called sprouting. MUAPs suggestive of sprouting are of longer duration, contain more phases, and may be of higher maximum amplitude than normal.

Myopathy Death or dysfunction of scattered muscle fibers results in MUAPs during voluntary muscle contraction that are of shorter duration and lower amplitude than normal (Fig. 3.3). Some MUAPs may be polyphasic from loss of synchronous firing. In myositis, there may be accompanying fibrillations due to inflammatory damage to adjacent motor nerve endings.

In myopathies that cause myotonia (such as myotonic dystrophy), insertion of the needle produces a train of high-frequency repetitive discharges in a positive sharp waveform that diminish in frequency and amplitude over a few seconds. When heard over a speaker, myotonic discharges sound like a "dive-bomber".

Nerve Conduction and Neuromuscular Junction Studies

Nerve conduction studies are undertaken to evaluate the functioning of motor, autonomic, and sensory nerves and neuromuscular junctions. It is possible to determine actual conduction velocities for nerves in the peripheral nervous system but conduction velocities cannot be determined in the central nervous system. In the CNS, only a nerve latency time can be obtained because the CNS nerves cannot be stimulated at various points along the nerve pathway. The test is performed by a physician with special training or by a skilled technician under a physician's supervision. The test is safe, inexpensive, mildly uncomfortable for the patient, and takes ½–1 h.

Indications for ordering nerve studies include to (1) determine whether a neuropathy is generalized or multifocal, (2) determine whether a neuropathy is mainly from demyelination or axonal loss, (3) localize the site of a nerve conduction blockade, and (4) determine and characterize neuromuscular junction abnormalities. In the common types of distal sensorimotor peripheral neuropathy, nerve studies seldom help in establishing the etiology but can confirm historical symptoms or exam signs.

Motor Nerve Function Motor nerve conduction velocity studies measure the velocity of the fastest motor nerve axons at various points along a peripheral nerve. Peripheral nerves can be stimulated to fire by application of an electrical impulse to the skin overlying the nerve.

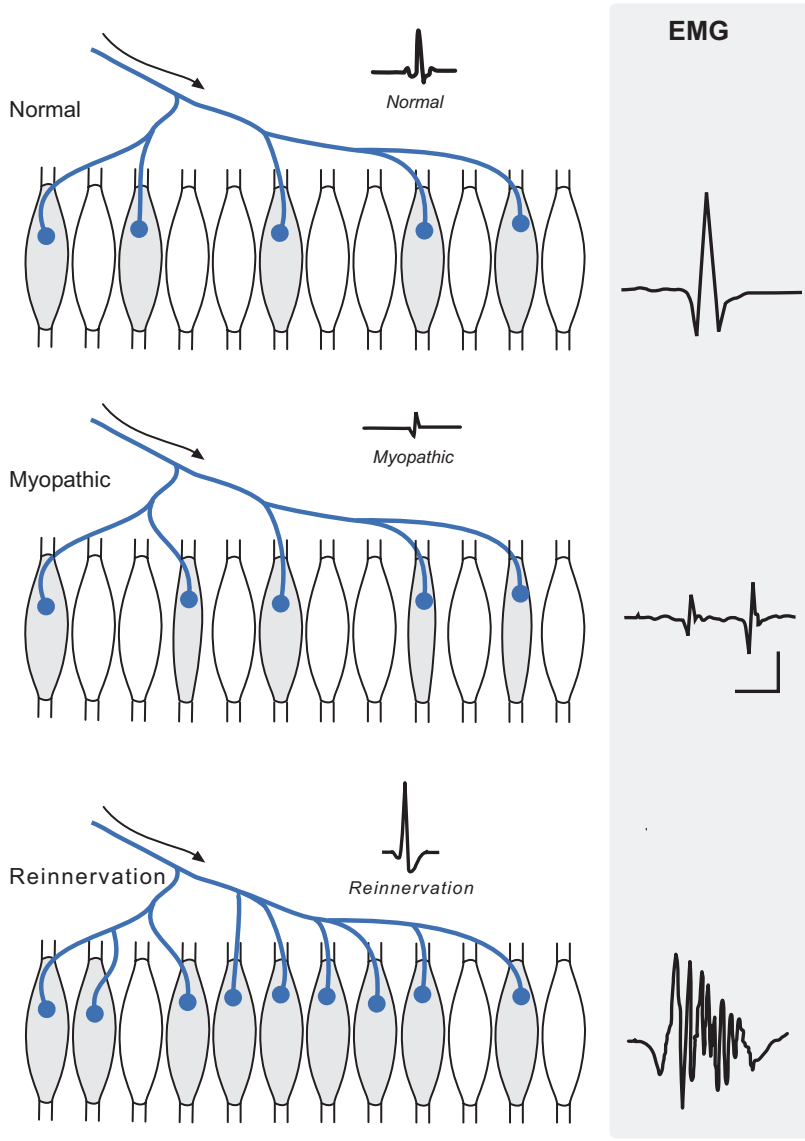

Fig 3.3 EMG of motor units in diseases

When a muscle contracts, its electrical signal can be detected by placing an electrode on the skin above the muscle belly. The muscle electrical signal is recorded, and the time from electrical stimulus to muscle contraction (latency) can be determined and displayed on an oscilloscope. A motor nerve velocity is determined as follows (Fig. 3.4). By moving the stimulating electrode along the nerve pathway, differing latencies in msec to muscle contraction are determined. By measuring the distance along the nerve pathway between two stimuli, one can divide the nerve distance in mm by the latency difference in msec to obtain the nerve velocity in meters per second. Normal motor velocity of the median and ulnar nerves is 50–60 m/sec and of the sciatic nerve is 40–50 m/sec. Slowing of the motor nerve velocity may reflect loss of myelin along the nerve (often causing slowing of velocities to 20–30 m/sec) or loss of the fastest motor nerves (lesser degree of velocity slowing). Slowing of a motor nerve may occur along the entire nerve pathway

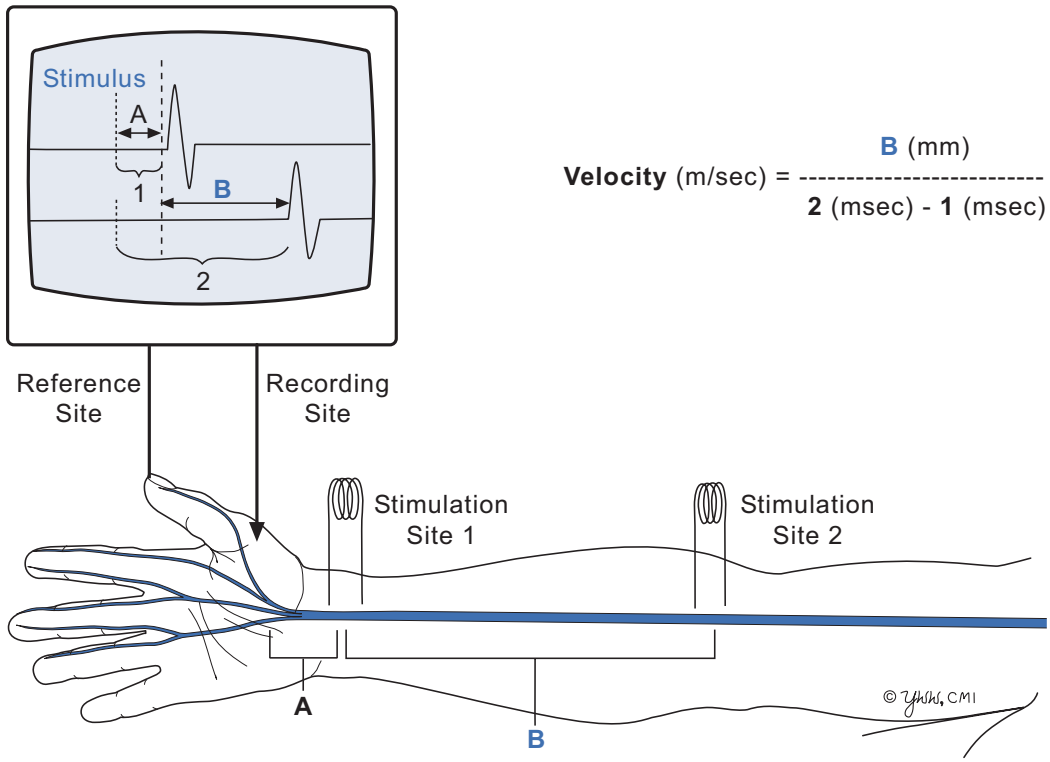

Fig 3.4 Motor nerve conduction velocity diagram

or at a localized point of nerve compression, such as the ulnar nerve at the elbow.

Sensory Nerve Function Evaluating sensory nerve function is more difficult as the normal signals are weaker and more diffuse following an electrical stimulus because the conduction velocities of different sensory axons vary considerably. Sensory nerves may be unmyelinated and conduct at ½–2 m/sec or thinly myelinated and conduct at 10–20 m/sec. The most common sensory nerve test determines the latency time from electrical stimulation of the skin of a finger to a skin recording electrode site over the median nerve just proximal to the wrist. A delayed median nerve sensory latency suggests compression of the nerve at carpal tunnel. The test is safe, mildly expensive, somewhat uncomfortable, and takes about 30 min.

Neuromuscular Junction Function Information about the function of the neuromuscular junction can be obtained from repetitive nerve stimulation studies. Placement of a skin recording electrode over the belly of a muscle and stimulating the motor nerve produce a compound muscle action potential (CMAP). If the nerve stimulation is repeated, the CMAPs appear identical on the oscilloscope. In diseases of the neuromuscular junction, the amplitude of the CMAPs may decrease or increase. In myasthenia gravis and botulism, repetitive nerve stimulation produces a decremental response in the CMAP. The test is safe, inexpensive, somewhat uncomfortable, and takes about 15 min.

Sensory Evoked Potentials Occasionally, there are indications to evaluate the integrity of central conduction along major sensory pathways (visual, auditory, and peripheral sensory system) called evoked potentials. As noted above, actual conduction velocities cannot be obtained but central modality-specific latencies can. Evoked potential tests record computer averages of the EEG that is time-locked to repeated (100–500 tri-

als) specific sensory stimuli such as sound, light, or electrical stimulation of peripheral nerve. The computer averaging reduces background EEG electrical activity to zero while enhancing the time-locked stimulus signal. Abnormalities are characterized by a delay for the time-locked signal average to reach its destination or distortions (usually a prolongation of the waveform and loss of signal amplitude). Sensory evoked potentials are safe, inexpensive, and comfortable. The major indication is the evaluation of possible diseases that cause CNS demyelination of these sensory pathways.

Structure

Lumbar Puncture (LP) and Cerebrospinal Fluid (CSF) Examination

Five important reasons for lumbar puncture are to (1) diagnose infections of the meninges, (2) diagnose cancer involving the meninges, (3) diagnose herpes simplex encephalitis and other encephalitides, (4) diagnose a small subarachnoid hemorrhage, and (5) introduce medications into the subarachnoid space or contrast media for a myelogram. In addition, there are several diseases where examination of CSF helps make a specific diagnosis. These diseases include multiple sclerosis, Guillain–Barre syndrome, and paraneoplastic syndromes. The LP is not limited to establishing diagnoses. Antimicrobial and anticancer drugs can be delivered intrathecally into the lumbar or cisternal CSF to treat patients with some forms of infectious meningitis or meningeal carcinomatosis. The LP is safe, mildly uncomfortable, and moderately expensive depending on tests ordered and takes up to 1 h.

Contraindications for LP There are times when it is not safe to perform a lumbar puncture. If the individual has a localized mass in the brain or meninges or obstructive hydrocephalus that is creating marked increased intracranial pressure, removal of CSF from the lumbar space will lower the CSF pressure below the foramen magnum. This in turn may allow brain to move through the tentorium (uncal herniation or tentorial herniation) or force cerebellar tonsils into the foramen magnum. To minimize this risk, a complete history and neurologic examination should always be done before the lumbar puncture. If the patient has signs of marked increased intracranial pressure (papilledema), focal neurologic signs (especially hemiparesis, aphasia, or ataxia), is comatose, elderly or immunocompromised, it is usually advisable to first obtain neuroimaging (usually a CT scan) to rule out a focal intracranial mass or obstructive hydrocephalus.

If the patient has a bleeding disorder, takes anticoagulants, or has a blood platelet count below 50,000/mm^3, there is a risk of developing an epidural or subdural hematoma at the site of lumbar puncture that occasionally compresses the lumbar and sacral nerve roots. These conditions should be corrected as much as possible prior to the lumbar puncture.

Anatomy and Physiology of the CSF Space CSF is primarily a clear selective ultrafiltrate of plasma produced by choroid plexus cells. Water is moved from the blood/choroid plexus to the CSF via aquaporins in the plexus epithelial cells. Proteins of low molecular weight (MW) reach CSF better than those of high molecular weight. As such, CSF has more albumin (MW 69 kDa) than immunoglobulins (MW 150 kDa). In addition, some proteins such as transthyretin are made by the choroid plexus and secreted into CSF. Finally, complex transport systems exist in blood vessels of brain and the CSF pathways to remove ions or proteins (such as potassium, excitatory amino acids) and to deliver molecules (glucose) to the CSF. These transporter systems may be active (require energy from mitochondria such as potassium–sodium transporter) or passive (no energy requirement such as the glucose transporter) and generally maintain their respective molecules within narrow concentrations. For the above reasons, the CSF: plasma concentration ratios vary greatly between molecules.

Approximately two-third of CSF is produced by the choroid plexuses located in the lateral and fourth ventricles (Fig. 3.5). The sources of the remaining CSF are unclear but include the exit

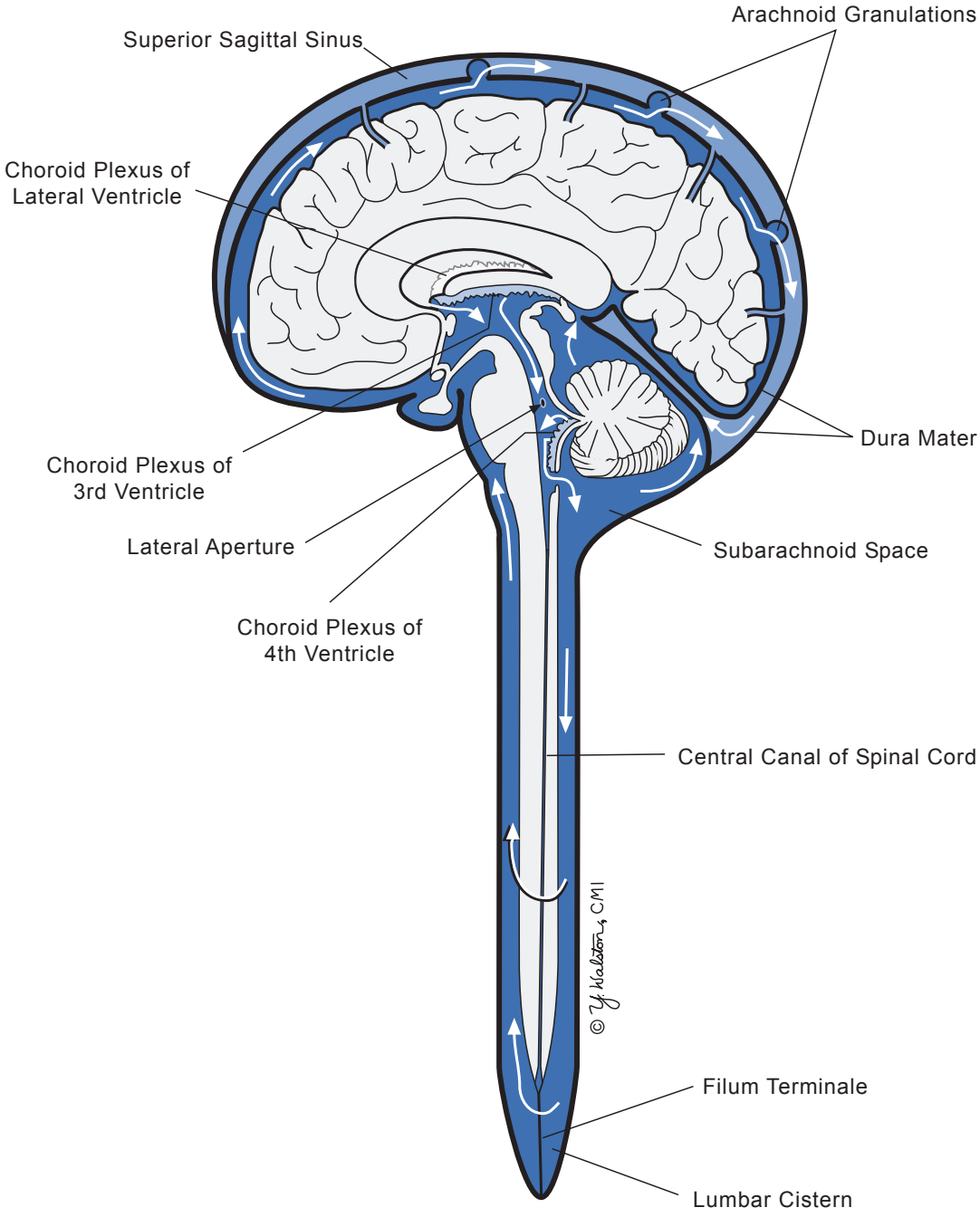

Fig 3.5 CSF flow diagram in CNS

of brain interstitial fluid. Choroid plexus CSF travels from the lateral ventricle into the third ventricle and along the aqueduct of Sylvius to reach the fourth ventricle. From the fourth ventricle, CSF passes via the foramina of Luschka and Magendie to exit the cerebellum into the subarachnoid space. Blockage of CSF pathways up to this point produces obstructive hydrocephalus. In the subarachnoid space, CSF travels up through the tentorium opening and over

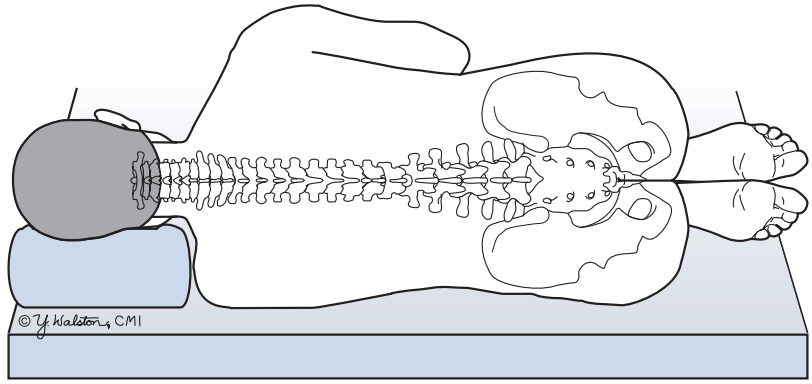

Fig 3.6 Patient placement for LP

the cerebral convexities to reach the superior sagittal sinus. Blockage of CSF pathways in the subarachnoid spaces is usually called communicating hydrocephalus since air introduced into the lumbar subarachnoid space can reach the lateral ventricle. At the superior sagittal sinus, CSF passes through arachnoid villi or Pacchionian bodies to reach the sinus. Thus, most CSF forms from blood and returns to blood.

In adults, the total CSF volume is approximately 140 ml. The ventricles contain 25 ml, the spinal cord subarachnoid space 30 ml, and the remaining 85 ml is in the subarachnoid spaces around the brain. CSF is produced at a rate of 20–25 ml/hour or 500–600 ml/day. Thus, CSF turns over about four times a day. CSF production is independent of CSF pressure (until a pressure of 450 mm CSF) but CSF absorption is dependent on CSF pressure in a linear fashion.

In adults, the spinal cord descends to about T12-L1, but in small children the spinal cord may descend as low as L2. Below that level, nerve roots travel to exit appropriate neural foramina. It is at the level of the nerve roots that it is safe to perform a lumbar puncture.

Technique of Lumbar Puncture Even after obtaining informed consent, it is important to continue to communicate with the patient, explaining each step of the procedure to reassure the patient and to make the procedure more comfortable. Occasionally, a mild sedative is helpful in the anxious patient. Whenever possible, the LP should be performed in the lateral recumbent position as this allows an accurate measure of the opening pressure. The patient, lying on a firm surface that does not sag, should be placed on his side with the knees curled toward the chin. The spinous processes should be in a horizontal line with the two iliac crests forming a perpendicular line. The intersection is usually the L4-L5 intervertebral space (Fig. 3.6).

The LP needle is usually inserted in the L3-4 space or the L4-5 space. The skin over these areas should be thoroughly cleaned with an antiseptic solution such as betadine. Wear sterile gloves and a mask during the procedure. Lidocaine may be injected intradermally and subcutaneously at the anticipated LP needle entry site. Normally, a 20-gauge needle is used as this needle does not bend during insertion and allows accurate measurement of CSF pressure. Occasionally, smaller needles are used but they may not allow accurate CSF pressure measurement. The LP needle is inserted bevel up through the skin and then angled slightly cephalad toward the umbilicus. It is important to keep the needle horizontal with the patient during insertion. There is usually a "pop" sensation as the needle passes through the dura into the subarachnoid space. One can stop the procedure at any step and remove the stylet to see whether CSF returns. If blood is encountered, the needle should be withdrawn and the patient repositioned before the next try, often at the next higher interspace.

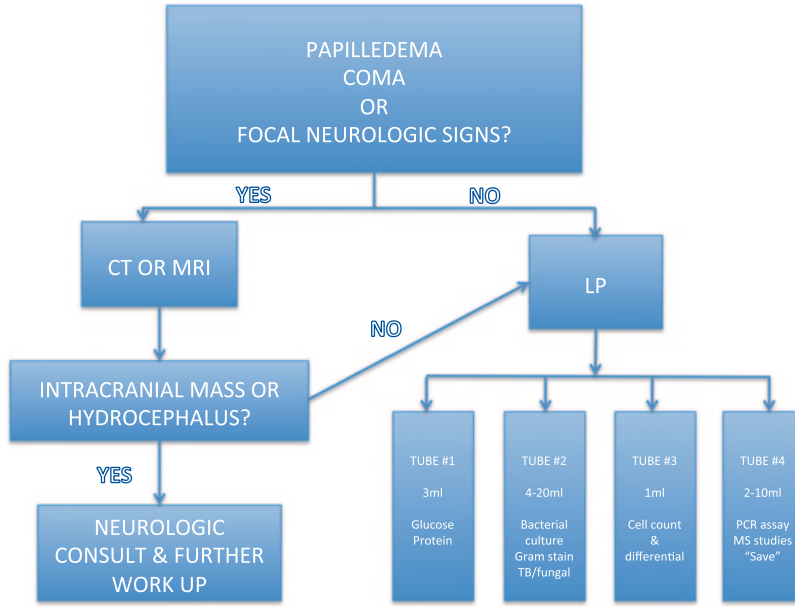

Fig 3.7 Outline of LP algorithm

Once CSF is encountered, attachment of a three-way stopcock and a manometer (usually comes with a commercial CSF kit) allows measurement of the CSF pressure. If the pressure is elevated, relaxation of the patient and slightly uncoiling the legs often reduce the pressure back down to normal levels. Four to five tubes are then used to collect CSF sequentially. In adults, 10–35 ml is usually collected depending on the tests to be ordered (Fig. 3.7). In small children, 3–5 ml is sufficient for standard tests in hospitals that have microchemistry facilities. Tube #1 is the most likely to have a skin bacterial contaminant and exogenous RBCs from the LP needle puncture that may give misleading reports if tube #1 is used for bacterial cultures or cell counts. It is advisable to collect an extra tube containing several milliliters of CSF and mark "save" on the tube in the advent additional tests are needed. In many laboratories, the "save" CSF tube is kept frozen for at least one month.

The CSF should promptly be taken to the clinical laboratory since white blood cells begin to degenerate and lyse after ½ h and glucose levels may fall due to metabolism by white blood cells. Normal values for commonly ordered tests are given in Table 3.2. A procedure note should immediately be recorded in the patient's chart that includes the location of the puncture, whether or not the spinal tap was traumatic, opening pressure, amount of fluid obtained, appearance of the fluid, and a list of tests ordered on the CSF. After the CSF test results are available, an additional note should give an interpretation of the LP findings.

Normal CSF Values Table 3.2 lists common normal findings in adult CSF. Neonates transiently have more cells in their CSF and higher protein levels. In general for adults, the upper limit of the CSF protein level equals their age. Determination of normal CSF glucose level is difficult when blood glucose is markedly elevated because high blood glucose saturates the blood-CSF glucose transporter. CSF polymerase chain reaction assays are increasingly being used to diagnose infections of the CNS even when the infectious agent cannot be isolated from CSF (See Infections of the central nervous system chapter).

Complications of Lumbar Puncture A traumatic lumbar puncture occurs in 10–20% of LPs. It most commonly occurs when the LP needle hits a tiny vein in Batten's plexus located on the dor-

Table 3.2 Normal lumbar CSF findings in adults

Test	Normal finding
Appearance	Clear and colorless against a white background
Opening pressure	70–180 mm CSF in recumbent position
Red blood cells	<5 RBC/mm^3
White blood cells	5–10 WBC/mm^3
Differential	Mainly mononuclear cells
Total protein	<45 to 60 mg/dl depending on assay technique (<30 mg/dl if cisternal CSF, <25 mg/dl if ventricular CSF)
Percent immunoglobulins	<15% of total protein
Oligoclonal bands	None or rarely one band
Glucose	>40 mg/dl (usually >60% of blood glucose)
Gram stain	Negative
Cultures	Sterile for bacteria, mycobacteria, fungi, and viruses
CSF-VDRL test	Nonreactive
Cytology	No malignant cells

Table 3.3 Analysis of bloody CSF

CSF finding	Traumatic LP	Subarachnoid hemorrhage
Color	1st tube—pink to red 3rd tube—clearer	All tubes uniform color
RBC count	Higher in 1st tube than 3rd tube	All tubes uniform
Color of supernatant fluid	Nearly colorless	Xanthochromic (yellow color)
Bilirubin	Absent	Present after first day
Clot	May occur on standing	Absent
Repeat LP at higher interspace	Often clear or nearly clear	Same as initial LP
Head CT	No blood in subarachnoid space	Blood may be seen in subarachnoid spaces

sal side of the spinal subarachnoid space. When this happens, fresh RBC and serum proteins from the bleed and CSF enter the needle. Often the number of RBC rapidly decreases from tube #1 to tube #3 or #4. However, this fresh blood may falsely elevate CSF WBC and protein levels. If the RBC and WBC counts and protein are done on the same tube, one simple rule of thumb is to subtract 1–2 WBC/mm^3 and 1 mg/dl protein for every 1000 RBC/mm^3. Table 3.3 (analysis of bloody CSF) gives an useful approach to distinguish a traumatic LP from a subarachnoid hemorrhage.

While not life-threatening, post-lumbar puncture headaches may be quite uncomfortable. The headache begins several hours after the LP and may last for several days. The headache is usually frontal and develops when the patient moves from a lying to a sitting or standing position. Returning to a lying position relieves the headache. The incidence of post-LP headache is highest in young adult women and is uncommon in children and the elderly. In young adults, the incidence is about 10%. The risk of a post-LP headache increases when the larger size LP needles are used. There is no evidence that drinking large quantities of water prevents a post-LP headache but lying prone for a few hours may be of benefit. With simple bed rest, the headache usually disappears within hours to a few days.

A brain herniation from lumbar puncture is the most feared complication but fortunately is quite rare (less than 2% even if the CSF pressure is elevated). If the patient has markedly elevated pressure, it is still important to collect at least 5 ml of CSF for diagnostic tests before withdrawing the LP needle. Once you withdraw the LP needle, CSF begins to leak out the hole in the dura. If the CSF pressure is unexpectedly markedly elevated, there are several things that

should be done immediately after the LP. The patient should be observed closely for signs of neurologic deterioration over the next 8 h. Prompt neuroimaging (CT or MRI) often identifies the cause of elevated CSF pressure. A secure intravenous line may be established should mannitol administration be required. Notification of a neurosurgeon that a potential problem exists is helpful should a surgical cause of the increased CSF pressure be identified. If brain herniation begins, the patient should be given intravenous (IV) mannitol, intubated, and hyperventilated to lower intracranial pressure.

Neuroimaging Tests

Computed tomography (CT) and magnetic resonance imaging (MRI) are the most widely used imaging techniques because they yield high resolution of the brain and surrounding structures. They are safe, performed in a reasonable period of time, and widely available in the United States. Both CT and MR images are presented as if one is looking at the patient upward from the foot of his bed. Thus, *the right side of the brain is located on the left side of the brain image*.

CT uses a beam of X-rays shot straight through the brain. As the beam exits the other side, it is blunted or attenuated slightly because it has hit dense living tissues on the way through the head. Very dense tissue, like bone, blocks lots of X-rays, brain blocks some, and CSF and water even less. As with conventional X-ray, bone appears bright because its high density blocks X-rays from darkening the film. Conversely, less-dense objects, such as CSF or fat, appear dark since X-rays can penetrate to expose the film. X-ray detectors positioned around the circumference of the scanner collect attenuation readings from multiple angles, and a computerized algorithm constructs the image of each slice. A standard CT creates horizontal (axial) brain slices that are about 1 cm thick and in a different plane than that used by MRI. The total X-ray exposure from CT is about that of a chest X-ray. Presently, only a few seconds are required to obtain one brain slice and 10–15 min for the entire brain.

MRI uses different physical principles than CT to create brain images. When brain protons are placed in a magnetic field, they oscillate. The frequency of oscillation depends on the strength of the magnetic field. Protons are capable of absorbing energy if exposed to electromagnetic energy at the frequency of oscillation. After the proton absorbs energy, the nucleus releases this energy and returns to its initial state of equilibrium. The transmission of energy of the nucleus is what is observed as the MRI signal (Fig. 3.8).

The return of the nucleus to equilibrium occurs over time and is governed by two physical processes: (1) T1, the time for relaxation back to equilibrium of the component of the nuclear magnetization which is parallel to the magnetic field and (2) T2, the time for relaxation back to equilibrium of the component of the nuclear magnetization which is perpendicular to the magnetic field. Contrast between brain tissues depends upon the proton density, T1, and T2. MR signals can be "T1- or T2-weighted" to accentuate select properties by changing the way the nuclei are initially subjected to electromagnetic energy.

T1-weighted images yield the sharpest and most accurate brain anatomy but less information about brain pathology. T2-weighted images better demonstrate brain pathology but are less suitable for brain anatomy. Table 3.4 gives tissue types that are bright and dark on T1- and T2-weighted images. When brain pathology is located adjacent to ventricles with CSF, it may be difficult to distinguish CSF from the lesions on T2-weighted images. In these cases, intermediate-weighted images (proton density images) or fluid-attenuated inversion recovery (FLAIR) images are helpful. Diffusion-weighted MRI scans help to identify acute infarctions.

The key to identifying the type of MR image lies in the CSF. On *T1-weighted image, CSF is DARK* and on *T2-weighted image, CSF is BRIGHT*.

Patient safety is of some concern when the patient is around the MRI machine due to the magnet's high magnetic field. A typical MRI magnetic field is 1.5 Tesla, meaning the magnet has a field strength 30,000 times that of earth. However, 3 or higher Tesla MRIs are becoming more com-

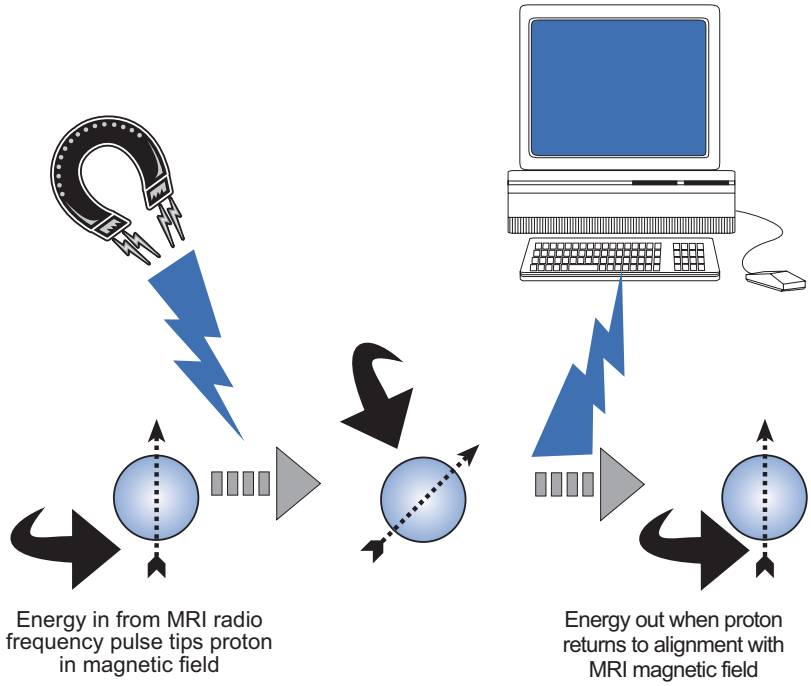

Fig 3.8 MRI basic principles

Table 3.4 Signal intensities/densities in neuroimaging

Neuroimaging	Bright	Dark
MRI T1-weighted	Fat Methemoglobin Gadolinium contrast	Bone or dense calcium CSF Edema or water Air Flowing blood
MRI T2-weighted	Edema or water CSF Methemoglobin (extracellular)	Bone or dense calcium Air Fat Flowing blood Iron-laden tissues Hemosiderin Deoxyhemoglobin Methemoglobin (within RBC)
CT	Bone Blood not in vessels CT contrast material Thrombosis of major vessels	CSF Edema or water Fat Air

mon. Ferromagnetic objects on the patient's or attendant's clothing can become missiles and fly inside the magnet. Cardiac pacemakers are contraindicated. Most modern surgical clips and orthopedic appliances are MRI-safe but older neurosurgical clips may be dangerous. Should a medical emergency occur while the patient is within the magnet, the patient must be removed from the MRI scanner room before attempting resuscitation since ventilators, crash carts, and emergency personnel often have ferromagnetic objects.

As seen in Table 3.5, the MRI is the superior neuroimaging test for most neurologic illnesses. Table 3.6 compares the advantages of MRI and

Table 3.5 Commonly ordered neuroimaging for neurologic conditions

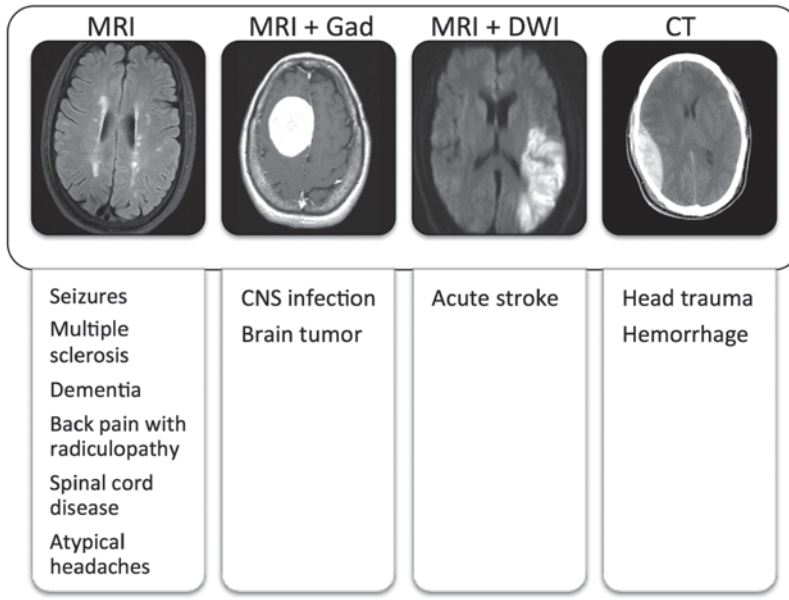

Table 3.6 Comparison of MRI and CT modalities

Advantages of MRI over CT	*Advantages of CT over MRI*
Better imaging of brain located adjacent to bone	Faster imaging time so restless, uncooperative patients can be scanned with fewer movement artifacts
Superior brain anatomy	Patients with ferromagnetic objects may get CT but not MRI
Detection of smaller brain lesions	Less claustrophobia
Better detection of subtle CNS pathology such as low-grade tumors	Better detection of subarachnoid hemorrhage, brain calcifications, and bone fractures
Can visualize major neck and cerebral arteries and veins (magnetic resonance angiography or MRA)	
No ionizing radiation so safer than CT, especially during pregnancy	

CT. In several new applications of magnetic resonance, magnetic resonance spectroscopy (MRS) can evaluate levels of brain metabolites such as N-acetylaspartate, choline, creatine, myo-inositol, and lactate. Often the magnet employed is of higher strength (2.0–4.0 Tesla). MRS presently has limited clinical indications but is used in the differentiation of brain abnormalities such as some brain tumors and abscesses. Functional magnetic resonance imaging (fMRI) evaluates changes in cerebral blood flow in responses to local changes in neuronal firing patterns. Thus, fMRI gives information about structure and indirect information about function. Neuroimaging tests are safe, expensive, comfortable, and take up to 1 h.

Single Photon/Positron Emission Computed Tomography (SPECT or PET)

When radiolabeled compounds are intravenously injected in tracer amounts, their photon emissions can be detected, much like X-rays in CT. The images are often shown in a color scale that represents the amount of the labeled compound accumulated in specific brain regions. Various com-

pounds may reflect blood flow, oxygen or glucose metabolism, or concentrations of specific neurotransmitter receptors. These tests are safe, expensive, mildly uncomfortable, and take an hour.

Brain, Nerve, and Muscle Biopsy

A small piece of brain, meninges, peripheral sensory nerve, or muscle is surgically removed for histologic examination and culture for infectious agents. Indications for a biopsy include to (1) determine the etiology of a brain mass, (2) culture a suspected brain infection that has not been isolated from CSF or other body sites, and (3) establish a specific diagnosis of a myopathy or neuropathy. Since the biopsy destroys tissue, it is performed usually when other safer diagnostic tests fail or during surgery to debulk a brain tumor of unknown type. A biopsy is expensive, uncomfortable to the patient, and has a risk of complications. For example, a brain biopsy has a 5% risk of subsequent seizures and all biopsy sites can become infected.

Molecular/Genetic Tests

The completion of the Human Genome Project and improving methods to link disease phenotypes to specific gene loci enable the diagnosis of many neurologic genetic diseases. *Point mutations*, which involve a single or a few base pair substitutions or deletion, lead to amino acid substitutions (missense mutations) [neurofibromatosis type 1], premature translation stop signals (nonsense mutations) [Duchenne and Becker muscular dystrophies], or abnormal RNA transcript splicing—and is the most common type of genetic abnormality seen in neurogenetic diseases. Other clinically important mutations come from DNA deletions, DNA duplications [Down's syndrome], or abnormal expansion of unstable trinucleotide repeats [Huntington's chorea and spinocerebellar atrophy]. Recessive genetic diseases usually are from mutations causing production of abnormal enzymes from both chromosomes so the normal enzyme from the opposite chromosome cannot compensate. Total or severe loss of important enzyme functions results in metabolic diseases affecting brain development or preventing normal turnover of brain proteins allowing them to abnormally accumulate in neurons. Dominantly inherited genetic diseases are mainly due to mutations affecting important proteins.

The genetic mutations of many genetic neurologic diseases can be detected using non-CNS host tissues, such as white blood cells, skin biopsy, or mouth mucosa cell scrapings. Assays for specific enzymes can be performed, such as hexosaminidase A to diagnose Tay–Sachs disease. Chromosomal banding and spectral karyotyping can detect gross deletions or duplications of chromosomal DNA. Cellular DNA can be screened for specific genetic mutations by several methods including polymerase chain reaction (PCR) assays, automated fluorescent sequencing, and Southern blotting, fluorescence *in situ* hybridization (FISH).

While these tests are constantly improving and new genetic mutations are being identified, molecular genetic tests have limitations: (1) failure to detect a given mutation does not rule out the suspected disease as the mutation site may be different from those searched for in the assay, (2) different mutations in the same gene can produce different phenotypes, and (3) mutations in the same gene can produce different phenotypes. In addition, incomplete penetrance, age-dependent onset, and other genes often modify the disease's phenotypic expression and rate of progression. Therefore, typically the most clinically useful genetic tests are in the diseases that are caused by one-gene abnormality. In diseases with complex genetic changes, diagnostic certainty is less with genetic testing. Despite this challenge, next-generation sequencing techniques are improving our ability to identify genetic variability in tens to hundreds of genes simultaneously.

A major advance in the diagnosis of infectious agents affecting the central nervous system (CNS) is the polymerase chain reaction (PCR) assay. PCR assays now exist for many viruses, bacteria, mycobacterium, fungi, and protozoa. Since the PCR assay identifies only a small, but

unique, fragment of the infectious agent DNA or RNA, the nucleic acid does not have to be fully intact or part of an infectious organism. As such, the PCR test often is positive when culture of the infectious agent is negative. The test is performed on CSF or biopsy tissue. Compared to conventional isolation methods, the PCR assay is sensitive, rapid (can be completed in hours to one day), less expensive, and safer (does not require infectious organisms).

PCR works on the following basic principles. First, unique short DNA fragments, called primers, are chemically synthesized as oligonucleotide primers. Second, the primers, free DNA nucleotides, and heat-stable DNA polymerase are added to the DNA mixture that contains DNA from the microorganism in question. The mixture is heated to melt and separate the double-stranded DNA and then cooled allowing the primers to hybridize to their complementary sequences on the separated strands of the microorganism's DNA. The DNA polymerase enzyme adds nucleotide bases to the ends of the primers to create a long segment of double-stranded DNA. Third, another application of heat splits the new DNA fragments apart to allow the cycle to repeat doubling the number of DNA templates. Using automated equipment, it is possible to make millions of copies of the desired template within hours. Fourth, since the DNA template molecules are all the same length and composition, they can be detected by gel electrophoresis or other methods.

Recommended Reading

Fishman RA. Cerebrospinal fluid in diseases of the nervous system. 2nd edn. Philadelphia: WB Saunders; 1992. (Excellent compendium of normal CSF values and changes that occur in many diseases)

Biskup S, Gasser T. Genetic testing in neurological diseases. J Neurol. 2012;259:1249–54. (Nice general review of the types of genetic disorders seen in neurologic diseases and current testing to detect them)

Disorders of Muscle

4

A mother brings her 2-year-old toddler in for evaluation to the pediatrician with the complaint that her son is leaning forward while walking. She reports that he was the product of a normal birth and largely normal development. He reached early milestones (holding head up and rolling over) at the normal times, but his walking was delayed until 16 months of age. She is now concerned that he is walking "funny". On exam, the little boy is alert and his sitting posture is normal. When he begins to walk, he has a waddling gait with excessive lordosis in his trunk. The pediatrician is concerned and orders blood tests including creatine kinase (CK).

Overview

The human body has over 600 muscles, which accounts for 40 % of total body weight. Muscles are divided into skeletal muscle (responsible for voluntary movement and innervated by anterior horn motor neurons or brainstem motor neurons), smooth muscle (involuntary muscles of gastrointestinal tract, genitourinary tract, blood vessels, and skin innervated by autonomic nerves), and cardiac muscle (heart muscle innervated by autonomic nerves). Each muscle type has distinct morphologic and biochemical characteristics that separate them and enable diseases to involve one or more muscle types. In simple terms, a muscle fiber is a long multinucleated cell that contains myofibrils for contraction and abundant mitochondria for energy production. Diseases of skeletal muscle are called by several general names: myopathy implying all types of muscle disease, myositis implying inflammation in the muscle, and muscular dystrophy implying degeneration of muscle, often hereditary.

The first step in diagnosing a muscle disease is to distinguish it from other causes of weakness (Table 4.1). However, there are exceptions to any categorization of weakness causes. For example, some skeletal muscle disorders are episodic (hyper- or hypokalemic periodic paralysis), some involve distal more than proximal muscles (distal and myotonic muscular dystrophies), some produce myotonia or sustained muscle contractions (myotonic muscular dystrophy), and some involve specific muscle groups (lid muscles and swallowing muscles in oculopharyngeal muscular dystrophy). Thus, for unknown reasons, all skeletal muscles are not equally susceptible to a given type of muscular dystrophy in spite of their apparent similarity in structure.

Table 4.2 lists differences between the various types of weakness that are helpful in localizing weakness to a muscle disorder.

Muscle diseases are divided into 4 broad categories: muscular dystrophy due to genetic abnormalities, channelopathies with abnormal sodium, calcium or potassium membrane ion channels,

Electronic supplementary material The online version of this chapter (doi: 10.1007/978-1-4939-2359-5_4) contains videos as supplementary material and can be accessed at http://link.springer.com/book/10.1007/978-1-4939-2359-5.

Table 4.1 Common features of primary skeletal muscle diseases

Proximal greater than distal weakness
Symmetrical weakness
Muscle atrophy proportional to degree of weakness
Muscle may feel doughy to palpation
Hypotonic muscle
Weakness slowly progresses
Weakness rarely painful
Loss of deep tendon reflexes is proportional to degree of weakness
Sensory loss does not occur
Serum creatine kinase (CK) is often elevated early in disease
Electromyography shows myopathic features

inflammatory myopathies, and secondary endocrine myopathies.

Duchenne Muscular Dystrophy (Muscular Dystrophies)

Introduction

Congenital muscular dystrophies are characterized by both genetic and clinical heterogeneity. They vary in the age of onset, location of muscle involvement, and whether they affect males or females. The most common muscular dystrophy is Duchenne muscular dystrophy (DMD), which is a severe, progressive disorder. The incidence is 1 in 3500 newborn boys. The *de novo* (new mutation) frequency is 1 in 3 cases. DMD is a lethal disorder of childhood associated with a marked deficiency or absence of dystrophin. The largest gene in the human genome, located on the X chromosome at Xp21, encodes dystrophin. Duchenne's muscular dystrophy is the most common disease associated with genetic mutations of the dystrophin gene. Collectively these diseases are called dystrophinopathies. As DMD is transmitted by X-linked recessive inheritance, nearly all patients are male. About 10% of female carriers have mild muscle weakness.

Pathophysiology

The dystrophin gene is the largest known, spanning about 2.2 megabases of DNA or almost 1% of the entire X chromosome. Muscle dystrophin is a large 427-kDa molecular weight protein of

Table 4.2 Distinguishing characteristics of limb weakness

Characteristic	Upper motor neuron (corticospinal tract)	Lower motor neuron (peripheral nerve)	Distal polyneuropathy	Neuromuscular junction	Skeletal muscle
Muscle involved	Distal > proximal and often unilateral	Distal > proximal	Distal > proximal	Proximal > distal	Proximal > distal
Muscle atrophy	Minimal	Marked	Moderate	Minimal	Moderate
Normal strength that quickly fatigues	No	No	No	Yes	No
Fasciculations	No	Common	No	No	No
Deep tendon reflexes	Increased	Decreased to absent	Decreased to absent	Normal or slightly decreased	Normal to decreased proportional to weakness
Sensory loss	May be unilateral	Yes	Yes	No	No
Family history positive	Uncommon	Uncommon	Uncommon	Uncommon	Common
CK elevation	No	No	No	No	Yes
EMG findings	None	Denervation or slow motor nerve conduction velocity	Few	Few	Myopathic

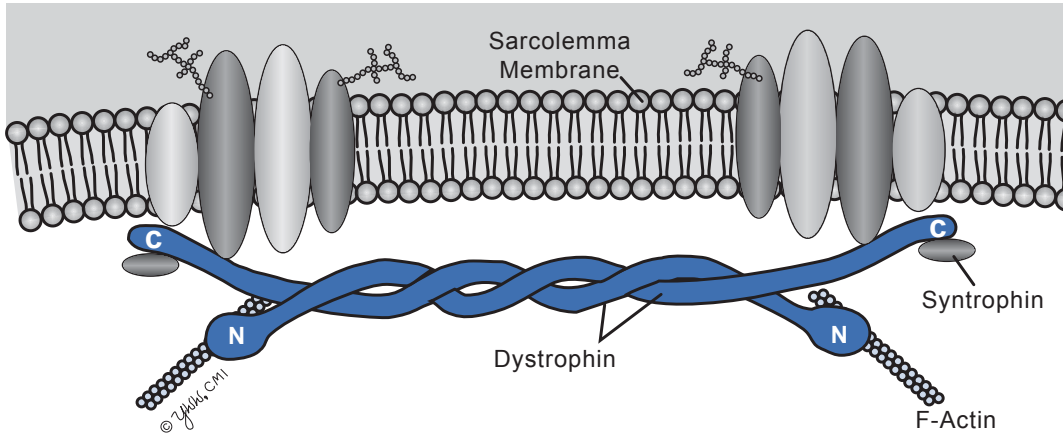

Fig. 4.1 Dystrophin molecule

3685 amino acids that is found primarily within skeletal, smooth, and cardiac muscles. Dystrophin isoforms are also present in cortical neurons, Purkinje cell neurons, glia, and Schwann cells. Dystrophin accounts for 5% of sarcolemmal cytoskeletal proteins in muscle. The protein is rod shaped and resides just beneath the sarcolemmal membrane as two parallel fibers (Fig. 4.1). The amino terminus is attached to actin, and the carboxyterminus binds to a transmembrane protein complex that is transmembrane located (Fig. 4.1). In muscle, dystrophin links myofibrillar elements with the sarcolemma, affording stability and flexibility to the muscle fiber.

Seventy-five percent of patients demonstrate large-scale deletions in the gene or have partial gene duplications, and the remaining are poorly characterized. Nearly 80% of deletions occur in the center of the protein. The remaining 25% of patients have small or point mutations. In DMD, the C-terminal domain is lacking and therefore the dystrophin protein is nonfunctional. In Becker muscular dystrophy (BMD), a milder form of DMD, the dystrophin protein, is internally truncated but contains the normal interacting domains—maintaining partial functionality.

Dystrophin gene mutations that cause DMD result in either the absence of dystrophin protein production or markedly truncated proteins that cannot attach to the transmembrane protein complex and are rapidly catabolized. The net result is the virtual absence of dystrophin and the DAP complexes along the sarcolemmal membrane. Quantitative studies of dystrophin have shown that less than 3% of normal dystrophin content is present in DMD muscle (Fig. 4.2).

The absence of dystrophin leads to membrane instability, myofiber leakiness of creatine kinase (CK), and susceptibility to injury from normal muscle contractions. Over time, the damaged muscle cell wall allows abnormal influxes of calcium and activation of cell proteases with amplification of disturbed calcium homeostasis, resulting in fiber necrosis, secondary inflammation, and apoptosis.

Although mature muscle fibers are postmitotic, skeletal muscle contains mononuclear muscle precursor cells that proliferate and fuse in response to stimuli from degenerating muscle

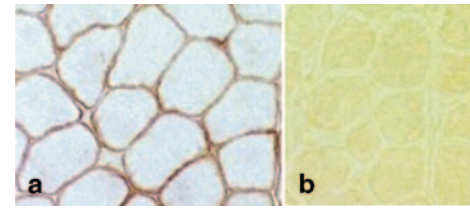

Fig. 4.2 **a** Normal dystrophin staining around rim of muscle fiber. **b** Absent dystrophin staining in Duchenne muscular dystrophy. (Courtesy of Alan Pestronk, MD)

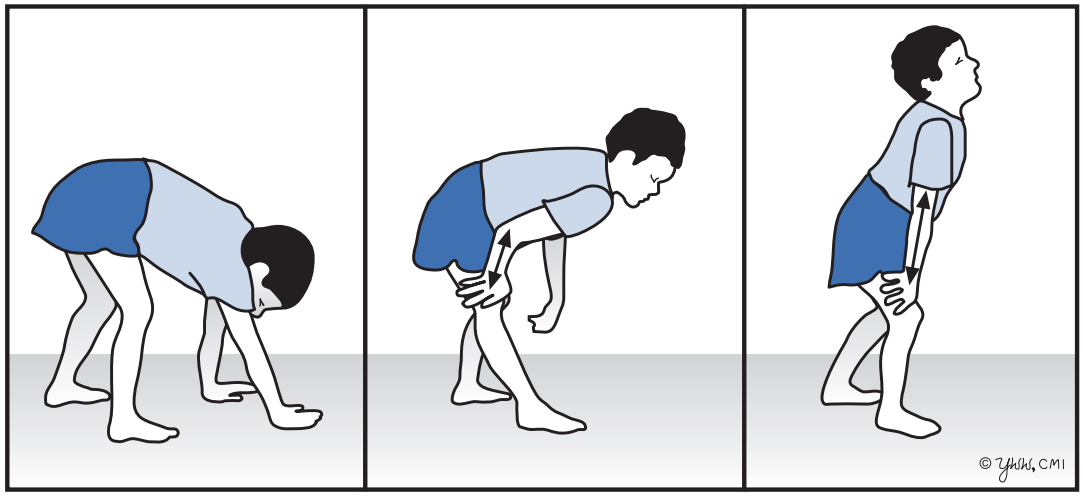

Fig. 4.3 Gower's maneuver

fibers. Since these regenerating muscle fibers are affected by the gene mutation, the new muscle fibers contain the dysfunctional dystrophin and the cycle repeats. Over time, fibrosis and scarring develop in the muscle. Degenerating muscle cells are replaced by fat cells. This fatty replacement and fibrosis result in a pseudo-hypertrophic appearance of the weakened muscles.

Mutations in the DMD gene cause a spectrum of diseases of which DMD and BMD are the most severe—but also includes X-linked dilated cardiomyopathy, cramps and myalgias, and metabolic derangements such as asymptomatic hyperCKemia.

Major Clinical Features

Although children with DMD have disease activity in the neonatal period (elevated serum CK and necrosis on muscle biopsy), they rarely have clinical symptoms until age 3–4 years. However, within the first year of life, boys with DMD can have mild language delay. Parents usually report difficulty in running or climbing, frequent falls, and enlargement of the calf muscles that feel firm and rubbery. By 4–5 years of age, the gait becomes wide-based and waddling (also known as Trendelenburg gait). Affected children often walk on their toes because of contractures of heel cords. Weakness is greatest in proximal muscles and produces a compensatory Gower's maneuver (placing hands on the knees and climbing up their thighs when trying to rise from the ground or a chair (Fig. 4.3).

In the early school years, the limb weakness progresses and is accompanied by excessive lordosis. There is relative clinical sparing of extraocular muscles and muscles of bladder and bowel sphincters as for unknown reasons these muscles lack dystrophin. By age 10–12 years, the child is typically unable to walk and confined to a wheel chair. By definition, boys who cease walking by age 13 years have DMD—whereas boys who are able to still walk independently to age 16 years have BMD. Deep tendon reflexes are lost, and joint contractors appear at the hip flexors and heel cords. By late teens, the weakness is profound, scoliosis is marked, and joint contractures are frequent. About 25% of children have IQ scores below 75, and the average IQ score is one standard deviation below the mean, from 80 to 90. Cognitive involvement is not progressive over the course of the disease. Some children develop smooth muscle involvement with gastroparesis and constipation. Cardiomyopathy, cardiac muscle damage, slowly develops. Kyphoscoliosis and weakness of respiratory muscles produce

a decreasing lung vital capacity and low maximal inspiratory and expiratory pressures.

The terminal stages of DMD are characterized by recurrent pulmonary infections and often congestive heart failure. The age of death ranges from 10 to 30 years with a mean of 18 years. Only 5% live beyond 26 years.

Although DMD is an X-linked disorder typically manifesting in males, manifesting females may show the spectrum of disease manifestation from mild weakness to the full Duchenne phenotype. They typically have the elevation in CK levels as found in affected males. Nonmanifesting carriers are typically unaffected and have normal muscle strength—although on detailed muscle metabolic testing there can be abnormalities consistent with lionization of muscle cells with abnormal dystrophin.

Major Laboratory Findings

In young children, serum CK level is always markedly elevated, often 100 times above the normal upper limit. In the late stages of DMD, the CK level falls as muscle mass disappears. The electrocardiogram is abnormal in two-thirds of patients.

The EMG demonstrates myopathic motor unit potentials and occasionally fibrillation potentials from segmental necrosis of muscle fibers (see Chap. 3 on common neurologic tests).

Muscle biopsy demonstrates a variation in fiber sizes, containing necrotic, regenerating, and large hyaline (hypercontracted, opaque, or large dark) fibers. Necrotic fibers have a glassy appearance from loss of the intermyofibrillar membranous network and are invaded by inflammatory macrophages and CD4+lymphocytes (Fig. 4.2). Fiber type grouping of remaining muscle fibers is normal. Electron microscopy of non-necrotic muscle fibers demonstrates defects in the plasma membrane where abnormal calcium influx occurs. Later in the disease, fibrosis and fatty replacement of muscle fibers are seen. Immunohistochemical staining demonstrates absence or near absence of dystrophin along the sarcolemma membranes.

Muscle MRI scans are being used as diagnostic tools as inherited muscular diseases show patterns of involvement that can be used clinically. Typically, a T1-weighted MR image is obtained in the lower extremity of an affected individual. The findings in DMD show fatty infiltration in leg muscles once boys with DMD reach ages 6 or 7 years. The lower leg muscles seem to be more affected with the fatty infiltration than the foot muscles are—and the posterior compartment (e.g. gastrocnemius) is typically more involved than the anterior compartment.

It is now possible to use genetic testing to detect both DMD and BMD. Deletion and duplication analysis is available as well as sequence analysis of the entire coding region. Prenatal diagnosis and carrier testing are also available.

Principles of Management and Prognosis

Management must be multidisciplinary. Education of the patient and family is primary after establishing a diagnosis. Use of corticosteroids has shown improved muscle strength in affected boys. Steroids are often offered at the point of clinical decline for a period of 18–36 months. No drugs have yet proven to reverse the pathologic process. There is much research in gene therapy in this disorder, but no clear efficacious strategy as yet. Theoretical approaches to the gene therapy include replacing the mutated dystrophin gene by introduction of a normal gene into muscle fibers via a plasmid or viral vector or by inoculation of genetically normal myoblasts that fuse with patient's regenerating muscle fibers. The mainstay of pharmacological therapy is corticosteroid administration, which may improve strength and performance for up to one year. Disuse of muscles will lead to worsening of the condition, so therapies that aim to keep patients mobile and active are essential. Range-of-motion exercises should be performed to prevent contractures. If contractures develop, bracing and surgical release may be performed. Once mobility is compromised, wheelchairs and other assistive devices should be viewed as a

passport to mobility and not a failure to walk. Once the child is confined to a wheel chair, attention should be directed toward minimizing scoliosis through posture and bracing. Breathing assistance may be needed just at night—or when severely compromised, ventilator support may be needed.

Dermatomyositis (Inflammatory Myopathy)

Introduction

Inflammatory myopathies are a heterogenous group of diseases characterized by inflammation in muscles. In some, there is an infectious etiology (trichinosis, viral myositis) but in most the etiology is unknown. Dermatomyositis (DM) has an immune-mediated pathogenesis. While DM can occur at any age, children from ages 5–14 and adults from ages 40–60 are the most likely to become symptomatic. As in most autoimmune disorders, females are more often affected. A genetic component such as HLA type may predispose to DM but DM is rarely found in more than one family member. The estimated incidence is 9.6 per million and prevalence is about 2 per 100,000 adults in the United States. DM appears to affect African-Americans at a greater rate than whites. A relationship between malignancy and DM has been noted for some time. The greatest risk of developing a malignancy in these patients appears to be within the first year after diagnosis and can persist for up to 5 years after diagnosis. An association of collagen vascular diseases such as systemic lupus erythematosus and Sjogren's syndrome has been noted.

Pathophysiology

Dermatomyositis appears to be an antibody-mediated disease in which complement is activated with deposition of membrane attack complexes in blood vessels—specifically intermediate-sized blood vessels. Destruction of the blood vessels leads to "watershed" ischemia producing muscle fiber necrosis, microinfarcts, and perifascicular atrophy (at edges of a muscle fascicle). The capillary destruction is not limited to muscles but may occur in skin (heliotrope rash of face, eyelids, and sun-exposed areas) and other organs such as lung (interstitial lung disease) and heart (cardiomyopathy).

Although not part of the diagnostic criteria for DM, autoantibodies are frequently found in patients with DM. There is not one particular autoantibody that is present in all patients with DM, rather 60–80% of patients have at least one myositis-associated antibodies when tested. New autoantibodies are continually being identified. At this time, we can test for antisynthetase autoantibodies and some dermatomyositis-specific antibodies—with a variety of targets. The clinical significance of these autoantibodies is unclear.

Major Clinical Features

Typically, weakness is proximal and first noted in muscles of the shoulder and pelvic girdle in a symmetrical fashion. Common complaints at presentation would be difficulty arising from a chair or difficulty washing hair or difficulty with climbing stairs. Muscle pain and soreness are uncommon. As the disease progresses, the patient may develop dysphagia and neck weakness. Occasionally respiratory muscles may become involved—requiring mechanical ventilation. The early skin rash is characterized by erythema (heliotrope appearance) accompanied by edema of the subcutaneous tissue affecting mainly the periorbital, perioral, malar, and anterior chest regions. Skin exposed to sunlight may also develop a similar rash. The rash often progresses to cause scaling, pigmentation, and depigmentation of skin with a brawny induration. Gottron's papules—an erythematous rash over the extensor surfaces of the hand and finger joints—are pathognomonic for DM.

Interstitial lung disease occurs in about 10% of patients usually after years of disease. Patients experience a nonproductive cough and dyspnea from bronchiolitis obliterans, interstitial pneumonia, and/or diffuse alveolar damage.

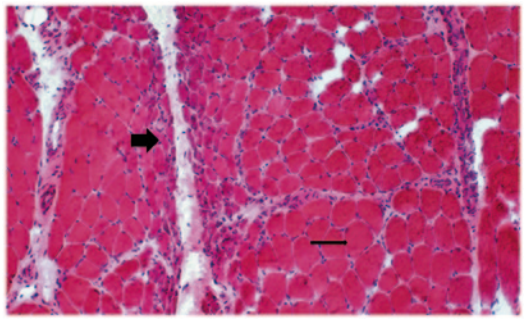

Fig. 4.4 Muscle biopsy of dermatomyositis showing atrophic perifascicular muscle fibers (*thick arrow*) and normal muscle fibers neighboring normal vascular perimysium (*thin arrow*). (Courtesy of Alan Pestronk, MD)

Major Laboratory Findings

Serum CK levels are elevated (3–30 times above normal). Other muscle enzymes such as aldolase, aspartate transaminase, and alanine transaminase can be elevated in at least 90% of patients with inflammatory myopathy.

The EMG in both demonstrates an irritative myopathy with myopathic changes (brief, small amplitude, abundant, polyphasic motor units) and signs of denervation from the associated inflammation (fibrillations and positive sharp waves).

MRI can identify chronic muscle damage by detecting fatty replacement of skeletal muscle. Although not part of the diagnostic criteria at this time, MRI could be useful in diagnosis, guiding muscle biopsy location, and assessing treatment effects.

Muscle biopsy in DM demonstrates muscle changes in the perifascicular region. Myopathic changes include necrosis and regeneration, muscle fiber atrophy (Fig. 4.4), and a reduction in cytochrome oxidase activity. Inflammatory changes are seen but do not correlate with severity of muscle disease.

Blood vessels demonstrate perivascular collections of inflammatory cells, arteritis, phlebitis, intimal hyperplasia of arteries and veins, and occlusion of vessels by fibrin thrombi. Adjacent to occluded vessels are ischemic and infarcted muscle fibers. In the majority of children with DM and in some adults with DM, there are immune complexes containing IgG, IgM, and complement (C3) within the walls of arteries and veins. These muscle and skin angiopathic changes at the electron microscope level are virtually diagnostic.

Principles of Management and Prognosis

Before treatment, a clear diagnosis is needed, which usually requires a typical clinical history, characteristic EMG findings, and a muscle biopsy showing inflammatory myopathy or diagnostic blood vessel damage. Corticosteroids represent the first line of therapy with an initially high dose that is tapered as the patient regains muscle strength and the CK level falls. If corticosteroids fail or adverse reactions develop, patients are given immunosuppressants such as azathioprine or methotrexate. These drugs may take 3–6 months of treatment before they are effective. Human immune globulin (IVIG) may be given initially to severely affected individuals.

The duration of DM disease activity in children is variable and may last several months to 4 years before becoming inactive. In adults, the 5-year survival is 90% and the 10-year survival is 80%. Individuals with malignancies, interstitial lung disease, or cardiomyopathy have a more severe disease course.

Statin Myotoxicity (Toxic Myopathy)

Introduction

Statin medications are widely used to treat hypercholesterolemia. Currently, approximately 30 million people take statin medications daily in the United States. While most patients tolerate the medications without problems, 10% of patients will develop muscle-related complications—ranging from mild muscle aches (myalgias) to serious muscle breakdown (rhabdomyolysis).

Statin-induced toxic myopathy occurs more frequently in patients who are taking dual therapy

with a statin and another lipid-modifying medication, gemfibrozil. Patients with an underlying myopathy (such as muscular dystrophy) or who have a genetic predisposition may experience statin-induced myopathy at a greater incidence.

Pathophysiology

The pathophysiology is unknown currently. There are several myotoxicity mechanisms known by which statins may cause the muscle damage: membrane excitability, mitochondrial function, ubiquinone depletion, calcium homeostasis, apoptosis induction, and genetic determinants.

Statins work by inhibiting 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA). HMG-CoA is a key enzyme in cholesterol synthesis. By interrupting normal cholesterol synthesis, a number of intermediates would be reduced. These intermediates play a role in posttranscriptional lipid modification of proteins (e.g. prenylation). Hypothetically, this deficiency could impair many energy processes within a cell. In addition, there is evidence that statin treatment is associated with membrane hyperexcitability. It is likely that there is a myriad of mechanisms, which may contribute to the myotoxicity of the statins—but they are, as yet, not well defined.

Major Clinical Features

There are a variety of clinical manifestations of myotoxicity in patients on statin medications. Myalgias may be the most frequent complaint—in approximately 10% of people. This is thought to be an underestimation of the true incidence. Asymptomatic hyperCKemia (elevated creatine kinase levels) is also found. More severe manifestations include acute rhabdomyolysis, unmasking of other myopathies, immune-mediated myopathies, and rippling muscle disease.

Major Laboratory Findings

Serum CK levels are the most commonly used marker for statin-induced muscle disease. Before starting a statin, a CK can be checked and periodically monitored. If CK is elevated prior to treatment, it may be a sign of an underlying myopathy and require more frequent monitoring of CK levels and clinical symptoms. After starting a statin, CK level 3 times normal should be monitored, but the statin can be continued. If the CK level continues to rise and reaches 10 times the normal limit, then the medication should be withdrawn.

Principles of Management and Prognosis

Without clear pathophysiologic knowledge of the statin myopathy, development of guidelines for management have been difficult. In general, current recommendations include the following: (1) using the lowest statin dose needed to achieve the therapeutic goal, (2) identifying patients at higher risk (e.g. personal or family history of muscle symptoms, hypothyroidism, and elevated CK levels), and (3) avoiding polytherapy with drugs inhibiting cytochrome P450. Currently, the most effective treatment for the statin-induced myopathies includes withdrawal of the offending agent. Other strategies have included taking alternative-day dosing or twice weekly dosing of statins or switching from one statin to another.

Primary Hyperkalemic Periodic Paralysis (Channelopathies)

Introduction

Channelopathies are a group of diseases with abnormal channels resulting from genetic disorders. Channels are pores in cell membranes that

allow ions to enter or exit a cell to depolarize or hyperpolarize the cell. These macromolecular protein complexes within the lipid membrane are divided into distinct protein units called subunits. Each subunit has a specific function and is encoded by a different gene. A channel may be non-gated, directly gated, or second-messenger-gated. Important directly gated channels include voltage-gated channels (sodium, potassium, calcium, and chloride) and ligand-gated channels (acetylcholine, glutamate, GABA, and glycine).

Genetic mutations in critical areas of a channel can produce an abnormal gain of function (additional properties not present in the normal protein) or loss of function (loss of properties present in the normal protein). Channelopathies primarily affect excitable cells such as muscle fibers and neurons and produce signs and symptoms that are often episodic.

Primary hyperkalemic periodic paralysis (hyperPP) belongs to a group of channelopathies with mutations in the voltage-gated sodium channel. Other sodium channelopathies include familial generalized epilepsy with febrile seizures, paramyotonia congenital, and hypokalemic periodic paralysis.

Pathophysiology

HyperPP is due to a dominant mutation in chromosome 17q35 that affects the α-subunit (SCN4A) of the sodium channel (Fig. 4.5). Two mutations (T704M and M1592V) account for 75 % of the cases.

The muscle membrane in a patient with hyperPP contains two types of sodium channels. A normal channel from the normal gene activates (opens) and then inactivates (closes) rapidly. However, the mutated sodium channel activates appropriately but inactivates (closes) abnormally slow.

In normal muscle, hyperkalemia causes a few normal sodium channels to open. The subsequent slight membrane depolarization is rapidly corrected as the channels close before the depolarization is sufficient to cause muscle contraction. However, in hyperkalemic PP muscle, the hyperkalemia opens both the normal sodium channel and the mutated sodium channel. The mutated sodium remains open for a prolonged period allowing excess entry of sodium into the muscle cell. The excess intracellular sodium in turn produces a prolonged depolarization. The net result is that the depolarized muscle fiber becomes paralyzed, electrically unexcitable, and nonresponsive to future nerve stimulation.

The sodium influx allows efflux of intracellular potassium into the extracellular space and also causes extracellular water to enter the muscle fiber resulting in hemoconcentration. Both result in a further rise in serum potassium. The elevated potassium triggers more muscle fibers to become persistently depolarized and rapidly the entire muscle becomes paralyzed. The cycle ends when the serum potassium returns to normal by the kidney's excretion of potassium and likely other corrective measures. The duration of paralysis may be 15 min to hours.

Normal individuals can develop muscle paralysis if their serum potassium rises above 7 mmol/L. Hyperkalemia may occur in renal failure, adrenal insufficiency, and exposure to the diuretic spironolactone.

Major Clinical Features

The paralysis attacks usually begin in the first decade of life and are infrequent. With increasing age, the attacks become more frequent. In severe cases, they occur daily. Most episodes occur in the morning before breakfast. Attacks during the day are often precipitated by strenuous exercise followed by rest. Other triggers include consumption of excess potassium, emotional stress, fasting, cold environment, and corticosteroid administration.

At the start of an attack, the patient may experience paresthesias or sensations of increased muscle tension. The patient then develops a flaccid generalized weakness and cannot move his arms, legs, and trunk. The weakness spares muscles of respiration, cranial nerves, and bladder and bowel sphincters. The attack lasts 15 min–1 h before spontaneously disappearing. Afterward

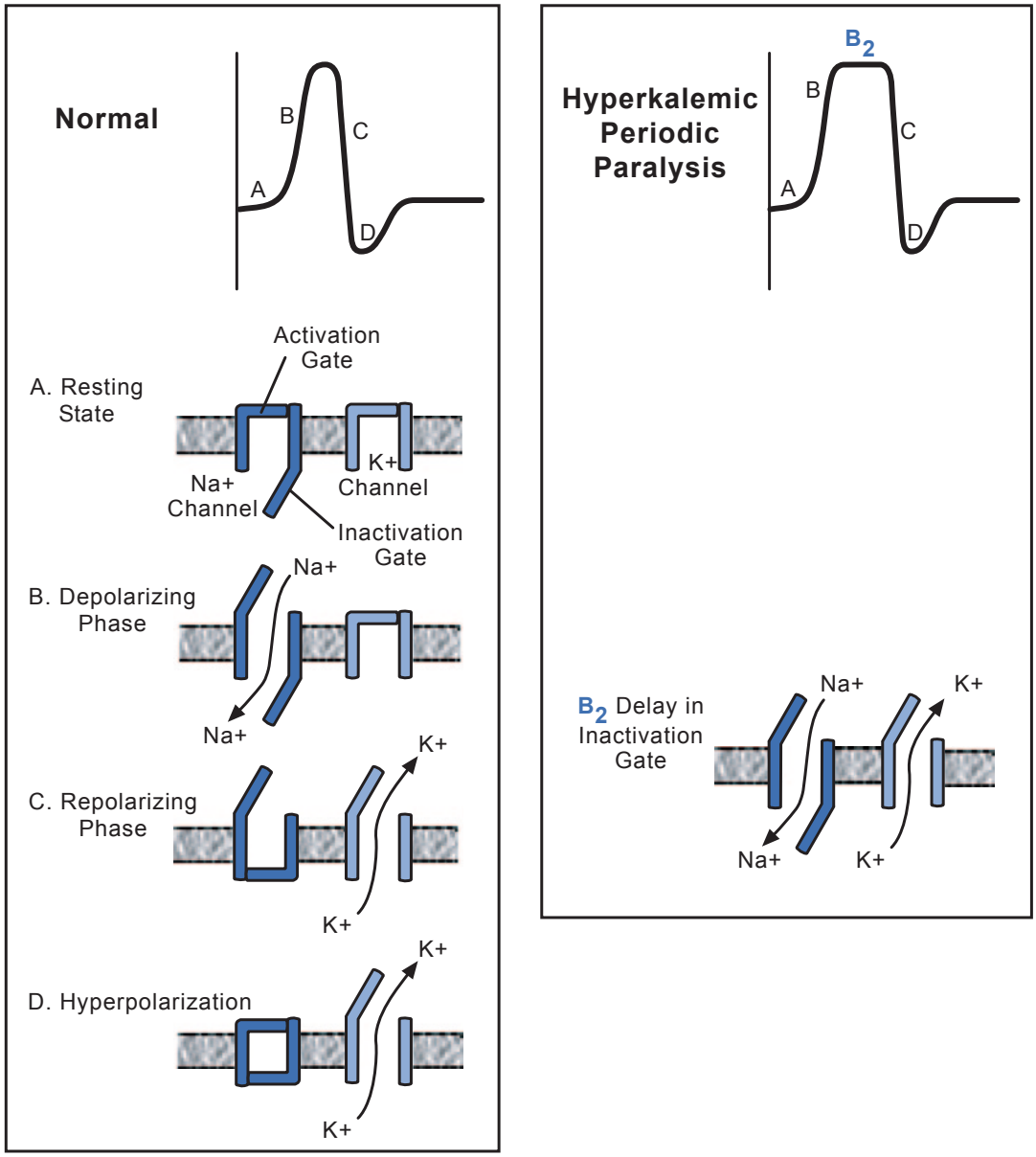

Fig. 4.5 Hyperkalemic PP is due to a dominant mutation in chromosome 17q35 that affects the α-subunit (SCN4A) of the sodium channel

the strength returns to normal and the individual commences their normal activity. Over years, patients with severe hyperPP may develop permanent muscle weakness.

One mutation causes varying amounts of myotonia between attacks. The clinical symptom of myotonia is essentially a slowing of relaxation of a normal muscle contraction and is commonly interpreted by the patient as "stiffness". Commonly, the patient cannot easily release his grip on an object. A cold environment often makes myotonia worse. In addition, interictally patients may experience lagging of the upper eyelid on downward gaze—called lid lag.

Major Laboratory Findings

During an attack, serum potassium rises up to 5–6 mmol/L but rarely reaches cardiotoxic levels. Serum sodium slightly falls as the ion enters muscle fibers. Renal excretion of potassium occurs with elevated urine potassium levels. The serum CK level is normal to slightly elevated during an attack.

Between attacks, serum potassium levels are usually in the upper normal range and urinary potassium levels are normal.

During an attack, EMG studies of paralyzed muscle show electrical silence. Between attacks, the EMG in the most common mutation is normal while myotonia is seen in the less common mutation. In myotonia, insertion of the EMG needle into a muscle causes a train of rapid electrical discharges that have a falling amplitude and frequency and sound like a "dive-bomber" when heard on the EMG speaker. Myotonia is due to increased excitability of muscle fibers from the channelopathy (sodium channels or potassium channels in other myotonic diseases), producing repetitive action potentials in individual muscle fibers.

Muscle histology may be normal or demonstrate non-specific changes to muscle fibers. In patients who develop permanent myopathy, muscle fibers may show vacuolations in muscle fibers, focal myofibrillar degeneration, and central nuclei.

Since the gene for hyperPP is known, blood tests are available for the detection of the most common mutations. However, the diagnosis is commonly made in a patient with periodic paralysis who has a dominant family history and transient elevation of serum potassium during an attack.

Principles of Management and Prognosis

Since most attacks are brief, many patients do not require any drug treatment. Some patients can abort or shorten an attack by consuming carbohydrates or performing mild exercise at the start of an attack. Patients with severe frequent attacks may benefit from chronic administration of thiazide or acetazolamide diuretics that lower serum potassium levels.

Video Legend

This video shows a 9 year-old boy with Duchenne Muscular Dystrophy.

Segment 1: Motor Exam

- Gower's maneuver getting up from floor. Due to the proximal muscle weakness, he begins on hands and knees with feet wide apart. Then straightens his legs and braces his hands on thighs in order to stand.
- Difficulty leaving the ground while jumping due to proximal leg weakness.
- Pseudohypertrophy of calf muscles is seen.

Segment 2: Gait Exam

- Waddling gait due to weakness of hip girdle muscles.

Recommended Reading

Pestronk A. Web site on neuromuscular diseases. www.neuro.wustl.edu/neuromuscular/index. (Outstanding, accurate, current outline information on clinical, laboratory, pathology and treatment of all muscle and peripheral nerve diseases)

Morrison LA. Dystrophinopathies. Handb Clin Neurol. 2011;101:11–39. (Good review of the muscular dystrophies—including pathophysiology and treatment recommendations)

Mammen AL. Autoimmune myopathies: autoantibodies, phenotypes and pathogenesis. Nat Rev Neurol. 2011;7:343–54. (Good review of the autoimmune myopathies)

Kushlaf HA. Emerging toxic neuropathies and myopathies. Neurol Clin. 2011;29:679–87. (Brief summaries in an easy-to-read format of emerging toxic neuropathies and myopathies)

Ryan AM, Matthews E, Hanna MG. Skeletal-muscle channelopathies: periodic paralysis and nondystrophic myotonias. Curr Opin Neurol. 2007;20:558–63. (Recent review of channelopathies)

Disorders of the Neuromuscular Junction

5

A 37-year-old woman presents to her primary care doctor with several months of feeling weak and seeing double. She reports that she first noticed the weakness when the family was moving into a new house. Her husband told her that she looked tired as her eyelids were droopy. Shortly after that, she noticed some double vision late in the day. She noted that packing the kitchen was particularly difficult when moving things from higher shelves down for packing. She had to take several rests in order to complete the packing. She thought this was normal and just related to the stress of moving. But the weakness and fatigue have not gotten better and became worried that something was really wrong. On exam, the patient has ptosis and fatigable weakness on holding her arms outstretched. A glove with ice is placed on her eyes with resolution of the ptosis. A clinical diagnosis of myasthenia gravis was made and the appropriate confirmatory tests were ordered.

Overview

In humans, all nerve to nerve, nerve to muscle and peripheral sensory receptor to nerve communication occurs via synapses. An electrical signal traveling along a nerve axon is converted at a specialized nerve ending called a synapse. At the synapse, the electrical signal triggers release of a neurotransmitter into the synaptic cleft. The neurotransmitter then crosses the synaptic cleft to attach to a specialized receptor that is part of an ionic channel, resulting in either local depolarization or hyperpolarization of the post-synaptic cell. When sufficient ionic channels have been stimulated by neurotransmitters, the post-synaptic cell either completely depolarizes or becomes inhibited from depolarizing. In summary, all human neural communication results from electrical to chemical to electrical transmission.

There are at least 30 different neurotransmitters, with the greatest number occurring in the CNS. In simple terms, neurotransmitters are classified into simple chemicals (acetylcholine, norepinephrine, dopamine), amino acids (gamma amino butyric acid [GABA], glycine, glutamine), or peptides (substance P, endorphins). The duration of the neurotransmitter effect may be milliseconds as in a brief opening and closing of an ionic channel to hours or days as when a re-

Electronic supplementary material The online version of this chapter (doi: 10.1007/978-1-4939-2359-5_5) contains videos as supplementary material and can be accessed at http://link.springer.com/book/10.1007/978-1-4939-2359-5.

ceptor stimulates intracellular second messengers that enzymatically affect intracellular pathways.

The specialized synapse that makes up the neuromuscular junction (NMJ) has been well studied and much of what we know about synapses in general come from the knowledge of the NMJ. When a nerve action potential reaches the nerve ending, voltage-gated calcium channels open and the influx of calcium then results in exocytosis of acetylcholine vesicles into the synaptic cleft (the space between the presynaptic nerve ending and the post-synaptic complex of the muscle fiber). When the acetylcholine binds to the receptor on the muscle, this causes local depolarization of the muscle membrane. Typically, when 60% of the acetylcholine receptor channels are depolarized, the entire muscle fiber depolarizes and contracts. However, in a disease state that limits neuromuscular transmission (e.g. synaptopathy), the muscle does not contract—leading to weakness.

Synaptopathies may occur from chemical or biologic toxins, antibodies directed against synaptic receptor molecules, or genetic mutations in the synaptic receptor or membrane channel. Synaptic disorders due to mutations in calcium, potassium, and sodium ion channels (called channelopathies) are responsible for episodic disorders such as seizures, migraine-type headaches, ataxia, myotonia, and weakness from Lambert–Eaton syndrome.

Synaptic disorders often have several suggestive clinical features: (1) excessive inhibition or excitation of one transmitter pathway, (2) signs and symptoms that are episodic or fluctuate considerably, and (3) signs that increase with continuing firing of the synapse.

This chapter focuses on diseases that result from toxins and antibodies affecting the neuromuscular junction to produce weakness.

Myasthenia Gravis

Introduction

Myasthenia gravis (MG) is the most common synaptopathy affecting the neuromuscular junction. In MG, autoantibodies directed against the post-synaptic acetylcholine receptor (AchR) interfere with normal neuromuscular transmission and cause symptoms. There are over 30,000 individuals with MG in the USA with a prevalence of 15 per 100,000 adults—although this is thought to be an underestimation of the true prevalence. The epidemiology of MG demonstrates two peaks. The first peak occurs mainly in women between ages 10 and 40 years, and the second peak occurs from ages 50 to 75 years, mostly in males.

MG is considered the classic humoral autoimmune disease based on well-characterized autoantibodies and the observation that these patients frequently develop other autoimmune diseases such as thyrotoxicosis, rheumatoid arthritis, and systemic lupus erythematosus.

Pathophysiology

Weakness in MG is the result of three processes that impair neuromuscular transmission. The most important one is circulating antibodies that form a functional blockade. In the most common form of MG, circulating IgG antibodies are directed at the AchR. These antibodies attach to the AchR located on key parts of the sodium/potassium channel, thereby interfering with opening the sodium/potassium channel (Fig. 5.1). When sufficient AchR are blocked by antibody, the muscle will not depolarize sufficiently to trigger contraction of the muscle fiber. A second factor contributing to the weakness is a faster rate of AchR degeneration due to cross-linking of antibodies. When AchR antibodies simultaneous attach to two adjacent AchR, a cell signal initiates internalization of both receptors and degrades them. The turnover rate is faster than replacement of new membrane AchR, resulting in a net loss of available AchR at the synapse. The final weakness factor develops because antibody attached to AchR triggers serum complement activation, producing secondary damage to the synaptic membrane. As a consequence of years of complement damage, the post-synaptic membrane loses its rich invaginations and becomes simplified in structure (Fig. 5.2a, b). In severe chronic cases, the post-synaptic membrane may have a two-third

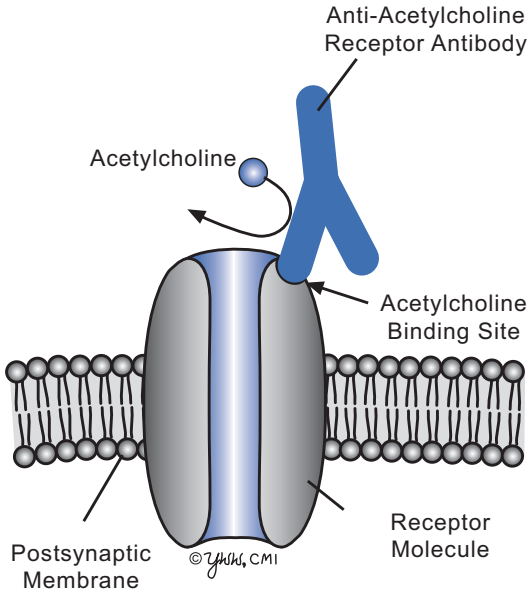

Fig. 5.1 In myasthenia gravis, acetylcholine receptor antibody blocks the acetylcholine-binding site

reduction in the normal number of AchR molecules, a number insufficient to initiate depolarization and contraction of the muscle fiber even if no acetylcholine antibodies were present. In these patients, pyridostigmine usage does not improve the probability of muscle fiber contraction.

The majority of early-onset, AchR+patients have an associated abnormality of their thymus gland. About 65% of these patients have thymic hyperplasia with germinal center lymphocyte proliferation, and 10% have a thymoma. Within the thymus, myoid cells (striated muscle cells) express AchR and may play a role in "priming" helper T cells within the thymus. It is not clear what might be the trigger for the development of the autoimmune response seen in MG, but the elements for the generation and maintenance of autoimmunity exist within the thymus. Surgical removal of the thymus gland often results in clinical improvement and a reduction in the number of circulating antibodies. In older individuals, the thymus is typically atrophic and it is not clear whether it plays a role in the autoimmune response.

Although AchR antibodies are often found, there were many patients who were considered "seronegative" and who did not have AchR antibodies detectable. There are several other antibodies that may play a role in "seronegative" MG, such as muscle-specific kinase (MuSK) antibodies. These are found in up to 70% of "seronegative" MG patients. MuSK plays a role in clustering of AchR at the NMJ. These patients are more likely to have swallowing and respiratory difficulties at their presentation than AchR+ patients.

Myasthenia gravis can occur in infants. Infants born to mothers with MG may have sufficient circulating antibodies to cause the infant to become floppy, weak, and have a poor suck. This transient syndrome lasts for several weeks until the maternal antibody disappears. Other infants have congenital MG that is due to genetic mutations in the AchR. These infants remain persistently weak and do not respond to immunosuppressive drugs.

Major Clinical Features

The clinical features result from blockade at the neuromuscular junction and affect skeletal muscles in a fluctuating and fatigable manner (Table 5.1). The disease usually has a subacute onset. Earliest symptoms are ptosis and diplopia. Patients complain of droopy eyelids and double vision that will vary during the day and worsen as the day progresses. In 80% of patients, they will begin with ocular symptoms and then progress to generalized weakness. Signs of bulbar muscle weakness appear with trouble chewing, swallowing, and speaking loudly—although for a minority of patients, the bulbar symptoms will be prominent early in the disease course. Some patients find they eat their big "dinner" meal for breakfast as they have trouble chewing meat by the end of the day. Limb weakness is common and affects proximal muscles greater than distal muscles. Although brief maximal muscle testing may appear normal, patients often cannot hold their arms outstretched for even a minute without fatigue. In severe cases, patients cannot walk and develop respiratory weakness. Sensation, mentation, and deep tendon reflexes are not affected.

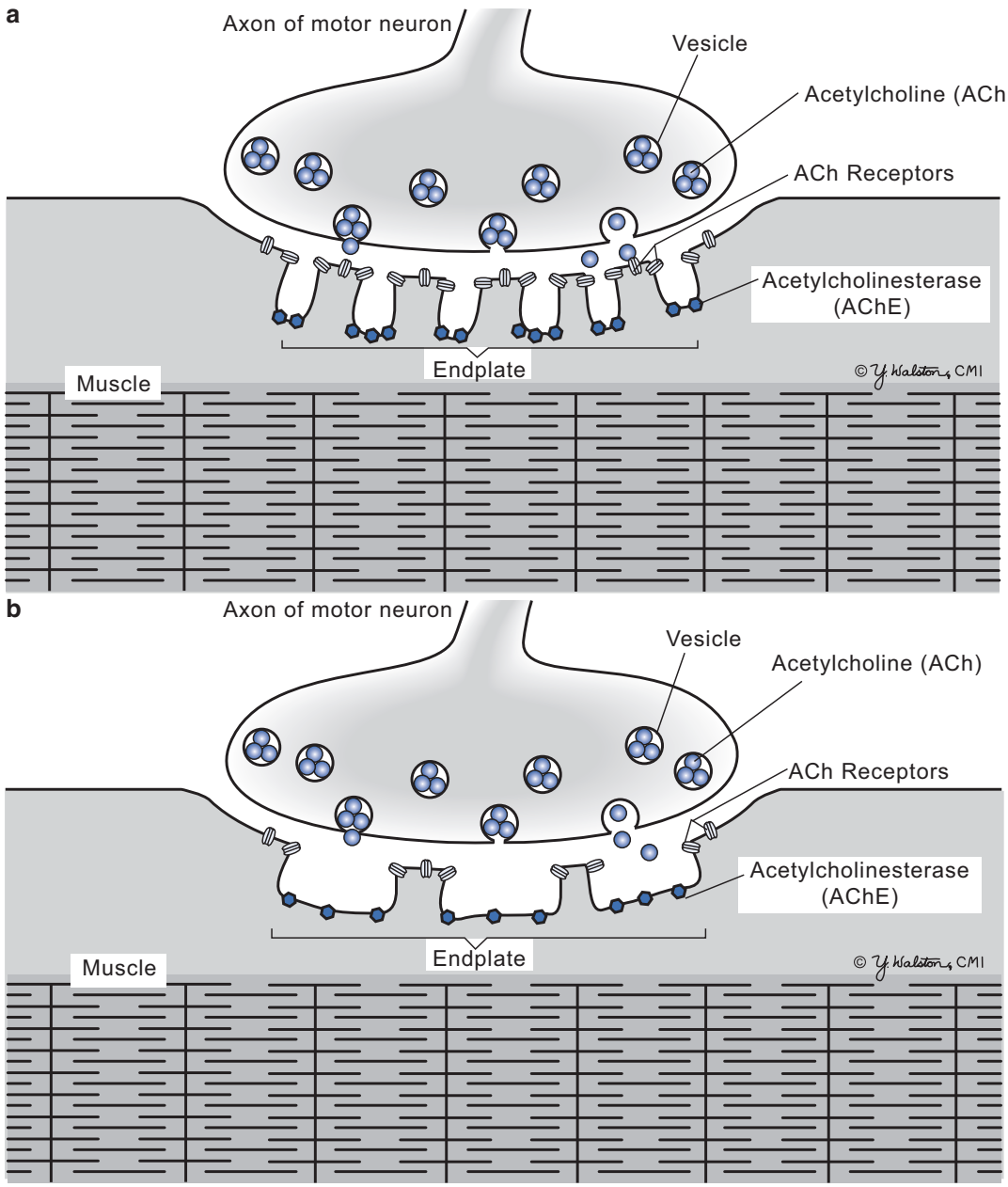

Fig. 5.2 Neuromuscular junction. **a** Normal. **b** Myasthenia gravis with simplified post-synaptic membrane

Maximal weakness appears within the first 3 years of clinical onset. About 10% of patients experience a spontaneous remission that occurs within the first 2 years. However, the rest of patients have a lifelong chronic illness that fluctuates in severity.

Major Laboratory Findings

Serum antibodies directed against the AchR are found in over 85% of patients with generalized MG. MuSK antibodies may be detected in patients with "seronegative" MG. The level of antibody titer does not always reflect disease severity

Table 5.1 Cardinal features of myasthenia gravis

Weakness	Bulbar muscles: ptosis, diplopia, dysarthia, dysphagia, chewing difficulty Limb muscles: proximal > distal
Fatigability of skeletal muscles	Increased weakness in afternoon or after exercise
Normal	Mentation Sensation Deep tendon reflexes

as the test detects all AchR antibodies including those that do not interfere with the functioning of the channel. However, for a given patient, a falling titer does reflect clinical improvement.

X-ray or CT of chest may demonstrate a thymoma. Elevated thyroxin blood levels indicating thyrotoxicosis are found in up to 5%.

Repetitive nerve stimulation (at rate of 3 per second) of proximal muscles (often the trapezius muscle) usually demonstrates a decremental fall of greater than 15% in the compound muscle action potential (see chapter 3 on common neurologic tests).

Tensilon test: This office test is helpful to establish the diagnosis of MG when there are clear ocular signs—although is performed rarely. Edrophonium (Tensilon) is a brief-acting anticholinergic drug that is slowly given intravenously to a patient. For the next 5–10 min, an untreated MG patient should have a clear objective improvement in ptosis. Often a saline injection precedes the administration of edrophonium to evaluate for a placebo effect.

More commonly, application of crushed ice in a latex glove to a patient's eye and looking for improvement in ptosis can be performed in the office. This test has a sensitivity of 90% in distinguishing ptosis due to MG from other causes.

Principles of Management and Prognosis

The goal of treatment is to improve strength and to reduce or eliminate circulating antibodies against the AchR. Symptomatic treatment aimed at improving strength is accomplished with anticholinesterase drugs. These drugs do not reduce circulating antibody titers but are the first line to improve the patient's strength. Pyridostigmine (Mestinon) is the main oral drug that is given to the patient several times a day. Anticholinergic medications act by interfering with acetylcholine esterase, the enzyme that cleaves acetylcholine in the synaptic cleft. Partial inhibition of this enzyme results in a longer time period that acetylcholine molecules can remain in the synaptic cleft to find unblocked AchR and increase the probability that sufficient AchR channels will open to fully depolarize and contract the muscle fiber. Too much pyridostigmine, however, can block all the acetylcholine esterase such that acetylcholine cannot be cleaved and removed once it attaches to an AchR. The inability to remove acetylcholine from the receptor causes a depolarizing muscle weakness that is called a "cholinergic crisis". In addition to weakness, a cholinergic crisis is characterized by hyperhidrosis, salivation, and lacrimation.

A number of treatments are aimed at reducing the amount of circulation antibody. Thymectomy, the surgical removal of the thymus gland, in a moderately severe patient often results in clinical improvement and a fall in antibody titer. Corticosteroids and other immunosuppressive drugs (azathioprine and cyclosporine) are commonly given to lower the antibody titer and improve strength. Recently, mycophenolate mofetil has been widely adopted in the treatment of MG due to its minimal side effect profile, but efficacy is somewhat controversial at this point. Intravenous immune globulin (IVIg) and plasma exchange by plasmaphoresis will temporarily reduce circulating antibody and improve strength for several weeks. These temporary methods can be used for patients requiring prompt clinical improvement such as for elective surgery, pneumonia, or a "myasthenic crisis".

Patients with MG should avoid drugs that affect the neuromuscular junction such as aminoglycoside antibiotics, chloroquine, and anesthetic neuromuscular blocking drugs (pancuronium and d-tubocurarine).

Using various combinations of pyridostigmine and immunosuppressants to lower circulating antibody levels, most patients lead fairly normal lives. Mortality due to respiratory causes is uncommon now (<5%) compared to >30% in the 1950s.

Lambert–Eaton Myasthenic Syndrome

An important synaptopathy that can mimic symptoms of MG is Lambert–Eaton myasthenic syndrome (LEMS). Although much less common than MG, it is important to diagnosis due to its association with malignancy. LEMS typically presents in mid-to-late life with proximal muscle weakness and variable autonomic failure (e.g. areflexia and dry mouth). Some patients may have associated cerebellar symptoms due to paraneoplastic cerebellar degeneration. The most common cancer associated with LEMS is small-cell lung cancer. As in MG, LEMS is mediated by autoantibodies, but in this case, they are directed at the presynaptic calcium channels rather than the AchR.

Diagnosis is made through detection of the antibodies and through repetitive nerve stimulation, which, in contrast, shows that compound muscle action potential amplitude increases in response to the nerve stimulation. After diagnosis is confirmed, a search for malignancy should be undertaken.

Prognosis in LEMS depends on whether it is associated with cancer or not. Typically, the weakness in LEMS does not affect the respiratory muscles as much as in myasthenia gravis, but the weakness can still affect the quality of life to a great extent. If the LEMS is associated with cancer, chemotherapy and treatment of the cancer are the first-line treatment. This may be sufficient in some patients. If LEMS is not associated with cancer or does not respond to chemotherapy, immunosuppressive treatments can be offered to suppress the autoimmune-generated antibody production and improve symptoms.

Botulism

Overview

Toxins have long been recognized to affect the neuromuscular junction, resulting in paralysis or muscle spasms. Drugs such as curare are known to block the post-synaptic excitatory acetylcholine receptors in the peripheral nervous system to produce paralysis. Hyperexcitable states result from intoxication with tetanus toxin or lysergic acid diethylamide (LSD). Tetanus toxin produced from *Clostridium tetani* blocks the inhibitory glycine receptor between the spinal cord Renshaw cell and the anterior horn cell. Lack of inhibition on anterior horn neurons causes them to repeatedly fire upon minor excitation producing profound muscle spasms. LSD appears to cause profound hallucinations by interfering with CNS serotonin synaptic receptors.

Botulinum toxin is the most potent biologic toxin known. The 50% lethal dose (LD_{50}) for humans has been calculated to be 0.1 μg for intravenous or intramuscular inoculation (wound botulism), and 70 μg for oral exposure (foodborne botulism). Botulism is a descending, symmetric, flaccid paralysis due to interrupted transmission of peripheral motor and cholinergic autonomic nerves at their synapses. Human disease mainly occurs from consumption of pre-formed botulinum toxin (foodborne botulism) and growth of *Clostridium botulinum* in the gastrointestinal tract of infants with subsequent absorption of the toxin (infant botulism). However, cases of wound botulism are increasing primarily in heroin addicts who subcutaneously (“skin popping”) inoculate *C. botulinum* spore-contaminated heroin (Fig. 5.3).

The incidence of botulism varies by type. Over 1000 cases of foodborne botulism are reported annually around the world and about 28 cases annually in the United States. About 40 cases/year of wound botulism are mainly from western states, primarily California, as a consequence of use of Mexican black tar heroin that is contaminated with *C. botulinum* spores. Nearly 70 cases/year of infant botulism occur in the United States.

Pathophysiology

The bacterium, *C. botulinum*, is a spore-forming anaerobic gram-positive bacillus that is commonly found in soil and water sediment around the world. *C. botulinum* produces 7 types of neurotoxins, with humans being intoxicated mainly by types A, B, or E.

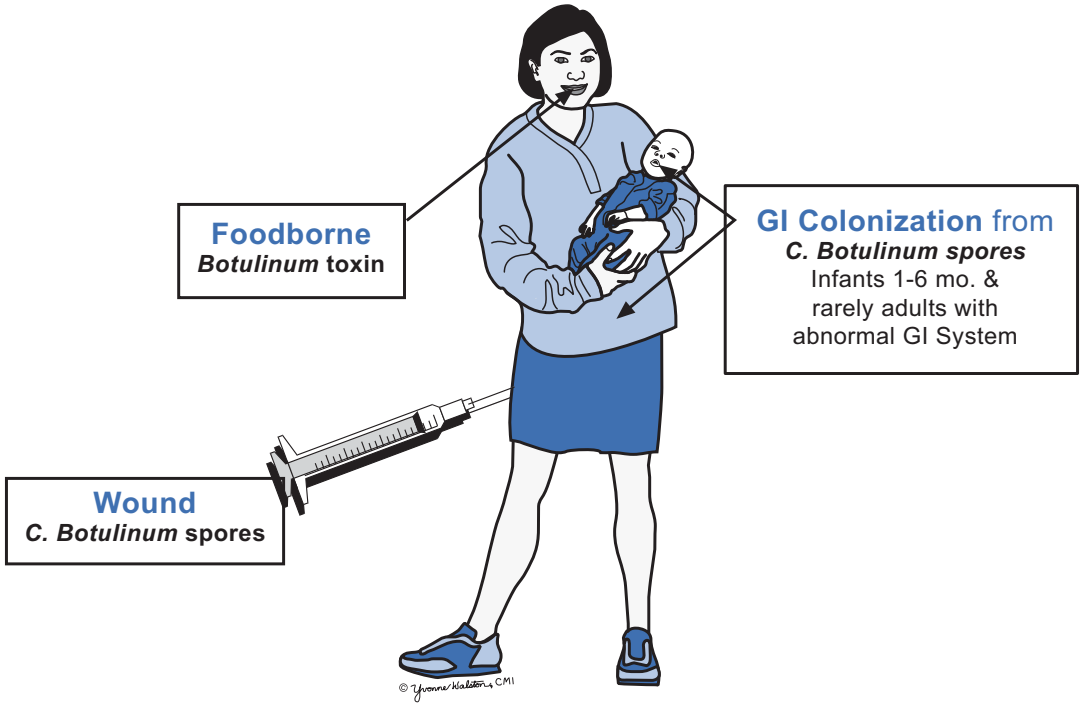

Fig. 5.3 Types of botulism

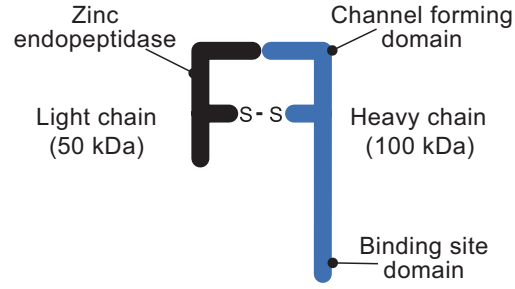

Fig. 5.4 Botulinum toxin

Botulinum toxin is an odorless and tasteless 150-kDa molecule that is comprised of a heavy chain (100 kDa) and a light chain (50 kDa) held together by a disulfide bond (Fig. 5.4). In foodborne botulism, the toxin is protected from stomach acid by other proteins released by *C. botulinum* that loosely attach to the toxin. In the upper intestine, the toxin is actively transported through intestinal lining cells by receptor-mediated transcytosis (crossing the cells as an intact molecule via a vesicle). Upon reaching the blood stream, toxin circulates until it reaches a peripheral acetylcholine synapse. The toxin does not cross the blood–brain barrier so does not affect brain cholinergic synapses. The heavy chain possesses a highly specific domain that attaches to the presynaptic side of the synapse (Fig. 5.5). The toxin is then internalized into the cytoplasm via an endocytotic vesicle. As the pH within the vesicle lowers, the toxin reconfigures and the heavy chain penetrates the vesicle wall allowing the light chain to pass through the vesicle wall and become free into the cytoplasm. The light chain, a zinc-containing endopeptidase enzyme, subsequently cleaves docking proteins called SNARE proteins. SNARE proteins enable vesicles containing quantal amounts of acetylcholine to fuse with the presynaptic membrane to release acetylcholine into the synaptic cleft. Thus, botulinum toxins block stimulus-induced and spontaneous quantal acetylcholine release on the presynaptic side of the cholinergic synapse. As a consequence of the light chain cleaving SNARE proteins, the muscle fails to contract and the cholinergic parasympathetic nerve fails to function. The resulting

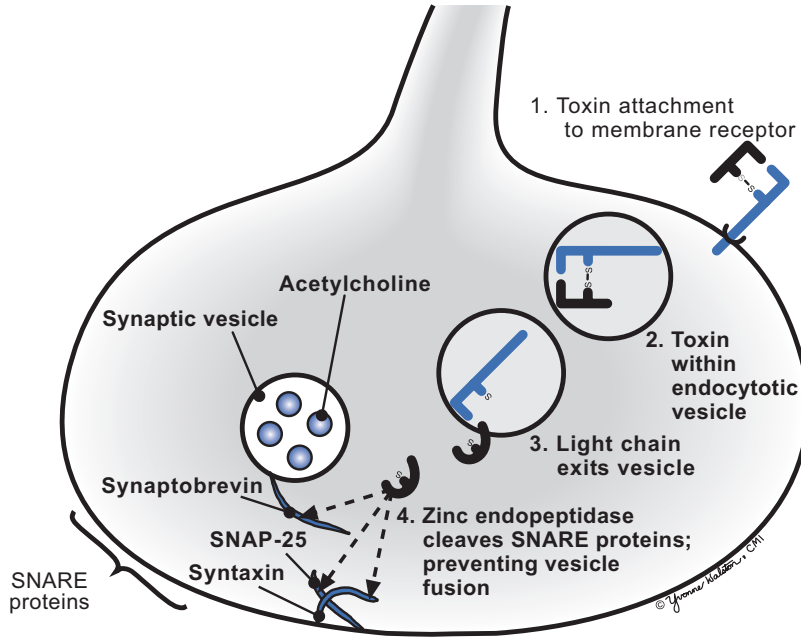

Fig. 5.5 Action of botulinum toxin at the synapse

synaptic failure continues for weeks to 6 months in part due to an abnormally slow catabolism of the light chain botulinium enzyme. The high potency of botulinum toxin results from its high specificity to attach only to a few membrane sites and that the toxin is an enzyme that cleaves critical proteins needed for synaptic function.

Clinical recovery occurs over 2–3 months and is due to terminal sprouting where the incoming axon at the paralyzed neuromuscular junction sends a new branch to the same muscle fiber forming a new synapse or by the neuronal cell body producing new SNARE proteins and sending them by axoplasmic flow to the distal terminal.

The pathophysiology of infant botulism is unique in that the disease results from the growth of *C. botulinum* in the gut with production of toxin rather than consumption of the pre-formed toxin. Infant botulism occurs only in children during the first 12 months of life with a peak at 2–3 months. After that age, the normal GI tract will not allow colonization of *C. botulinum*. The infant consumes *C. botulinum* spores by eating dust, honey, or other food substances that contain spores. In the immature gut, the spores germinate, colonize, and produce botulinum toxin that is slowly absorbed.

Major Clinical Features

Foodborne botulism: After ingestion, the mean incubation period is 2 days, with a range from 0.5 to 6 days. The longer the incubation period, the milder are the symptoms. Botulism classically presents with symmetric, descending flaccid paralysis with prominent bulbar palsies in an afebrile patient with a normal sensorium. Prominent bulbar palsies include diplopia, external ophthalmoplegia, dysarthria, dysphonia, dysphagia, and facial weakness. Blurry vision from paresis of accommodation and diplopia from sixth cranial nerve palsy are early signs. Limbs become weak over 1–3 days and may become completely paralyzed. Deep tendon reflexes become depressed or absent. Weakness of respiratory muscles develops and may be severe enough to require

intubation and mechanical ventilation. Smooth muscle paralysis typically involves constipation, paralytic ileus, and urinary retention. In *wound botulism*, the clinical picture is similar.

Infant botulism: Infants develop an illness that progresses over hours to 20 days (mean 4 days) that is characterized by constipation (no defecation for 3 or more days), lethargy, hypotonia (floppy infant), poor cry, poor feeding, and loss of head control.

Major Laboratory Findings

The CSF and blood typically are normal. The clinical diagnosis is made on a characteristic clinical picture and abnormal nerve studies. Nerve conduction studies show widespread low-amplitude compound muscle action potentials with normal distal latencies, conduction velocities, and sensory nerve action potentials. If the nerve receives 10 s of fast repetitive electrical stimulation (30–50 Hz), there is an increment in the compound muscle action potential amplitude secondary to increased release of acetylcholine quanta.

The definitive diagnosis is the demonstration of botulinum toxin in serum, stool, or suspected food or isolation of *C. botulinum* from a wound site. The most sensitive diagnostic test for the presence of botulinum toxin is a biologic test involving mice. In this test, mice are intraparenterally inoculated with the suspected toxin plus or minus the specific antitoxin. If the toxin-injected mice become paralyzed but not when the antitoxin is also administered, the diagnosis is established. These tests are positive in about three-fourths of clinically diagnosed cases.

Principles of Management and Prognosis

Treatment should begin promptly after there is a suspicion of botulism or a clinical diagnosis is made. Aims of treatment are to: (1) support respiration, (2) prevent progression of the paralysis by use of antitoxin, and (3) prevent pulmonary or other complications until spontaneous recovery occurs.

Weakness and respiratory failure may rapidly progress within hours. Patients should be hospitalized in an intensive care unit with careful monitoring of respiratory function. Intubation and mechanical ventilation are required in over half of the patients. Use of a ventilator averages about 2 weeks but can be as long as 2 months.

State health officials should be immediately notified to bring antisera and to help should there be additional cases as seen in a common source outbreak of foodborne botulism. For botulism in adults, administration of equine trivalent (type A, B, and E) botulism antitoxin should be as soon as possible without waiting for laboratory confirmation. The antitoxin eliminates circulating toxin but does not remove toxin that has already entered the neuromuscular junction. Therefore, the antitoxin will not reverse paralysis that has occurred but will prevent progression of the weakness and may shorten hospitalization. A single 10-mL vial sufficiently neutralizes circulating toxin found in all forms of botulism. Because the antitoxin is produced in horses, there is a 3 % incidence of allergic reactions, including anaphylaxis. In infant botulism, human botulinum antitoxin is available called human botulinum immune globulin-IV (BIG) that has similar effects but eliminates the administration of a foreign protein. Use of BIG has been shown to shorten the time on a ventilator and hospitalization.

Excellent nursing care will minimize complications. Yet despite everything, the mortality rate is from 5 to 15 %. Patients who survive will regain normal muscle strength but often complain of fatigue for years.

Clinical Uses of Botulinum Toxin

Although clearly a deadly, potent neurotoxin, botulinum toxin has been harnessed for therapeutic use through intramuscular injection. FDA-approved indications for medically necessary in-

jections include strabismus, blepharospasm, 7th cranial nerve disorders, cervical dystonia, spasticity in flexor arm muscles, and migraine. There is increased use for urogenital and gastrointestinal indications. In addition to these medical indications, botulinum toxin for cosmetic reasons is commonly administered.

Video Legend

This video shows a 67 year-old man with Myasthenia Gravis.

Segment 1: Symptom Description

- Patient describes his ocular myasthenia symptoms: diplopia, ptosis and fatigue.

Segment 2: Cranial Nerve Exam

- Diplopia at both extremes of gaze
- Binocular diplopia—the diplopia resolves with covering one eye
- Patient does not have full excursion with lateral gaze
- Ptosis
- Divergent gaze due to NMJ weakness
- Normal jaw and neck strength

Recommended Reading

Spillane J, Beeson DJ, Kullmann DM. Myasthenia and related disorders of the neuromuscular junction. J Neurol Neurosurg Psychiatry. 2010;81:850–7. (Good overview of NMJ disorders)

Sobel J. Botulism. Clin Infect Dis. 2005;41:1167–73. (Good overview of botulism)

Titulaer MG, Lang B, Verschuuren J. Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. Lancet Neurol. 2011;10:1098–107. (Nice review of Lambert-Eaton syndrome)

Disorders of Peripheral Nerves

6

A 30-year-old woman, pregnant with her first child, noted intermittent wrist pain predominantly at night, for which she shakes her hands to relieve. Over time, she has wrist pain most of the time and it has moved into the palm of the hand. Several weeks ago, she noticed numbness and tingling in her fingertips—especially her thumb and index finger. In her job as an academic neurologist, she types notes and papers and these symptoms are becoming more intrusive. She makes an appointment with one of her colleagues who performs a physical exam and nerve conduction studies. She is diagnosed with carpal tunnel syndrome (as she suspected) and begins conservative treatment with good response.

Overview

The peripheral nervous system (PNS) involves all nerves lying outside the spinal cord and brainstem except the olfactory and optic nerves that are extensions of the central nervous system itself. All peripheral nerve axons are invested either with a wrapping of myelin made by Schwann cells (myelinated nerve) or by cytoplasm of Schwann cells (unmyelinated nerve). This chapter will focus on motor and sensory nerves and excludes the sympathetic and parasympathetic nerves.

The entire peripheral nerve divides into three compartments. Between each spinal cord level and the corresponding dorsal root ganglion (DRG), motor and sensory fibers separate into dorsal or ventral roots. Distal to the dorsal root ganglion, sensory and motor fibers combine. Those nerves innervating limbs travel to the brachial or lumbar plexus. In the plexus, sensory and motor nerve axons separate and recombine to form named peripheral nerves. Peripheral nerves carry motor, sensory, or autonomic fibers, often in a mixture with a 2:3 ratio of myelinated to unmyelinated fibers.

Although a few peripheral nerves contain only sensory fibers (e.g. sural nerve) or motor fibers (vagus nerve to diaphragm), most peripheral nerves have their own territory of skin and specific muscles. Each spinal cord root innervates a defined area of skin sensation (dermatome) (see Chap. 2, Fig. 2.4a and b, neurologic exam) and a defined group of muscles (myotome) that is different from the innervation of a specific nerve. Knowledge of the anatomical distribution of peripheral nerves helps determine the location of a lesion (root, plexus, or peripheral nerve).

Electronic supplementary material The online version of this chapter (doi: 10.1007/978-1-4939-2359-5_6) contains videos as supplementary material and can be accessed at http://link.springer.com/book/10.1007/978-1-4939-2359-5.

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Peripheral nerve diseases are traditionally classified in different ways: (A) motor, sensory, or mixed nerve diseases; (B) polyneuropathy where multiple nerves are involved in a typically distal pattern; (C) mononeuropathy with single nerve involvement; and (D) demyelinating vs. axonal diseases. Demyelinating peripheral nerve disease is also discussed in Chap. 10 on disorders of myelin.

Pathophysiology

Peripheral nerve damage occurs by six basic mechanisms: (1) axon transection, (2) axon compression [compression neuropathy], (3) neuron death, (4) metabolically sick neurons unable to support the distal axon [dying-back neuropathy], (5) demyelination, and (6) synapse dysfunction.

Following transection or severe compression, the axon distal to the injury degenerates (Wallerian degeneration) over a period of a few weeks. However, the axon segment proximal to the lesion does not. The sensory territory of the nerve is lost resulting in anesthesia, and the muscles innervated by the peripheral nerve become weak or paralyzed.

A motor unit, defined as the lower motor neuron and all of its muscle fibers, may contain 10–1000 muscle fibers. Each muscle fiber only receives innervation from one motor neuron. Following loss of motor neurons, muscle fibers become paralyzed. After about 10 days, the muscle fiber undergoes biochemical changes as the neuromuscular junction degenerates. The muscle then produces acetylcholine receptors diffusely instead of only at the synapse. These new acetylcholine receptors make the muscle supersensitive, and spontaneous depolarization can be detected when an electromyographic needle electrode passes into the involved fiber (fibrillations and positive sharp waves). The muscle fiber undergoes atrophy and may involute to one-fourth the original size but does not die.

If the neuron becomes metabolically sick, the nerve can no longer maintain the most distal part of its axon. The distal motor and sensory axons slowly degenerate ("dying-back" neuropathy). The longer the axon length, the more susceptible the nerve to metabolic damage. As a consequence, symptoms (often sensory loss) develop first in the toes (the longest axon).

Peripheral nerve myelin damage can occur due to death of the attached Schwann cell, from immune attack or from degenerative processes of the myelin sheath. The loss of myelin, usually in segments (segmental demyelination), interrupts transmission of sensory or motor signals, producing symptoms of weakness or numbness. The cause of the myelin damage may be genetic (hereditary sensorimotor neuropathy like Charcot–Marie–Tooth disease), autoimmune (Guillain–Barre syndrome), toxic (lead), or infectious (leprosy). Unlike the central nervous system, the peripheral nervous system can recover to some extent following damage. Mechanisms of recovery include the following: (1) spontaneous recovery of the axon; (2) regeneration of the distal part of nerve axons; (3) axonal sprouting of intact adjacent axons; and (4) remyelination. If the entrapment or crush injury is not severe and the cause corrected, the existing axons recover over minutes to weeks. Following nerve transection or severe crush injury, the proximal axons grow outward, provided the nerve sheath remains intact, at about 1 mm/day, so months are required before return of strength or sensation occurs. Following death of the motor neuron, the now "orphaned" muscle fibers generate an unknown trophic factor that triggers adjacent motor axons to undergo segmental demyelination. This segment sprouts a branch axon that reinnervates the muscle fiber, making it part of a new motor unit.

Clinical Features that Suggest Peripheral Nerve Diseases

Specific Peripheral Nerve Damage

- Both sensory loss and muscle weakness are present.
- Sensory loss and muscle weakness occur in the territory of the peripheral nerve.
- Involved muscles atrophy after a month down to one-fourth their former size.

- Sensory changes cause loss of pain, touch, temperature, vibration, and position sense if the lesion is destructive or produce pain or paresthesias if the lesion is irritative.
- Diminished or loss of tendon reflex corresponding to the involved nerve occurs.
- Secondary trophic skin changes may slowly develop from lack of autonomic nerve innervation.
- Onset may be acute or gradual depending on etiology.
- Involvement is unilateral and seldom bilaterally symmetrical, although multiple nerves may be involved (mononeuritis multiplex).

Distal Symmetrical Polyneuropathy or "Dying-back" Neuropathy

- Maximum loss of sensation should be in toes and feet.
- Sensory and motor loss should be symmetrical.
- Onset is gradual and not acute.
- Loss of sensation is usually greater than loss of strength.
- Painful dysesthesias may occur mainly in the feet.
- Fingers lose sensation when the leg neuropathy advances to about the knee.
- Muscle loss in the feet usually begins as "hammer toes" or pulling back of toes dorsally due to weakness of flexor intrinsic foot muscles without corresponding weakness of extensor muscles located in the leg ("Charcot foot").
- Trophic changes in the foot and nails are common from loss of autonomic nerves.

Demyelination of Peripheral Nerves

- Major finding is weakness with minimal loss of myelinated sensory fibers for vibration and position sense.
- Weakness is usually bilateral and symmetrical.
- Pain, touch, and temperature sensations are preserved.
- Onset may be abrupt (Guillain–Barre syndrome), subacute (lead), or gradual (hereditary sensorimotor neuropathy).

Diabetic Distal Symmetrical Polyneuropathy

Introduction

Peripheral neuropathy is common with a prevalence of about 2–17%—with the higher number reflecting the prevalence in patients with disease or toxic exposure known to be associated with polyneuropathy. The myriad causes include metabolic disturbances (diabetes mellitus, uremia), toxins (alcohol, cisplatin, arsenic), vitamin deficiencies (B12, B2), genetic (hereditary sensorimotor neuropathy, porphyria), immune-mediated (Guillain–Barre syndrome, chronic inflammatory demyelinating polyneuropathy), vasculitis (rheumatoid arthritis, Sjogren's syndrome, polyarteritis nodosa), and neoplastic (lymphoma, multiple myeloma, paraneoplastic neuropathy). Diabetic neuropathy accounts for over half of all causes of polyneuropathy.

Diabetes mellitus affects more than 236 million people worldwide. Diabetic neuropathy, present in about 10% of patients at the time of diagnosis, rises to over 50% when the diabetes has been present for years. While diabetes causes several types of peripheral nerve diseases, distal peripheral polyneuropathy accounts for over 90% of cases. Not only can the diabetic neuropathy cause pain and disability, but it is also associated with increased cardiovascular disease and mortality. Even one of the bedside tests sensitive for the presence of diabetic neuropathy—diminished vibration threshold—has been shown to be a risk factor for mortality in diabetic patients.

Pathophysiology

Pathologically, there are abnormalities found in both the axonal and myelin components of the nerve fiber. Axonal degeneration of nerve fibers is seen—with axonal loss seen distally. There is demyelination from Schwann cell dysfunction, proliferation of Schwann cells, remyelination, and onion-bulb formation. These changes are present predominantly in the small myelinated

and unmyelinated sensory nerves—corresponding to the clinical symptoms of anesthesia and painful sensations. In addition to the nerve fiber changes, there are vascular abnormalities in the endoneurial capillaries. There is marked thinning of the basal lamina—a hallmark of a diabetic microangiopathy.

The pathogenesis of diabetic neuropathy while multifactorial, likely stems from persistent hyperglycemia. Patients with impaired glucose tolerance who do not yet meet criteria for diagnosis with diabetes also show neuropathy (although milder than the diabetic patient) with prominent small nerve fiber involvement. At the nerve cell body (in the dorsal root ganglion), there is cellular injury leading to impaired protein and lipid syntheses and impaired axonal transport. At the distal end of the nerve, due to the impaired transport, there is nerve degeneration. The degeneration is exacerbated by the loss of skin trophic support. The nerve initially (over a period of many years) becomes dysfunctional in a distal to proximal fashion, but in severe cases there is total nerve loss. Other proposed pathogenic mechanisms include the following: (1) hyperglycemia-induced increases in polyol pathway activity with accumulation of sorbitol and fructose in nerves and secondary axonal damage; (2) microvascular disease of peripheral nerves leading to nerve ischemia and hypoxia; (3) advanced glycation end products can affect monocytes and endothelial cells to produce cytokines and adhesion molecules; (4) reduction in expression or binding of neurotrophic factors; and (5) vulnerability of mitochondria in dorsal root ganglion sensory neurons who, in the face of hyperglycemia, produce reactive oxygen species which can damage nerve fibers.

Major Clinical Features

The insidious syndrome initially affects the toes bilaterally and symmetrically. Here, the loss of small unmyelinated axons diminishes appreciation of pain and temperature. As axon loss progresses to involve the foot and then the lower leg, the numbness ascends with it. Because of the inability to appreciate pain, injuries of the foot and ankle can lead to secondary foot ulcers and traumatic arthritis of joints (Charcot joints). Often the patient remains unaware of the loss of sensation in the feet until secondary foot or ankle problems develop. When the neuropathy has marched to the knees, the patient usually notes loss of sensation in fingertips (Fig. 6.1). Over time, the anterior aspect of the trunk can be affected. In rare cases, the neuropathy can even involve the top of the head—where the longest fibers of the trigeminal nerve terminate.

In many patients with diabetic polyneuropathy, damage to small axons leads to persistent foot pain (see chapter 20 on pain). The pain, typically described as burning, constant, prickling, and painful to light touch (allodynia), may be so uncomfortable that the patient seeks medical attention. This pain may be more severe at night and cause disruptions in sleep.

Large, sensory, myelinated axon damage with subsequent loss of vibration and position sense in toes and feet produces gait and balance problems. Motor nerve axons may be involved with weakness of intrinsic foot muscles.

Autonomic nerve axons are also impaired, leading to loss of sweating, thinning of involved skin, asymmetrical pupils that poorly accommodate to darkness, erectile dysfunction, loss of ejaculation, constipation and/or diarrhea, and orthostatic hypotension. Other common manifestations of the autonomic neuropathy in diabetes are resting tachycardia and gastroparesis.

Major Laboratory Findings

Since the neuropathy begins distally in the feet and involves unmyelinated axons, nerve conduction studies of sensory and motor nerves of the leg may initially show mild changes as electrophysiological studies seldom detect abnormalities in unmyelinated axons. With more symptoms developing, nerve conduction velocities slow due to demyelination and loss of myelinated fibers. As the neuropathy progresses, the findings of axonal degeneration predominate with diminished amplitude of compound muscle action po-

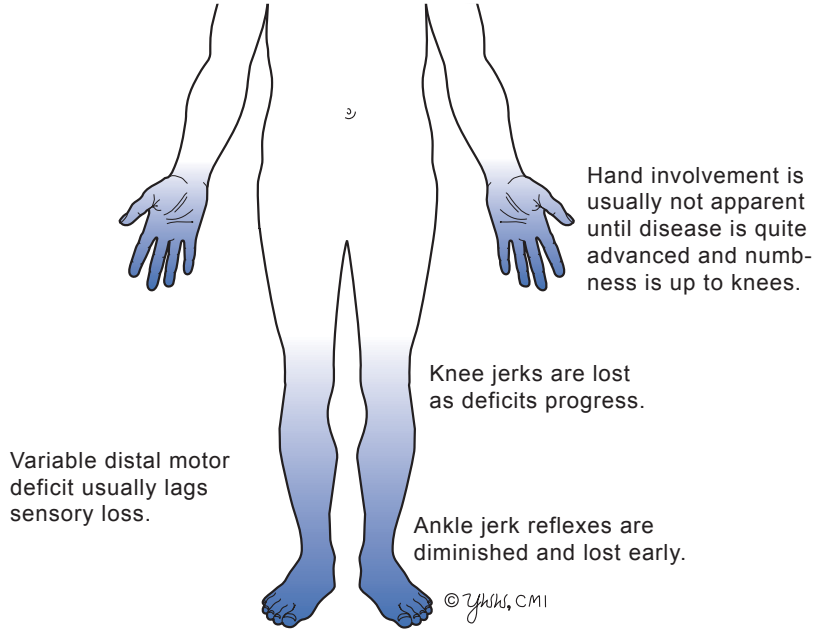


Fig. 6.1 Peripheral polyneuropathy distribution

tentials and sensory nerve action potentials—due to nerve fiber loss. Needle electromyography of intrinsic foot muscles shows denervation potentials. There is relative preservation of proximal conduction velocities.

A nerve biopsy, while seldom performed, shows non-specific axonal damage to both myelinated and unmyelinated axons. A nerve biopsy should come from a sensory nerve (like the sural nerve) that has a small area of sensory innervation. Biopsy of a mixed nerve will lead to paralysis of innervated muscles and thus is only performed on an intercostal nerve.

Skin punch biopsy (3–4 mm full thickness biopsy) with immunohistochemical staining for peripheral nerve axons is becoming more popular. The histologic sections demonstrate marked reduction in the density of epidermal nerve fibers that is helpful, but not diagnostic, for diabetic neuropathy. Thus, the diagnosis relies mainly on the clinical history, neurologic examination of the peripheral nervous system, and exclusion of other etiologies. However, when a peripheral nerve is affected by two different diseases, the signs and symptoms of a peripheral neuropathy develop earlier, produce more intense symptoms, and have a poorer recovery.

Principles of Management and Prognosis

The management of diabetic neuropathy can be divided into preventing progression of the neuropathy, minimizing problems from anesthesia of feet and hands, and reducing the burning foot pain.

Numerous studies demonstrate that good control of blood glucose can slow, halt, or reverse progression of the neuropathy. Glucose control involves weight loss, exercise, and use of hypoglycemic agents. While optimum glycemic control can reduce the risk of neuropathy, the risk of transient hypoglycemia increases.

Foot anesthesia predisposes to ulceration and infection. Proper footwear minimizes foot and ankle trauma. The individual should be instructed to regularly inspect their feet for signs of infection or ulceration and to place their hand in shoes to detect objects in the soles. If loss of position sense in the feet declines, the patient should use

night-lights and caution when walking on uneven surfaces or in the dark.

Treating the patient with a painful peripheral neuropathy is a challenge. For many patients, the pain is reduced with tricyclic antidepressants (amitriptyline and nortriptyline) in low doses. Tricyclic antidepressant medications occasionally can increase the effects of postural hypotension in patients with autonomic neuropathy. Anticonvulsants, such as gabapentin or carbamazepine, may be slowly added if the pain relief is insufficient. In some patients, the foot pain spontaneously subsides when the sensory neuropathy progresses to anesthesia.

Carpal Tunnel Syndrome

Introduction

Carpal tunnel syndrome (CTS) is an example of compression mononeuropathy. Up to 15% of individuals experience occasional symptoms suggestive of CTS. However, the prevalence of symptomatic carpal tunnel syndrome is estimated at up to 9.2% in women and 6% in men with the peak prevalence in older women. CTS can be seen in work-related musculoskeletal disorders caused by repetitive movements and strain. Fortunately, few individuals develop sufficient signs and symptoms to require surgical treatment.

Pathophysiology

The pathophysiology of CTS is not completely worked out but the final step is compression of the median nerve in the carpal canal under the transverse carpal ligament. Several mechanisms may be involved including lesions reducing the size of the carpal tunnel, processes causing swelling of the tendon sheaths such as overuse, and tissue swelling from fluid retention as in pregnancy or myxoedema. MRI findings include swelling of the median nerve just proximal to the carpal tunnel, flattening of the nerve within the carpal tunnel, bowing of the flexor retinaculum, and increased signal intensity of the median nerve. With the addition of gadolinium, the MRI often demonstrates intraneural edema in the median nerve.

About one-third of patients have associated conditions such as pregnancy, inflammatory arthritis, Colles' fracture, amyloidosis, hypothyroidism, diabetes mellitus, acromegaly, wrist infections, obesity, alcoholism, malnutrition, and use of corticosteroids or estrogens. The remaining two-thirds have their CTS associated with repetitive, often forceful, activities of the hand and wrist.

Major Clinical Features

The symptoms and signs of CTS correspond to the distribution of the distal median nerve (Fig. 6.2b). Patients usually complain of pain, tingling, burning, and numbness that involve the palmar aspect of the thumb, index finger, middle finger, and often the radial half of the ring finger. The fifth digit is only occasionally involved. The symptoms, often worse at night, may awaken the individual with hand discomfort extending into the lower arm that causes the individual to shake their hand ("flick sign"). Symptoms tend to be worse following a day of increased repetitive activity and often increase with driving.

Early, clinical exam shows normal sensation in the hand and no weakness or atrophy of median nerve-innervated muscles. As the disease advances, two-point discrimination in the median nerve distribution (finger tips) diminishes and atrophy occurs in the thenar muscles (opponens pollicis and abductor pollicis brevis).

Helpful, but not diagnostic, bedside tests include Phalen's and Tinel's signs. In Phalen's maneuver, the patient reports that flexion of the wrist for 60 s elicits pain or paresthesias in the median nerve distribution. Tinel's sign occurs when lightly tapping the volar surface of the wrist causes radiating paresthesias in the first four digits. For both tests, the sensitivity is about 50% but the specificity is slightly higher.

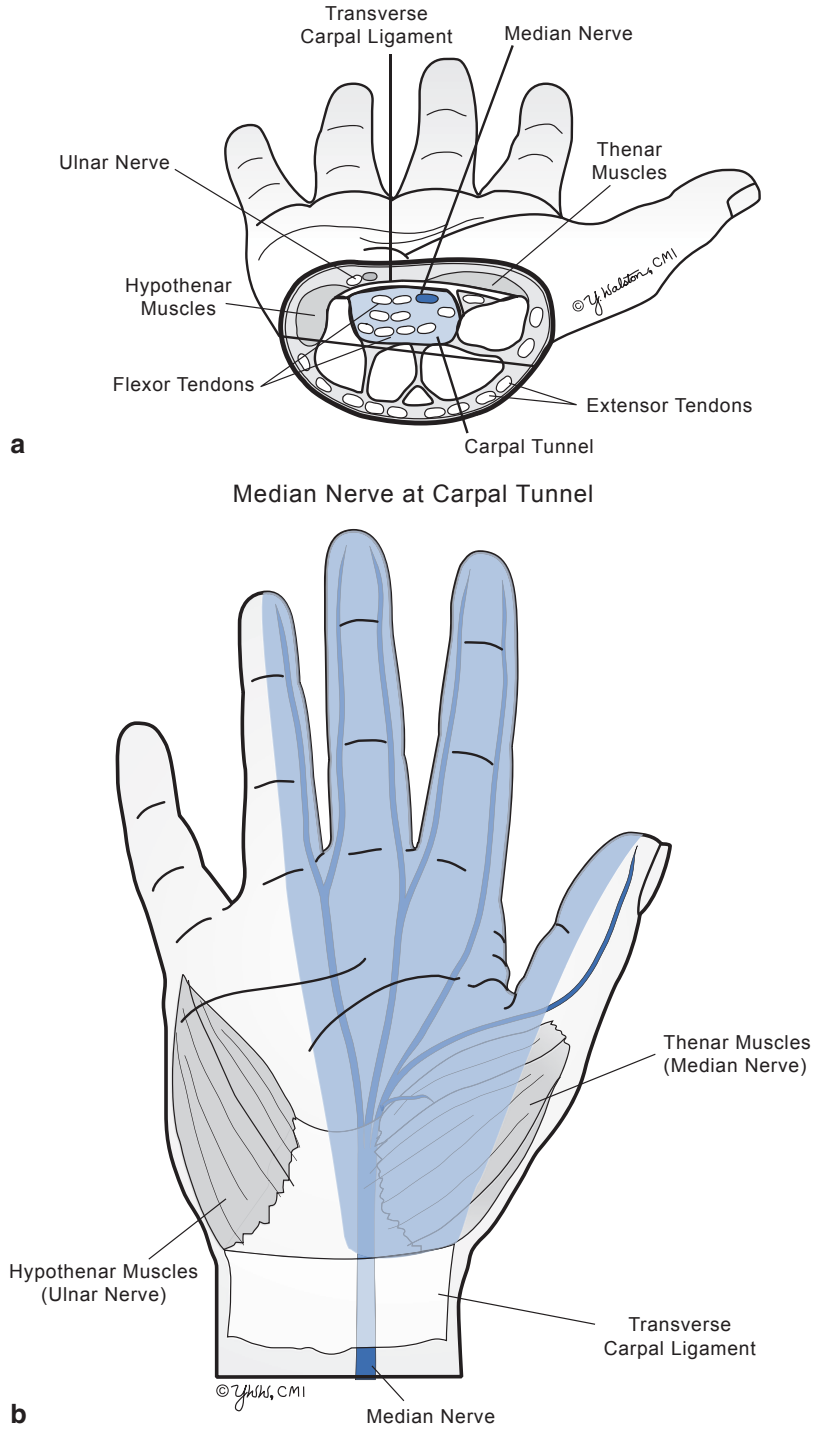


Fig. 6.2 Median nerve. **a** Carpal tunnel syndrome. **b** Sensory distribution

Major Laboratory Findings

Abnormal delay of median nerve sensory latency across the wrist is the major laboratory test that confirms the clinical diagnosis. If median nerve axonal loss occurs, the electromyogram of thenar muscles may show evidence of denervation.

Principles of Management and Prognosis

When CTS arises from other medical conditions, treatment of the underlying condition often improves the symptoms. Thus, administration of replacement thyroid hormone in the patient with hypothyroidism, use of anti-inflammatory drugs for wrist arthritis, and delivery of the pregnancy will improve symptoms. Similarly, reduction of the triggering repetitive wrist movement may improve symptoms.

Use of a wrist splint that holds the wrist in the neutral position helps symptoms in many patients. Wearing the splint at night may improve symptoms within a week. Oral and injected steroids can be transiently helpful. Local injections with lidocaine and long-acting corticosteroids into the carpal tunnel can give striking relief but symptoms return after weeks to months in 60 %. Injections can be repeated a total of 3–4 times. Ultrasound treatment of CTS is currently controversial. Surgery is usually recommended to patients developing objective sensory or motor axonal loss of the median nerve. The surgeon usually releases the transverse carpal ligament (roof of the carpal tunnel) (Fig. 6.2a, 6.2b) under direct visualization or through an endoscope. Over three-fourths of patients experience pain relief within days after surgery but full use of the hand may take several weeks.

Bell's Palsy

Introduction

Bell's palsy or idiopathic peripheral facial nerve palsy is the most common cause of cranial nerve 7 dysfunction. The facial nerve contains around 10,000 axons of which 70 % are motor nerves (special visceral efferent) that innervate muscles of the face. The remaining fibers include general visceral efferent nerves that are parasympathetic nerves to the lacrimal and submandibular glands; special visceral afferent nerves that carry taste from the anterior two-thirds of the ipsilateral tongue; and general somatic afferent nerves that transmit sensation from the skin of the ear pinna and external auditory canal. The facial nerve travels with the auditory nerve in the internal auditory canal and enters the facial canal where it soon reaches the geniculate ganglion containing the neuronal cell bodies for taste and ear sensation. The greater petrosal nerve, the first branch, travels to the lacrimal gland. The second branch runs to the stapedius muscle, and the third branch, chorda tympani nerve, travels to the tongue. The nerve exits the facial canal at the stylomastoid foramina where it passes through the parotid gland and spreads out to innervate 23 facial muscles (but not the masseter and lateral and medial pterygoid muscles which are innervated by the trigeminal nerve).

Numerous diseases cause facial palsy in adults, including trauma (facial trauma or basal skull fracture), infections (Lyme disease, otitis media, syphilis, meningitis, mumps), tumors (parotid tumors, sarcoma, facial nerve meningioma), and brainstem disorders (multiple sclerosis, strokes). However, almost 60 % of cases are considered idiopathic and due to Bell's palsy.

Bell's palsy occurs over 65,000 times a year with an equal racial and sex distribution. Cases occur in all ages but the incidence increases with age. It is rare for Bell's palsy to be bilateral or to recur.

Pathophysiology

The pathogenesis of Bell's palsy remains poorly understood. MRI and pathologic studies show the facial canal, especially in the tympanic and labyrinthine segments as the site of pathology. The nerve becomes edematous and may develop mild to moderate Wallerian degeneration with varying amounts of surrounding lymphocytic inflammation. The geniculate ganglion may appear

normal or have inflammation. Early theories suggested ischemia to the facial nerve lead to nerve edema and nerve compression from the walls of the facial canal. Later, the ischemia concept was dropped and the nerve edema was considered idiopathic. Recently, viral infection theories have focused on varicella-zoster and herpes simplex viruses as potential viruses that reactivate in the facial nerve or geniculate ganglion to cause nerve damage, edema, and inflammation. The data regarding herpes simplex virus-1 are intriguing but at this point mainly circumstantial.

While varying degrees of Wallerian degeneration develop, all axons are rarely destroyed. As such, spontaneous recovery usually occurs with 80% of patients completely recovering. Twenty percent of patients may experience complications such as paralysis, pain, and aberrant reinnervation—all which occasionally result in facial disfigurement and cause social anxiety and distress.

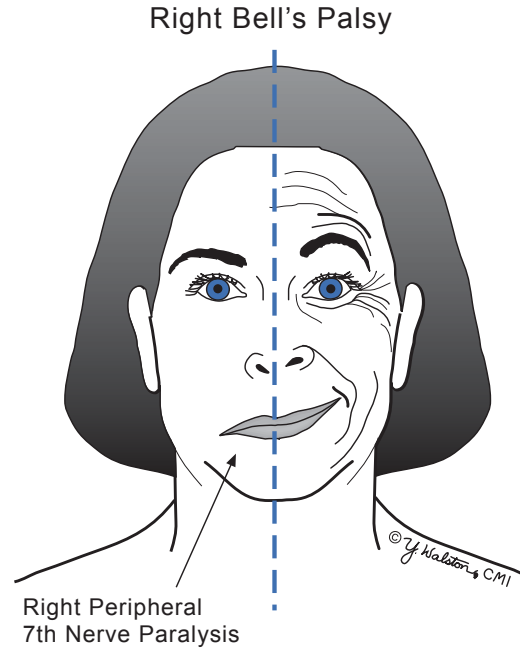


Fig. 6.3 Bell's palsy

Major Clinical Features

In about one-third of patients, a prodrome of dull ear pain is noted for 1–3 days that persists when the facial weakness develops. The pain is likely due to irritation of 7th nerve pain fibers going to the ear pinna, external ear canal, and occasionally middle ear mucosa. The onset of the unilateral facial weakness is abrupt but can worsen over the next 4 days (Fig. 6.3). The weakness is of the lower motor neuron type affecting equally the upper and lower face. Patients often cannot completely close their eyelid to cover the cornea. If there is diminished tearing, the sclera soon becomes inflamed and painful and the cornea may become dry. In the lower face, the patient often has difficulty fully closing his mouth and chewing is difficult because of biting the cheek mucosa on the weak side. Drooling often appears on the weak side. Because Bell's palsy involves the horizontal portion of the facial canal and geniculate ganglion, in 17% there is unilateral diminished tearing from dysfunction of the greater petrosal nerve. In 30%, the branch to the stapedius muscle is affected and unilateral hyperacusis (loud noises are uncomfortable) develops because of loss of the stapedius reflex (inability of the stapedius muscle to contract in response to loud noises to dampen the inner ear ossicles carrying sound vibration from the tympanic membrane to the oval window). In 50% of patients, there is diminished or absent taste to sweet, salt, or bitter substances placed on the anterior front side of the tongue from dysfunction of the chorda tympani nerve.

The presence of symptoms and signs from dysfunction of branches of the 7th cranial nerve in the facial canal is helpful in establishing that the origin of the 7th cranial nerve damage must be at least that proximal and thus excludes the cause of the facial paralysis being distal to the stylomastoid foramen.

In 10–15% of patients, vesicles appear on the skin of the ipsilateral ear pinna, external auditory canal, or skin below the pinna. Varicella-zoster virus can be isolated from the vesicles, which establishes the diagnosis of herpes-zoster oticus or Ramsay Hunt syndrome. In this case, the varicella-zoster virus became latent in the geniculate ganglion during childhood chicken pox and reactivated many years later.

Major Laboratory Findings

Remarkably few laboratory abnormalities exist in Bell's palsy. The patient has a normal hemogram, erythrocyte sedimentation rate, and serum electrolytes. The CSF is normal. If the CSF has a pleocytosis, the facial palsy etiology is likely due to an inflammatory or infectious process, such as varicella-zoster virus, Lyme disease, neurosyphilis, or sarcoidosis. Cranial MRI with gadolinium may show enhancement of the facial nerve within the facial canal. The EMG, normal for the first 3 days, shows a steady decline in activity and after 10 days, denervation potentials begin to appear. At autopsy of individuals without a history of Bell's palsy, herpes simplex, and varicella viral DNA can frequently be detected by polymerase chain reaction in the geniculate ganglia. This suggests that these viruses became latent in that ganglion but whether exacerbation of the latent herpes simplex virus produces Bell's palsy remains controversial.

Principles of Management and Prognosis

Management of the patient with Bell's palsy involves treating the acute facial palsy and preventing complications. If there is incomplete paralysis of facial muscles, there is an excellent prognosis for full to satisfactory recovery that spontaneously occurs within 2 months. With complete facial paralysis, full to satisfactory recovery spontaneously occurs in about 80% over 1–3 months. In an effort to improve outcome, patients are often given corticosteroids for several days with the hypothesis that the corticosteroids will lessen facial nerve edema, reduce nerve pressure, and prevent nerve ischemia. Currently, there does not seem to be benefit from antiviral medications in the treatment of idiopathic Bell's palsy. Observing vesicles on the ear pinna suggests a varicella-zoster viral infection, and another antiviral drug (famciclovir, penciclovir, or high-dose acyclovir) should be given to the patient.

Frequently, the patient will have facial weakness such that they cannot fully close the eyelid, exposing the cornea to abrasions and drying. After applying ointment, these patients should tape their eyelid closed while sleeping. Some patients have diminished tearing in the involved eye and require frequent application of liquid tears. A few patients will have aberrant regeneration of the facial nerve during recovery leading to synkineses (unintentional facial movements accompanying volitional facial movements) and/or crocodile tears (lacrimation when salivating).

Video Legend

This video shows a 48 year-old woman with Chronic Inflammatory Demyelinating Polyneuropathy.

Segment 1: Motor Exam
- Exam of muscle bulk in feet shows weakness in small muscles of foot resulting in high arch.
- Strength in lower extremities is 4/5 with weakness greater distally than proximally.

Segment 2: Reflex Exam
- 2+ reflexes (normal) in brachioradialis, biceps and patellar bilaterally
- Absent Achilles reflexes bilaterally

Segment 3: Gait Exam
- Ankle dorsiflexion weakness results in toe dragging.

Recommended Reading

Alfonso C, Jann S, Massa R, Torreggiani A. Diagnosis, treatment and follow-up of the carpal tunnel syndrome. Neurol Sci. 2010;31:243–52. (A synthesis of current knowledge in carpal tunnel syndrome).

British Medical Research Council. Aids to the examination of the peripheral nervous system. 5th edn. Philadelphia: Saunders; 2010. (Superb booklet that outlines how to test each muscle, describes areas of sensation for all peripheral nerves, and easily can be kept in doctor's bag).

Gilden DH. Bell's Palsy. N Engl J Med. 2004;351:1323–31. (Excellent review with good illustrations).

Said G. Diabetic neuropathy—a review. Nat Clin Pract Neurol. 2007;3(6):331–40. (Good review of the pathophysiology, clinical presentation and treatment of diabetic neuropathy).

Disorders of the Spinal Cord and Vertebral Bodies

7

A 45-year-old healthy woman executive who is an avid jogger first noted that her time to complete a 2-mile jogging course became progressively longer. Over the next 3 months, she became more fatigued after exercising and her endurance was less. By 6 months, she noted twitching in both leg muscles plus a few arm muscles even on days when she did not exercise. Her internist noted brisk deep tendon reflexes but her muscle strength and sensation appeared normal. Laboratory tests for anemia, electrolytes, and liver function were normal. No diagnosis was made. By 9 months, she knew her leg muscles were weak. She saw a neurologist who found mild atrophy and weakness in several leg muscles, spontaneous fasciculations in both arm and leg muscles, and mild atrophy and fasciculations of her tongue. Her deep tendon reflexes were brisk and she had bilateral Babinski signs. MRI of her spinal cord was normal but the electromyogram demonstrated fibrillations and positive sharp waves in many arm and leg muscles. A variety of blood tests were normal. A diagnosis of amyotrophic lateral sclerosis was made based on the multiple spinal cord levels of both upper and lower motor neuron disease plus involvement of bulbar muscles.

Overview

For many years, the spinal cord was conceived of as a conduit that carries impulses from the brain to the trunk and limbs and vice versa. We now know that spinal cord functions are not solely passive but rather modulate or generate many afferent and efferent pathways. For example, endorphin-containing neurons in the dorsal horn actively modulate afferent peripheral pain fiber impulses, resulting in diminishment or enhancement of perceived pain (see Chap. 20 on neuropathic pain). Important aspects of normal walking appear to be generated from clusters of motor neurons located in the lower thoracic and upper lumbar spinal cord. Rapid limb withdrawal from a painful stimulus and deep tendon reflexes do not involve the cortex but result from local circuitry in the cord.

The spinal cord, which is about the diameter of a thumb, extends caudally from the medulla to the first or second lumbar vertebrae in adults and slightly lower in infants (Fig. 7.1). From L2 to S2, the central vertebral canal is composed of nerve roots ending in the cauda equina. The absence of spinal cord below L2 is the reason why a lumbar puncture can be safely performed in the lower lumbar area.

Electronic supplementary material The online version of this chapter (doi: 10.1007/978-1-4939-2359-5_7) contains videos as supplementary material and can be accessed at http://link.springer.com/book/10.1007/978-1-4939-2359-5.

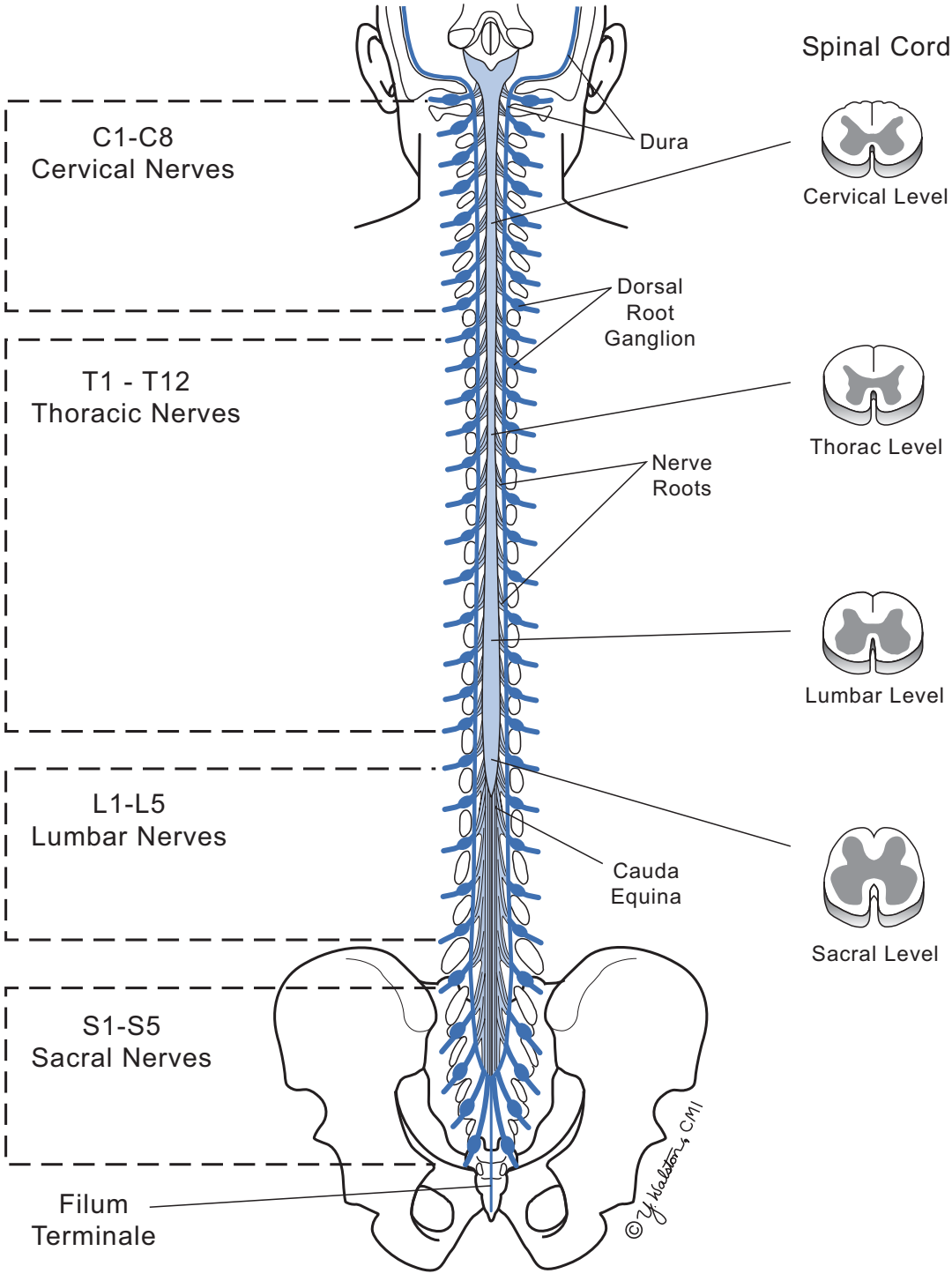


Fig. 7.1 Diagram of spinal cord and vertebral bodies

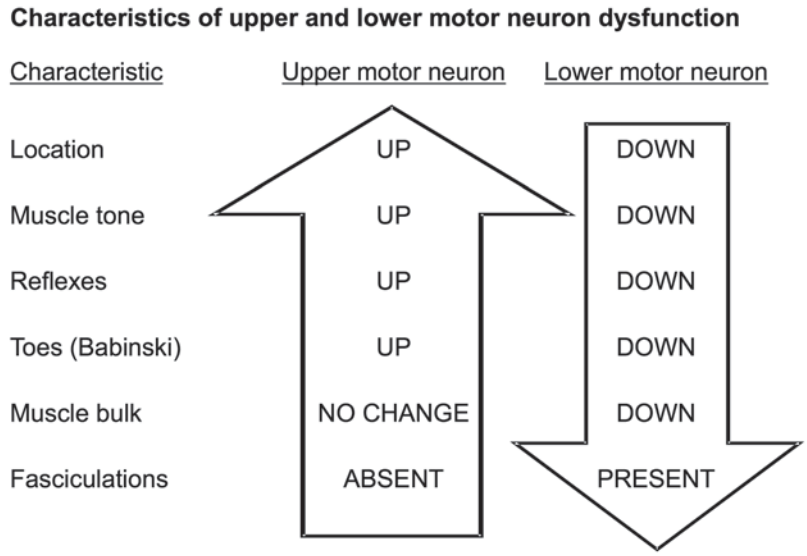


Fig. 7.2 Characteristics of upper and lower motor neuron disease

Spinal cord dysfunction results from traumatic, inflammatory, demyelinating, ischemic, nutritional, malignant, and degenerative conditions. Diseases affecting the spinal cord usually present as one of three clinical scenarios—two of which involve spinal cord parenchyma and one involves spinal cord roots. The first scenario is degenerative with loss of specific spinal cord elements as seen in amyotrophic lateral sclerosis (ALS) and subacute combined degeneration (vitamin B_{12} deficiency). The second is from a lesion at one level of the spinal cord as seen in back or neck trauma, cervical myelopathy from central protruding intervertebral disk or acute transverse myelitis. The final scenario is from compression of exiting spinal cord nerve roots producing a radiculopathy (sensory and motor dysfunction of a single dermatome/myotome) due to focal lesions such as posterolateral prolapse of a vertebral disk or a neurofibroma compressing a spinal cord root.

Clinical signs depend on the level of the spinal cord damage and whether the damage involves part or all of the cord. Thus, to understand the clinical signs produced by lesions in spinal cord parenchyma, one must know the differences between upper motor neuron and lower motor neuron dysfunction (Fig. 7.2) and anatomic location and function of key spinal cord tracts (Fig. 7.3, and Tables 7.1, 7.2).

Amyotrophic Lateral Sclerosis

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that is uniformly fatal affecting primarily upper and lower motor neurons. Both the clinical and pathological features, as well as recent advances in genetics, suggest considerable heterogeneity in the phenotype of ALS. The disease is commonly known as Lou Gehrig's disease, named for the famous baseball player who developed ALS in 1939. The term "amyotrophic" refers to muscle atrophy and "lateral sclerosis" refers to hardening noted on palpation of the spinal cord from gliosis following degeneration of the lateral corticospinal tracts. Not only is the cause of most cases unknown, but there is also controversy about where the disease begins. A dying-forward hypothesis argues the degeneration begins in motor neurons in the cortex and proceeds downward to involve the anterior horn cells (the motor neurons in the spinal

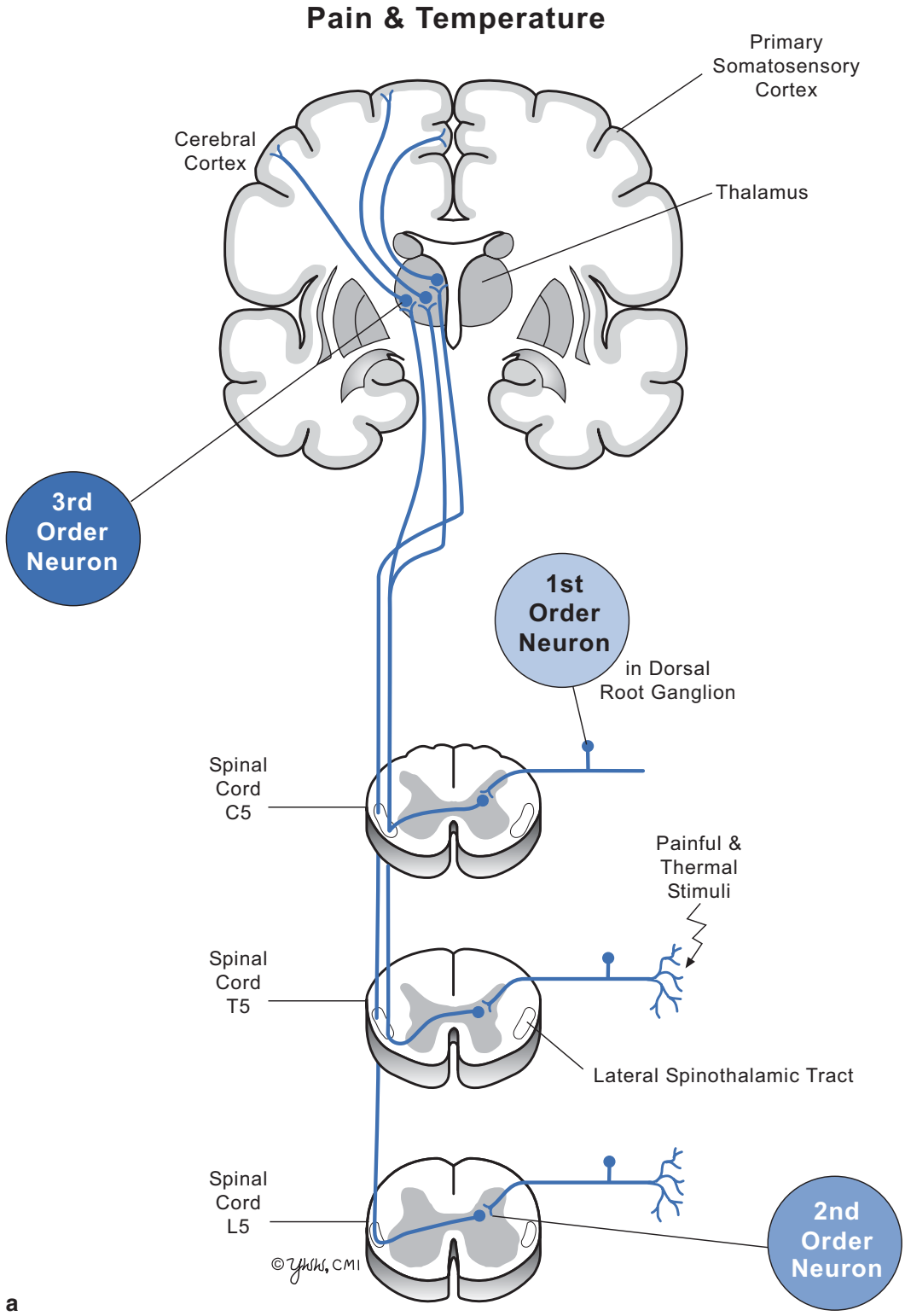
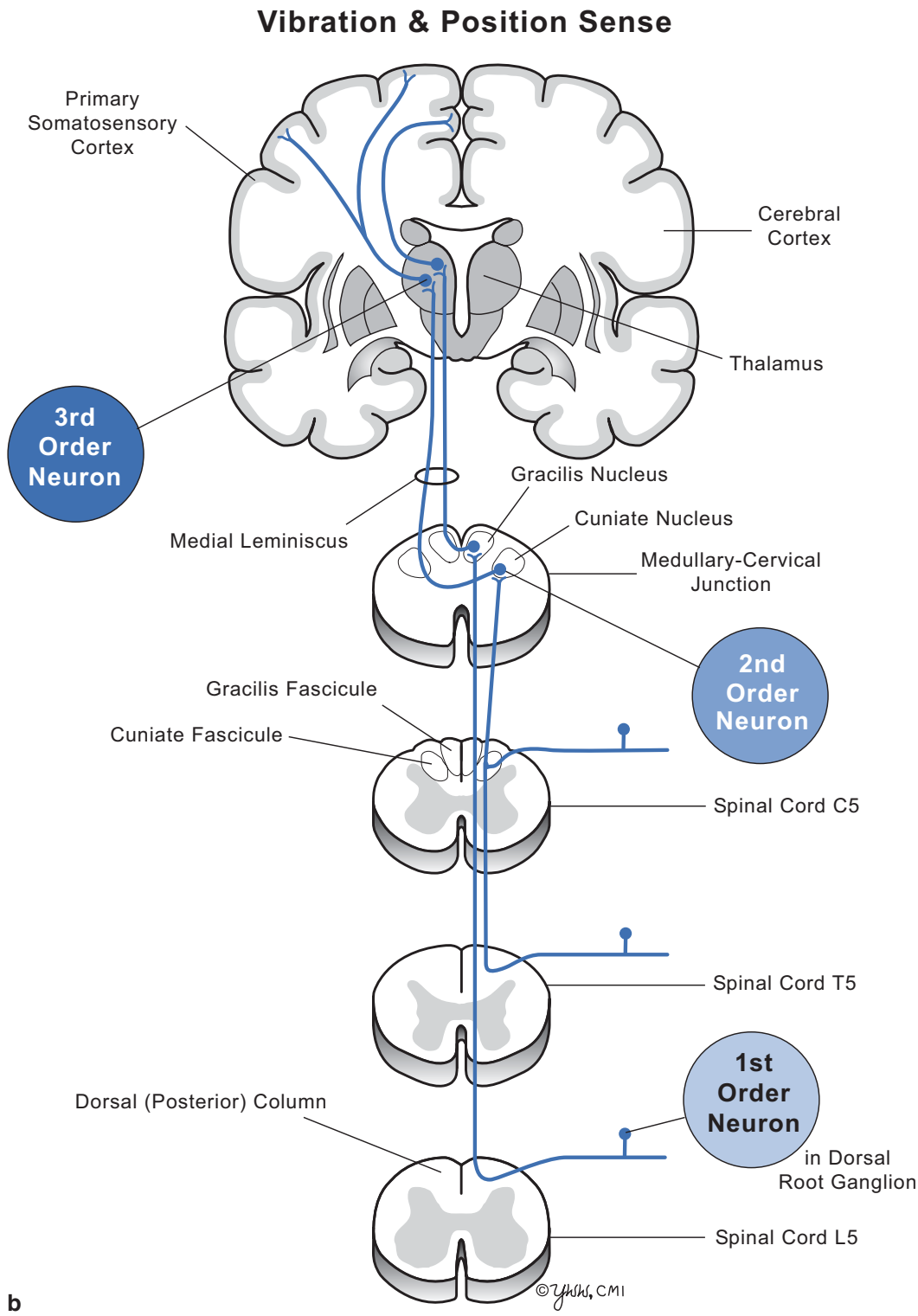


Fig. 7.3 Diagram of cervical, thoracic, and lumbar cord with pathways. **a** Pain and temperature.



b

Fig. 7.3 (continued) **b** Vibration and position sense

Table 7.1 Major spinal cord tracts and their function

Tract	Direction	Function	Location in spinal cord	Point of tract crossing to opposite side of spinal cord or medulla
Corticospinal	From brain	Motor	Lateral	Medulla
Spinothalamic	To brain	Pain, temperature	Lateral	Near site of spinal cord entry
Dorsal column	To brain	Vibration and position sense	Posterior	Medulla

Table 7.2 Major spinal cord neuronal groups

Name	Function	Location in spinal cord
Anterior horn	Lower motor neurons	Ventrolateral gray matter
Dorsal horn	Modulation of afferent sensory impulses	Dorsolateral gray matter
Intermediolateral horn	Sympathetic neurons	Intermediolateral gray matter of thoracic spinal cord
Lateral horn	Parasympathetic neurons	Lateral gray matter of sacral spinal cord

cord). The dying-backward hypothesis proposes ALS begins at the muscle or neuromuscular junction with a loss or abnormal production of a trophic factor critical for the viability of motor neurons.

The incidence of ALS is 2 cases per 100,000 person years with a lifetime prevalence of 4 cases per 100,000. About 5,000 Americans are diagnosed with ALS annually. Analysis of incidence studies suggests the incidence is remaining stable. The peak age of onset ranges between 40 and 60 years with a marked decline after 75 years. The male-to-female ratio is 1.5:1. Most cases are sporadic but 5 % are hereditary.

In the typical case, the diagnosis is straightforward. For atypical onset cases, the differential diagnosis includes cervical spondylotic myeloradiculopathy, multifocal motor neuropathy, X-linked spinobulbar muscular atrophy (Kennedy's disease), thyrotoxicosis, and elongated spinal cord tumors.

Pathophysiology

The pathogenesis of sporadic ALS is unknown. The main clinical and pathologic features are death of upper and lower motor neurons of the spinal cord and brainstem. Motor neurons may be more vulnerable to a variety of pathological processes because they: (1) are large, (2) have long large axons, (3) have high metabolic demands requiring optimal mitochondrial function, (4) are vulnerable to oxidative stresses and dysregulation of calcium homeostasis, and (5) are reliant on efficient synaptic glutamate reuptake transport mechanisms. No animals have been recognized to spontaneously develop a clinical or pathological picture of ALS. Thus, the several current hypotheses are derived from studies involving genetic causes for ALS, animal models of the genetic mutations, and sporadic human cases. The most common mutation (20 % of total cases) producing hereditary ALS stems from a missense mutation in the Cu/Zn superoxide dismutase (SOD1) gene. The mutated superoxide dismutase protein acts through an unknown "gain of function" producing the accumulation of superoxide with abnormal free radical formation in the spinal cord. Mitochondrial disruption is also thought to play a role as altered mitochondrial morphology is seen in skeletal muscle and spinal cord motor neurons in ALS. Excitotoxicity is thought to contribute to motor neuron injury mainly from excessive glutamate, the main excitatory transmitter in the CNS, possibly by an impaired uptake mechanism. Elevated CSF glutamate levels occur in some ALS patients, and riluzole, a drug that inhibits synaptic glutamate release, produces a modest prolongation of survival. Pathological protein aggregation occurring as ubiquitinated inclusions in the cytoplasm of

neurons and glia is a cardinal feature of ALS. A major protein constituent of the inclusions is TAR DNA-binding protein 43 (TDP-43), which is important in RNA and DNA processing. Several ALS mutations are now recognized to affect this protein. Other hypotheses include dysregulated transcription and RNA processing, endoplasmic reticulum stress, impaired axonal transport, and neuroinflammation.

Motor neurons of the spinal cord and brainstem show simple atrophy and accumulation of intracytoplasmic ubiquitinated inclusion bodies containing TAR DNA-binding protein 43 leading to cell death and secondary astrocytic gliosis. There is a greater than 50% reduction in the number of large motor neurons in the anterior horns of the cervical and lumbar spinal cord with a corresponding loss of large myelinated axons in the ventral roots and peripheral nerves going to the limbs. Interestingly, there is little anterior horn cell loss in the thoracic and sacral spinal cord, accounting for relative preservation of autonomic function and bladder and bowel function. The lower cranial nerves leading to bulbar muscles of the face (especially CN 7, 9, 10, 11, and 12) are more affected than cranial nerves supplying oculomotor muscles (CN 3, 4, and 6).

In the cerebral cortex, there is depletion of giant pyramidal neurons (Betz cells) and motor neurons in the fifth layer of the motor cortex with secondary degeneration of the corticospinal tracts.

Loss of lower motor neurons leads to muscle fiber denervation and weakness. Studies show that weakness progresses at a relatively constant rate throughout most of the disease. In early stages of the illness, a compensatory mechanism enables denervated muscles to become reinnervated and temporarily regain function. Following death of a motor neuron, a denervated muscle fiber produces an unknown trophic factor that signals adjacent motor axons to send a branch axon (sprouting) toward the denervated fiber with subsequent reinnervation of the fiber. This compensatory mechanism eventually fails when the replacement motor neuron dies.

There is now evidence that ALS produces more than damage just to the motor system. It has been recognized that some ALS patients share clinical and pathological features with frontotemporal lobe degeneration and three mutations have been linked to both conditions.

Major Clinical Features

Patients with ALS are typically divided into 4 phenotypes. Two-thirds of patients present with limb weakness, while 30% present with bulbar dysfunction (dysarthria or dysphagia.) The remaining one-third develops respiratory dysfunction at disease onset, or “pure upper motor or lower motor neuron” signs.

Symptoms and signs of ALS are primarily those of a progressive upper and lower motor neuron loss. Loss of motor cortex neurons (upper motor neurons) leads to: (1) limb spasticity, (2) hyperactive reflexes, (3) Babinski signs, (4) limb paresis, and (5) pseudobulbar palsy (dysarthria, dysphagia and pseudobulbar affect with emotional reactions that are labile, exaggerated, and often inappropriate).

Loss of anterior horn neurons (lower motor neurons) causes the following: (1) arm and leg muscle weakness that is symmetrical or slightly asymmetrical; (2) muscle atrophy; (3) widespread muscle fasciculations; (4) eventual loss of reflexes; and (5) respiratory weakness from loss of phrenic nerve neurons to the diaphragm and neurons to accessory respiratory muscles.

Loss of bulbar lower motor neurons produces the following: (1) atrophy of the tongue (small tongue with serrated edges); (2) fasciculations of tongue; (3) atrophy of masseter muscle and muscles involved in swallowing producing dysphagia that can cause choking and malnutrition; (4) dysarthria making speech slow and difficult to understand; and (5) mild to moderate lower facial muscle weakness and atrophy.

Of note, muscles involved in eye movements and bladder and bowel function are seldom involved. Sensation and autonomic nerve function are preserved.

The weakness usually begins distally in the limbs and progresses to involve bulbar muscles, but in 20% the process begins in bulbar muscles.

Upper motor neuron signs may predominate early but subside as the lower motor neuron disease progresses and masks them.

Cognitive impairment identified by careful neuropsychological testing develops in about 25% but is seldom noted by physicians as it is often subtle and coincides with the patient becoming depressed, fatigued from their weakness, or developing dyspnea. When recognized, the cognitive impairment is characterized by a personality change, irritability, poor insight, impulsivity, and impaired judgment. Frank dementia or aphasia is uncommon.

Typically because the onset of ALS is slow and variable, the correct diagnosis is often delayed for a year while other diagnoses are pursued.

Major Laboratory Findings

No specific diagnostic test for ALS exists. The hemogram, electrolytes, B_{12}, and liver and renal function studies are normal. Serum creatine kinase may be mildly elevated, especially in rapidly progressive disease. CSF is usually normal but may have a slightly elevated protein level.

The EMG shows evidence of widespread denervation involving muscles of multiple myotomes. Common findings include (1) fibrillations and positive sharp waves, (2) reduced motor unit firing rates, and (3) neurogenic motor units of long duration, multiple phases, and increased amplitude (large polyphasic motor unit potentials). Early motor nerve conduction velocity is normal but slows later in the illness due to loss of the large myelinated axons that have the fastest conduction. However, evidence of slowing of conduction velocities from demyelination should not be present.

The diagnosis of ALS is usually established in a patient who has upper and lower motor neuron clinical signs involving arms and legs, and ideally, bulbar muscles plus EMG confirmation of lower motor neuron findings in several limbs. Usually a cervical MRI is done to rule out cervical spinal cord disease.

A muscle biopsy is occasionally done when the diagnosis is uncertain. Involved skeletal muscle fibers show changes typical for denervation that include pyknotic nuclear clumps involving sarcolemmal nuclei and atrophy of fibers leading to small angulated fibers with concave borders that are all the same fiber type. Early, the atrophic fibers are scattered but later they occur in clusters called “group atrophy”. The cluster has all the same fiber type staining. Normally, a cross section of skeletal muscle stained for fiber type presents a checkerboard appearance of type I and II fibers. Group atrophy is seen when muscle fibers lose their original motor unit, gain a new motor unit from sprouting of an adjacent motor nerve that in turn dies leaving a group of muscle fibers all of the same type.

Genetic testing can be done in patients with a family history of ALS-like syndromes. Advances in neuroimaging made possible the finding of subtle structural changes both within and outside the motor and premotor cortex, but these are not part of the diagnostic criteria currently.

Principles of Management and Prognosis

No drug has been found that stops the progressive loss of motor neurons. However, riluzole increases the survival of ALS patients by 3 to 6 months. Riluzole inhibits the release of the excitatory neurotransmitter glutamate. The goal of management is to make the patient as functional and comfortable as long as possible. Family and friends are valuable in supporting the patient and minimizing the reactive depression that commonly develops. Usually a multidisciplinary team approach is taken for the medical care. As patients weaken, crutches and wheelchairs are needed. When dysarthria becomes severe, assistive communication devices allow patients to continue expressing themselves. Managing dysphagia presents a challenge. Patients can swallow semisolid foods (e.g. pureed table foods) better than solid food or liquids. To prevent malnutrition and cachexia, a feeding gastrostomy or jejunostomy may be required. Inability to swallow

leads to pooling of saliva in the posterior pharynx causing choking, drooling, and aspiration. Home suction equipment may be needed to minimize choking. Administration of anticholinergic drugs or botulinum toxin injections into the salivary glands may reduce production of saliva.

Respiratory weakness and failure become serious problems and usually trigger the terminal event of aspiration pneumonia. Early in the illness, a compassionate but frank interview with the patient and often family should focus on the patient's terminal wishes and these should be placed in a living will. Non-invasive positive pressure ventilation improves dyspnea, increases the patient's quality of life, and slightly extends the life expectancy. Few patients desire assisted invasive mechanical ventilation, such as via a tracheotomy, for the rest of their lives as they become progressively immobile. Respiratory measurements of forced vital capacity, the sniff nasal inspiratory pressure test, and overnight pulse oximetry are useful to follow a patient's breathing capacity.

For sporadic ALS, the mean illness duration is 3 years but 10–15% of patients live 5 years or more. Favorable prognostic indicators include age less than 50 years, lower limb onset, and long interlude from first symptom to diagnosis. Poorer prognostic indicators include bulbar onset, old age, malnutrition, known respiratory or cardiac disease, and impaired cognition.

Table 7.3 Major causes of spinal cord disease

Acute inflammatory transverse myelitis
Viruses *Enteroviruses*
Poliovirus
HIV myelitis (AIDS)
Arboviruses, esp. *West Nile virus*
HTLV-1 myelitis
Bacteria, fungi, parasites *Acute epidural abscess esp. Staphylococcus*
Tuberculosis (Pott's disease of vertebrae with secondary cord compression)
Mycoplasma pneumoniae
Schistosomiasis
Tabes dorsalis from *Treponema pallidum*
Non-infectious inflammation of spinal cord Post-infectious myelitis
Post-vaccination myelitis esp. vaccinia, varicella, rubeola, rubella, rabies
Multiple sclerosis
Neuromyelitis optica (Devic's disease)
Autoimmune systemic lupus erythematosis, Sjogren's and sarcoidosis
Myelopathy from non-inflammatory spinal cord disease
Trauma to spine and spinal cord *Intervertebral disk herniation with cord compression*
Vascular spinal cord diseases Arterio-venous malformation
Infarction of spinal cord
Syringomyelia (syrinx)
Degenerative diseases *Amyotrophic lateral sclerosis*
B_{12} deficiency
Genetic diseases Adrenomyeloneuropathy

Italics indicates the more common causes

Acute Transverse Myelitis and Myelopathy

Introduction

Myelitis implies inflammation within the spinal cord that may be focal or diffuse to involve the entire width of the spinal cord. Acute transverse myelitis (ATM) implies involvement of a large portion of the cross-sectional area of the spinal cord although such lesions often extend vertically in the spinal cord to varying extents. It is often clinically difficult to be certain whether the cause is from localized inflammation or from another myelopathic process such as ischemia. Therefore, the diagnosis of ATM is usually based on characteristic signs and symptoms plus neuroimaging that identify a specific spinal cord level of involvement. Table 7.3 lists the major causes of acute transverse myelitis and myelopathy but the majority of ATM patients have no identified etiology and are classified as idiopathic.

ATM is uncommon with an incidence ranging from 1 to 4 cases per million per year. Both children and adults are involved with no sex preference. Peak incidences occur in the second and fourth decades. Statistically, cases in children are commonly post-infectious or post-vaccination, cases in young adults are often the first mani-

festation of multiple sclerosis or neuromyelitis optica, and cases in older adults are predominately a disk herniation onto the spinal cord, spinal cord mass, or ischemia.

Pathophysiology

Damage to the spinal cord occurs by several mechanisms. One mechanism is from an expanding mass locally destroying that part of the spinal cord such as an arteriovenous malformation hemorrhage, ependymoma, bacterial abscess, or schistosoma in the spinal cord. The second mechanism is damage to the white matter from diseases that damage myelin such as post-infectious transverse myelitis, multiple sclerosis, and neuromyelitis optica. The third mechanism is local ischemic damage such as from angiitis in systemic lupus erythematosus or occlusion of spinal cord/radicular arteries from cardiac emboli or air emboli in decompression sickness. The fourth mechanism is direct infection of spinal cord oligodendrocytes or neurons, as seen in viral infections such as varicella-zoster virus and poliovirus. A fifth mechanism is direct compression of the spinal cord from a protruding disk or trauma.

Pathology in ATM demonstrates localized areas of inflammation with lymphocytes and monocytes, varying focal areas of segmental demyelination, axonal injury, microglial and astrocyte activation, and variable amounts of necrosis and hemorrhage.

Major Clinical Features

The clinical features of idiopathic ATM include rapid onset of symptoms and signs usually over hours to a few days. ATM may be preceded by an upper respiratory infection in about one-third of patients, especially children. Limb paresthesias and back pains are common early symptoms. The patient usually develops the following: (1) paraparesis or tetraparesis, (2) sphincteric disturbance, (3) bilateral Babinski signs, (4) variable back pain, and (5) a sensory level most often at the thoracic level. If the sensory level is in the thoracic area, paraparesis develops while lesions involving the high cervical spinal cord often produce tetraparesis and impaired respiration. Lesions in the lumbar spinal cord produce varying degrees of leg weakness. The anatomic location of the lesion may not be lower than the identified sensory level. However, as afferent sensory fibers often climb several segments before synapsing with dorsal horn neurons, the lesion location may actually be several spinal cord segments higher. Headache and neck stiffness are uncommon unless the lesion is in the cervical spinal cord. The presence of a peripheral neuropathy, progression over several weeks, and signs of hemispheric involvement (e.g. language deficits) are not part of ATM and other diagnoses should be considered.

Major Laboratory Findings of ATM

The CSF usually shows a pleocytosis (10–150 lymphocytes/mm^3), moderately elevated protein level (80–500 mg/dl), and normal glucose level. CSF oligoclonal bands are unusual except when the lesion is due to multiple sclerosis. Infectious agents are rarely recovered from CSF but may be identified by PCR. In post-infectious transverse myelitis, no infectious agents are identified.

In post-infectious transverse myelitis, the T2-weighted MR images usually demonstrate a spinal cord lesion that widens the spinal cord. The lesion, maximal in the central spinal cord area, often extends vertically over 1–3 spinal cord segments (Fig. 7.4). Multiple sclerosis lesions are characterized by the following: (1) extension over fewer segments than post-infectious lesions or than the lesions produced in neuromyelitis optica; (2) may be present at several spinal cord sites; and (3) often have similar lesions in the white matter of the brain. Spinal cord tumors and abscesses are well circumscribed and strongly enhance with gadolinium.

The diagnosis of idiopathic ATM is usually made by consistent clinical and neuroimaging findings and ruling out other specific causes of acute myelopathy. These laboratory tests may include MRI of the brain, serum tests for B_{12}, paraneoplastic antibodies, copper, neuromyeli-

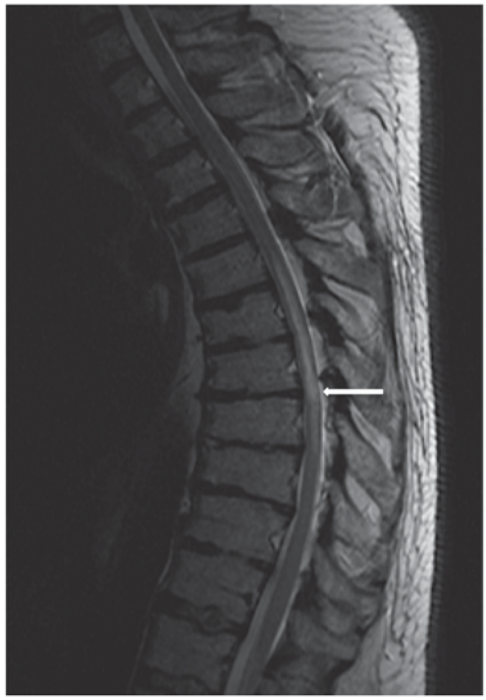


Fig. 7.4 Sagittal T2 MRI of thoracic spine of transverse myelitis showing abnormal T2 (*bright*) signal extending for slightly over 2 vertebral levels (indicated by *white arrows*). (Courtesy of Blaine Hart, MD)

tis optica aquaporin 4 antibodies (See Chap. 10 for full discussion), CSF tests for oligoclonal bands, antibody or PCR assays for varicella, Epstein–Barr, human herpes simplex 6, poliovirus, enteroviruses, West Nile, HTLV-1, HIV, and autoimmune tests for sarcoidosis, systemic lupus erythematosis, mixed connective tissue disorder, and Sjogren's syndrome.

Principles of Management and Prognosis of Idiopathic ATM

Patients should be hospitalized usually in an intensive care unit during the acute stage. Catheterization of the bladder may be necessary. High-dose corticosteroids are often given as soon as the diagnosis is made but their efficacy is not fully proven. Physical therapy is required during rehabilitation. About one-third make a good recovery, one-third a moderate recovery (able to walk), and one-third a poor recovery (need a wheelchair). Recurrence of idiopathic ATM is rare and should raise consideration of another etiology.

Other causes and management of myelopathy or myelitis are listed in Table 7.3. B_{12} deficiency is presented in Chap. 19, Alcohol and vitamin deficiencies; multiple sclerosis is covered in the demyelinating Chap. 10; and neuromyelitis optica and spinal cord are briefly described below.

Spinal Cord Trauma

In the USA, the annual incidence of spinal cord injury is 50 cases per million population or about 10,000 spinal cord injuries a year. A quarter of a million Americans currently live with spinal cord injuries at a cost of 4 billion dollars each year. Forty percent of injuries occur from auto accidents, 25 % from violent encounters, and the rest from sporting accidents, falling, etc. Eighty percent of injuries occur in men. A wide variety of clinical signs occur depending on the location and extent of the spinal cord trauma. If the lesion involves C3–5 spinal cord segments, the phrenic nerves innervating the diaphragm can be affected. Respiratory weakness or secondary pneumonias can occur. In addition to spinal cord injury, cardiac arrhythmias, hypo- or hypertension, blood clots in leg veins, leg muscle spasms, autonomic dysreflexia causing severe hypertension, pressure sores in limbs or buttocks, pain, bladder and bowel dysfunction, and sexual dysfunction can be present to variable degrees.

Spinal cord injury due to trauma can be accompanied by vertebral column injury and often traumatic brain injury. The most common type of injury is a fracture-dislocation. Spinal cord damage is usually secondary to a vertical compression of the spinal column with the addition of anteroflexion or retroflexion (hyperextension). If the patient has a congenitally narrow spinal cord canal, the spinal cord damage is often worse. The spinal cord pathology is a traumatic necrosis resulting from shearing or compression of the spinal cord with destruction of gray and white matter and variable hemorrhages. Unfortunately, recovery from major spinal cord trauma is lim-

ited although minor trauma (called "stingers" in sports injuries) may cause only transient spinal shock with complete recovery.

Low Back Pain with Radiculopathy or Lumbar Spinal Stenosis

Introduction

Two-thirds of adults experience one or more episodes of low back pain. Sciatica to most neurologists refers to a radiculopathy involving one of the lower extremities and is related to disk herniation. However, it is often loosely used to refer to back pain of any origin that travels down the leg and thus is often not due to a herniated disk. Although most patients do not seek medical attention, low back pain is a common reason patients do see a physician. The annual prevalence of radicular low back pain is about 10% with a lifetime incidence of about 25%. About 1% of U.S. adults are chronically disabled from low back pain. The estimated annual U.S. cost for back pain is 50 billion dollars.

Low back pain affects both men and women. The peak age of onset ranges between 30 and 50 years of age. The incidence of lumbar spinal stenosis is not known exactly, but it is the most common indication for spinal surgery in patients older than 65 years of age.

Low back pain is a symptom and not a disease. Studies have found that low back pain can originate within many spinal structures including facet joints, ligaments, vertebral periosteum, paravertebral muscles, adjacent blood vessels, annulus fibrosus, and spinal nerve roots. In addition, back pain may be a referred symptom from abdominal structures such as the abdominal aorta, gastrointestinal tract, kidney, bladder, uterus, ovaries, and pancreas. This chapter will primarily focus on low back pain from a laterally protruding lumbar disk that creates sufficient stenosis (narrowing) at the lumbar spine neural foramina to cause a radiculopathy (signs and symptoms belonging to one nerve root) and lumbar spinal stenosis.

Table 7.4 Warnings that the low back pain may be serious

First clinical signs before age 20 or after 60 years
Recent back trauma
Fevers
Constant pain that is worsening
Abdominal pain, masses, or bruits
History of malignancy, esp. prostate cancer
Long-term use of corticosteroids or immunosuppressive drugs
Unexpected recent weight loss and malaise
Recent infections such as urinary tract or GI infection, herpes zoster, epidural abscess, HIV
Bladder or bowel dysfunction
Bilateral leg pain or weakness
Muscle weakness involving several myotomes
Hyperreflexia or Babinski signs

In the evaluation of a patient with low back pain, the clinician should first determine whether the back pain could be referred from the abdomen or is coming directly from a vertebral structure. The presence of Table 7.4 red flags should prompt a careful physical exam with attention to the abdomen and the ordering of laboratory tests based on the history and exam. Finally, the history and exam should help determine whether a radiculopathy or cauda equina syndrome (compression of lower lumbar and sacral nerve roots) is likely to be present.

Pathophysiology

The stability of the spine results from integrity of four structures: vertebral bodies, intervertebral disks, ligaments between the vertebral bodies, and paraspinous and other muscles. The voluntary and reflex contractions of the paraspinous, gluteus maximus, hamstrings, and iliopsoas muscles are important in preventing vertebral injury, as ligaments are not sufficiently strong to resist the enormous forces that can affect the lower back. In the healthy disk, the center contains the gelatinous, spongy nucleus pulposus that is surrounded by an envelope of fibrous tissue called the annulus fibrosus. These give the disk the ability to act as a shock absorber to the everyday trauma of walking and jumping. After the

second decade, deposition of collagen, elastin, and altered glycosaminoglycans in the nucleus pulposus causes it to progressively lose water and the cartilaginous end plate becomes less vascular. The resulting disk becomes thinner, bulges, and with injury, extrudes. Disk bulges are common and may be present in 50% of asymptomatic adults over the age of 50 years. On the other hand, extrusion of the nucleus pulposus may be symptomatic producing local back and radicular pain from an inflammatory response due to TNF-α, IL-1, IL-6 cytokines and from the extrusion fragment compressing or stretching nerve roots as they exit the neural foramina.

When the disk protrudes posterolaterally, the protrusion may compress a nerve root (Fig. 7.5). Over 90% of clinically significant lower extremity radiculopathies stem from a L4–5 or L5-S1 disk herniation with compression of the L5 or S1 nerve root.

The acute cauda equina syndrome develops from central spinal canal compression of the low lumbar and sacral nerve roots. Upper extremity radiculopathies mainly develop from compression of C5, C6, and C7 nerve roots.

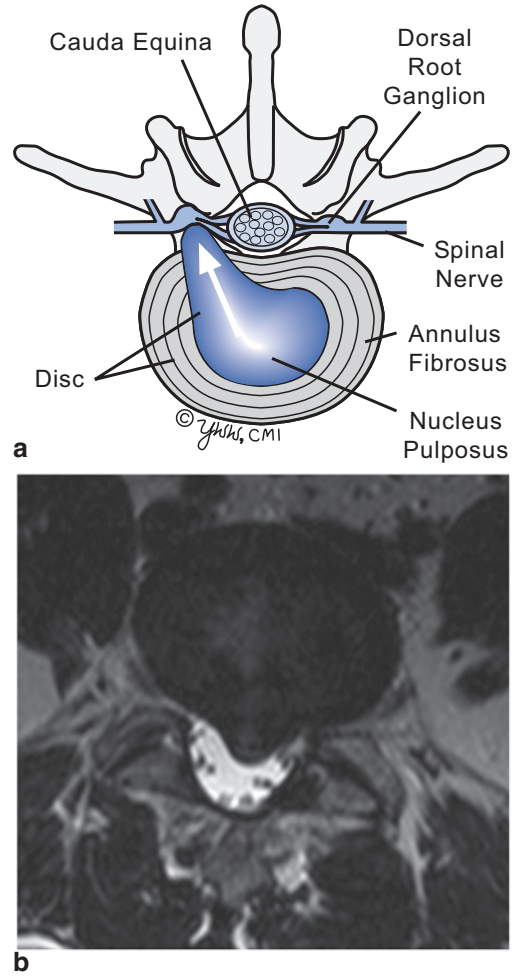


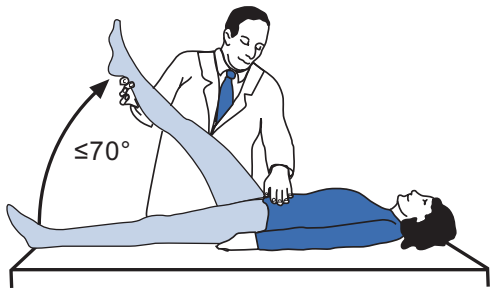
Fig. 7.5 **a** Lateral protrusion of disk (*top view*). The disk compresses the nerve root as it exits the neural foramen. **b** MRI of spine (*axial view*) in a 31-year-old man with acute L4–L5 disk protrusion (note that radiological convention is inverted compared to the anatomical drawing in 5A). (Courtesy of Blaine Hart, MD)

Major Clinical Features

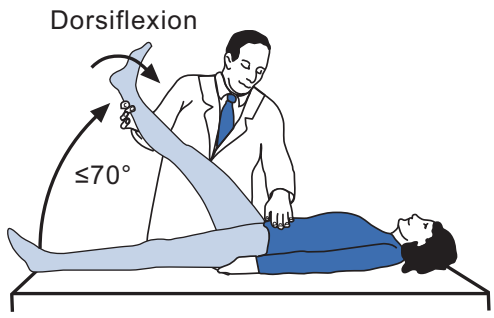
Patients with back disease may complain of stiffness, limitation of movement, spine deformity, and several types of pain. Local pain comes from irritation of pain fibers in the lower back. Patients describe this pain as steady, aching, poorly circumscribed and occasionally as sharp. Patients usually complain of back pain worsened by bending, twisting, or lifting. They may often tighten back muscles (involuntary splinting) to prevent vertebral movement affecting the painful area. Referred pain may be present in patients describing a diffuse deep ache in the buttocks, pelvis, flank, lateral hip, groin, and anterior thigh. Muscle spasm pain is usually paraspinous and associated with tightening of paraspinous muscles to prevent motion of the involved vertebrae. Radicular or "root" pain from stretching, irritation, or compression of a spinal root is described as sharp, throbbing, or burning intense pain (sciatica) that radiates from the back down a leg in varying patterns depending on the root involved (Fig. 7.5). The pain may increase upon bending forward. Coughing, sneezing, and straining at stool (valsalva maneuvers) may aggravate the pain.

As noted above, the patient should not have an abdominal mass or bruit that would suggest referred abdominal pain to the back. An enlarged prostate should not be present as that suggests possible prostate cancer metastasis to vertebrae.

Examination of the back should include inspection of the lower back to determine whether local muscle spasms are present and whether the pain increases by body movements such as bending forward or backward. The vertebral bodies should be palpated and percussed to determine if focal tenderness is present. The presence of localized pain to a specific tender vertebra should raise concerns of a possible localized process such as epidural abscess, vertebral metastasis, or vertebral fracture. With onset of acute radicular pain, the patient may prefer lying supine with their legs flexed at the knees and hips or walking to lessen the pain.



Positive Test: Pain at ≤70° elevation, aggravated by ankle dorsiflexion



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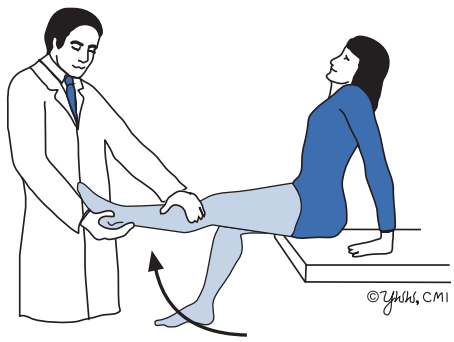


b

Fig. 7.6 **a**) Straight leg-raise test. b) Sitting straight leg-raise test.

The straight-leg-raising test can help in determining radicular pain but is not diagnostic (sensitivity 90 % but specificity only 25 %). The patient may be sitting or lying supine. The leg is elevated slowly to about 70° and then the foot is dorsiflexed (Fig. 7.6). Patients with radicular pain describe sciatica pain that radiates below the knee and not merely in the back or hamstring tightness and is particularly intense in the buttock just lateral and below the sacroiliac joint. A crossed leg test (Lasèque test) is also helpful and performed in a supine patient by lifting up the contralateral leg and reproducing sciatic pain in the affected leg (sensitivity only 30 % but specificity 85 %). A radiculopathy may also produce relative numbness in a particular dermatome, leg paresthesias, weakness of muscles in the involved myotomes, and loss of the ankle or knee reflex (Fig. 7.7). In the patient with chronic radiculopathy, the involved muscles may be hypotonic and atrophic from nerve degeneration.

The L5 radiculopathy is common and usually due to an L4/5 disk protrusion. Patients complain of pain in the hip, posteriolateral thigh, lateral calf, and dorsal surface of foot and first or second toes. Paresthesias may be felt in the entire territory or distal part. Numbness may occur over the lateral calf and medial aspect of the dorsum of the foot including the first two toes. Weakness, if present, involves extensors of the big toe and foot with difficulty walking on heels. The ankle jerk may or may not be diminished.

The patient with an S1 radiculopathy typically complains of pain in the mid-gluteal region, posterior part of the thigh, posterior calf, and heel and lateral foot to the 4th and 5th toes. Paresthesias and sensory loss are mainly in the lateral foot and toes. There may be weakness of plantar flexion of the big toe and foot, making walking on toes difficult. Occasional hamstring weakness is noted and the ankle jerk is diminished or lost.

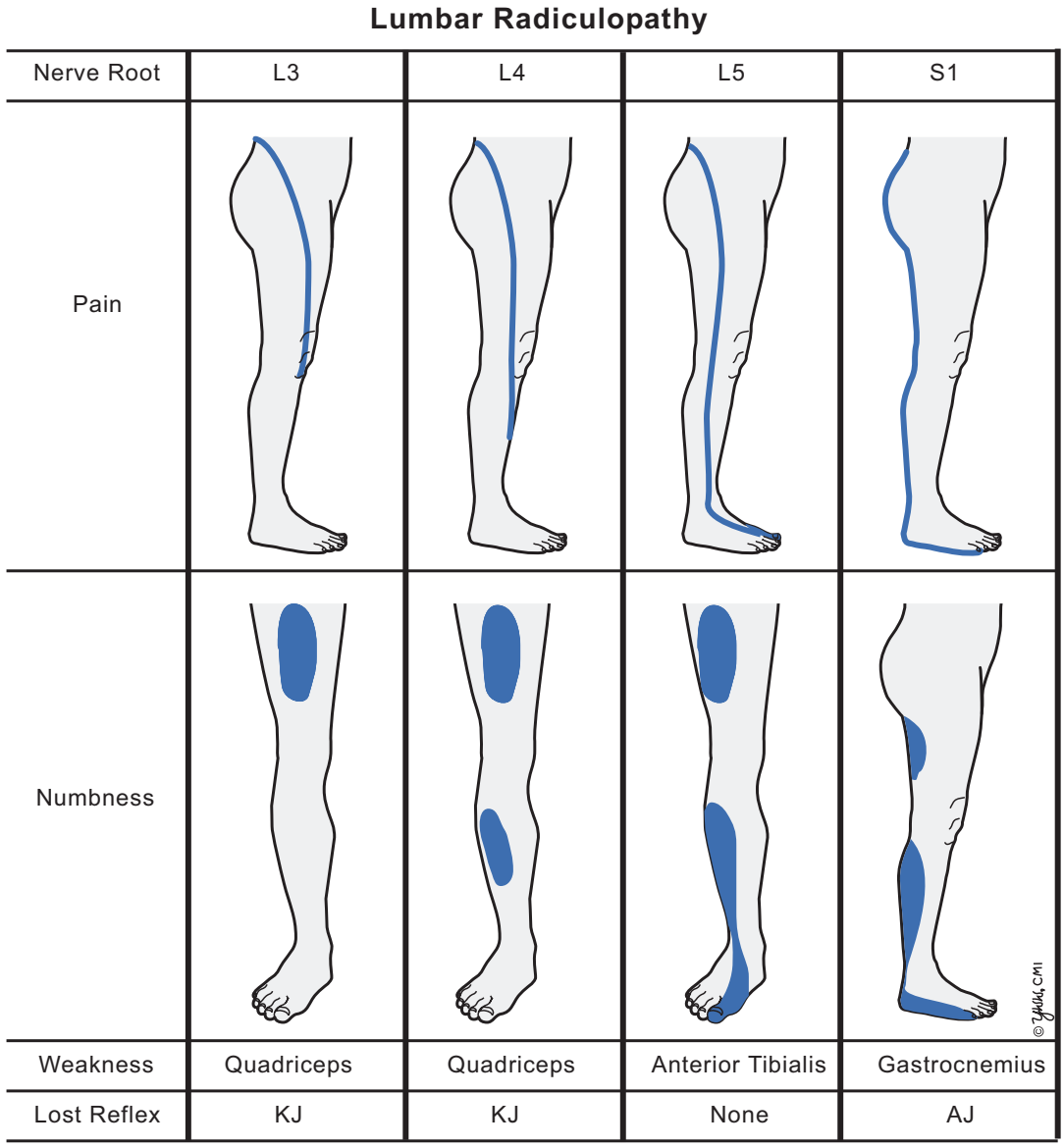


Fig. 7.7 Lumbar radiculopathy. KJ, knee jerk; AJ, ankle jerk

Patients with cauda equina syndrome from lumbar spinal canal stenosis have neurogenic claudication or discomfort and pain radiating beyond the spinal area into the buttocks and frequently into the thigh, which is exacerbated by lumbar extension and improved with lumbar flexion. Patients are more comfortable sitting than prolonged standing or walking. The patient may experience bowel and bladder dysfunction and "saddle" numbness in the perineum and medial thighs. If lumbar roots are involved, weakness in the legs develops. Patients may have proprioceptive fiber loss in their feet, walk with a broad-based gait, and demonstrate a positive Romberg sign with swaying or falling when standing with their feet together and eyes closed. It is necessary to rule out hip osteoarthritis, vascular claudication, and a peripheral neuropathy that can mimic some of the above clinical features.

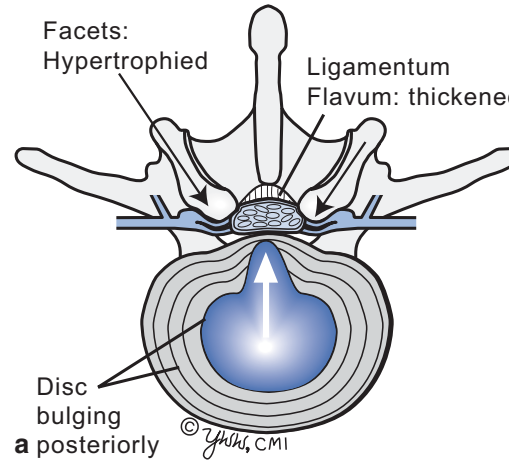
Major Laboratory Findings

The CSF is normal or has slightly elevated protein. The EMG in a patient with radiculopathy shows no changes for 3 weeks. After 3 weeks, the radiculopathy may produce sufficient root compression to destroy motor axons producing denervation changes in involved muscles that include fibrillations and positive sharp waves detected by EMG. An MRI is the most sensitive neuroimaging technique used but CT myelography can detect abnormalities as well. Epidural infections, tumors, and vertebral dislocations are easily detected. Herniated disks and whether the herniation impinges on a spinal root or neural foramina can be seen. It is important to note that disk abnormalities are commonly seen on neuroimaging, especially after middle age, and thus may be incidental and noncontributory to the patient's symptoms. Neuroimaging findings must always be correlated with the history and neurologic exam before surgery at that root is undertaken.

Neuroimaging of the patient with lumbar spinal stenosis usually shows bulging of a lumbar intervertebral disk, hypertrophy of adjacent facets, and thicken ligamentum flavum that serve to narrow the cross-sectional area of the central canal and neural foramina (Fig. 7.8). However, 20% of normal older individuals show similar neuroimaging findings.

Principles of Management of Lumbar Disk Herniation/Lumbar Spinal Stenosis and Prognosis

Back pain is usually divided into acute (<2–3 months duration) and chronic (>3 months). For most patients with acute low back pain and sciatica who do not exhibit any "red flags of worry," the prognosis is very favorable with over 60–75% of patients making a good recovery by 3 months. Most patients do not require neuroim-



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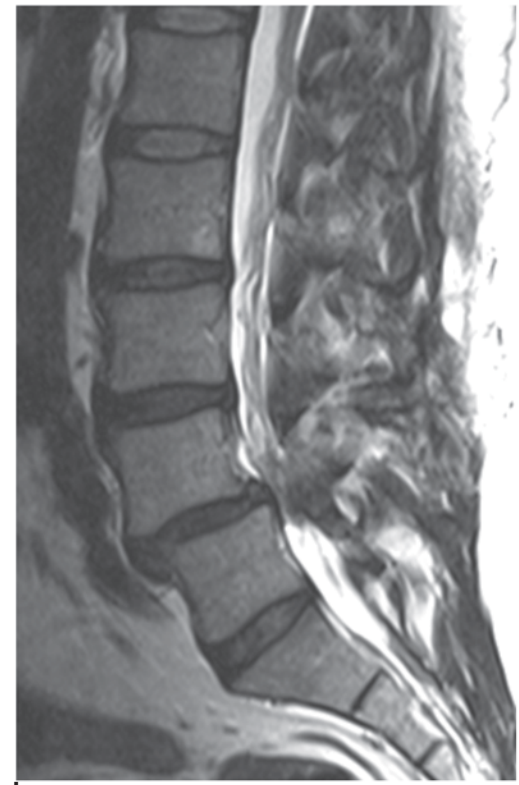

b

Fig. 7.8 **a** Central protrusion of disk (*top view*). The disk compresses the spinal canal and if severe, can impinge on the spinal cord itself. **b** T2 MRI of spine (*sagittal view*) showing severe spinal stenosis at L4–5 from facet hypertrophy and spondylolisthesis. (Courtesy of Blaine Hart, MD)

aging of the spine particularly since over 50% of age-matched asymptomatic individuals show imaging signs of a disk herniation. There are several useful principles of acute management. Information about the anatomy and physiology of disk herniation and its usual management and outcome is helpful to allay patient fears and requests for immediate surgery. Simple acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDS), or short-term use of opioids usually improves discomfort to tolerable levels. Long-term opioids have not been shown to be beneficial. Patients should not be placed on bed rest and should be encouraged to rapidly return to normal activities. They should limit strenuous activities requiring lifting and bending. Traction, physical therapy, massage, spinal manipulation, diathermy, ultrasound, biofeedback, acupuncture, and transcutaneous electrical stimulation may offer temporary relief but have no proven long-term efficacy. Weight reduction to ideal body weight is beneficial as excess weight places awkward stresses on the back when lifting and twisting. Nicotine is thought to constrict vascular beds in the paraspinous muscles delaying natural recovery so stopping smoking is encouraged. Most exercise programs begin with walking short distances and simple back exercises which slowly progress in duration and intensity. Regular aerobic exercises and swimming have been shown to increase range of motion, relieve back pain, and prevent recurrences.

If moderate to severe radicular pain or radicular sensory or muscle weakness persists longer than 3 months, more aggressive management is usually undertaken. At this point, the pain appears to have become neuropathic pain. As such, tricyclic antidepressants and gabapentin may offer some relief. Transforaminal periradicular injections of anesthetics with corticosteroids are often performed through the lateral foraminal approach using radiological guidance. The purpose of the local steroid injection is to reduce inflammation around the nerve root exiting the foramina. Epidural injections have been shown to offer temporary pain relief of 1–2 months but seldom offer permanent pain relief. Serious complications from this procedure are low. Patients experiencing immediate pain relief who lose weight and follow aerobic exercise programs often experience longer pain relief.

Several surgical approaches are commonly done for patients with persistent radicular pain or objective radicular signs. Randomized studies of back surgery vs. conservative therapy have been difficult to analyze due to the high rate of crossover to surgical treatment in patients originally assigned to conservative therapy. Nevertheless, back surgery for patients with sciatica for >2–3 months is felt to provide faster relief of pain than does conservative treatment, but the 1 year and beyond results are similar. The rate of reoperation from a “failed back” operation is about 10% at 4 years.

Management of the patient with lumbar spinal stenosis usually begins with nonoperative steps including bicycling exercises that allow back flexion and are better tolerated than walking or swimming. Lumbar corsets worn only a few hours a day help maintain a posture of slight flexion and are helpful without weakening the paraspinal muscles. Acetaminophen and NSAIDS help control back pain. Epidural injections of anesthetics and corticosteroids may relieve leg pains but do not influence functional outcome or need for surgery at 1 year. The principle goal of surgery is to decompress the central spinal canal and the neural foramina, eliminating pressure on the nerve roots. A common approach is laminectomy and partial facetectomy with or without fusion procedures. About 75% of patients have some degree of symptomatic relief after surgery.

Video Legend

This video shows a 62 year-old man with Amyotrophic Lateral Sclerosis (ALS).

Segment 1: Cranial Nerve Exam
- Normal eye movements
- Normal jaw, neck and tongue strength

Segment 2: Motor Exam
- Distal weakness in upper extremities
- Marked atrophy of hand muscles
- Observing for muscle fasciculation
- Signs of upper motor neuron lesion with spasticity on tone exam

Segment 3: Reflex Exam
- Mixed findings of both hyperreflexia (upper motor neuron) and absent reflexes (lower motor neuron) characteristic of ALS

Recommended Reading

Kierman MC, Benjamin SV, Cheah BC, Turner MR, Eisen A, Hardiman O, Burrell JR, Zoing MC. Amyotrophic lateral sclerosis. Lancet Neurol. 2011;377:942–55. (Excellent review of clinical, differential diagnosis, pathology, and management of ALS)

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Katz JN, Harris MB. Lumbar spinal stenosis. N Engl J Med. 2009;358:818–25. (Nice clinical review of features and management of lumbar spinal stenosis)

Deyo RA, Weinstein JN. Low back pain. N Engl J Med. 2001;344:363–70. (Good review of causes and conservative management of back pain)

Disorders of the Brainstem and Cerebellum

8

A 44-year-old woman with a history of alcoholism is brought to the emergency room by her husband. He reports that over the past 2 days, she has been confused and sleepy. Her examination showed jaundice and lethargy. On laboratory examination, her serum sodium was found to be 124 mmol/L. Correction of her serum sodium commenced but her mental status worsened requiring admission to the intensive care unit. She developed spastic quadriparesis and had only limited ability to move her eyes up and down. MRI of the brain revealed hyperintensity in the pons suggestive of central pontine myelinolysis. She was supported with mechanical ventilation and nutrition. Despite this support, she passed away within a month of her initial presentation.

Overview

The brainstem comprises the mesencephalon, pons, and medulla. It lies at the caudal end of the spinal cord and extends upward to the basal ganglia. There are three main functions of the brainstem. It provides transit and processing nuclei for ascending and descending pathways that convey signals to and from the cerebellum, cerebrum, and spinal cord. Second, it is important for integrative functions such as consciousness, sleep–wake cycle, muscle tone, posture, and autonomic centers that control respiration, blood pressure, and gastrointestinal functions. Finally, the brainstem is the home of cranial nerves 3–10, whose incoming fibers terminate in brainstem nuclei and motor fibers originating in the brainstem nuclei. No other part of the central nervous system is packed with so many critical axon tracts and nuclei. Important axon tracts include the corticospinal tract conducting motor impulses from the cortex to the spinal cord and long sensory tracts conducting information from the spinal cord to the thalamus, cerebellum, and cortex.

In determining the location of lesions involving the brainstem, it is useful first to determine whether the lesion is within the brainstem (intra-axial) or lies outside the brainstem along the cerebello-pontine angle (extra-axial). Extra-axial lesions initially affect cranial nerves through entrapment or compression with later signs developing from compressing brainstem structures or from compressing the Aqueduct of Sylvius producing obstructive hydrocephalus. A typical extra-axial lesion would be an acoustic neuroma that begins in the Schwann cells of the eighth cranial nerve, slowly extends medially out

Electronic supplementary material The online version of this chapter (doi: 10.1007/978-1-4939-2359-5_8) contains videos as supplementary material and can be accessed at http://link.springer.com/book/10.1007/978-1-4939-2359-5.

L. E. Davis, S. Pirio Richardson, *Fundamentals of Neurologic Disease,* 2nd Edition
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Table 8.1 Signs and symptoms pointing to possible brainstem lesions

Brainstem location	Signs/symptoms	Possible structures
Midbrain	Upward eye movement, superior oblique weakness, and pupil constriction dysfunction	CN III, IV
	Contralateral arm and leg weakness	Midbrain or pontine corticospinal tract
	Contralateral arm and leg loss of pain and temperature sensations	Spinothalamic pathways
	Contralateral arm and leg loss of vibration and proprioception	Medical lemniscus
	Coma	Reticular activating center
Pons	Ipsilateral facial numbness, chewing problems	CN V
	Diplopia from ipsilateral loss of horizontal eye movement	CN VI
	Weak ipsilateral facial muscles	CN VII
	Ipsilateral hearing loss, dysequilibrium, vertigo	CN VIII
	Disconjugate lateral gaze or skew deviation from internuclear ophthalmoplegia	Medial longitudinal fasciculus
	Dysarthria and dysphagia	Pontine corticobulbar tracts
	Ataxia	Pontine corticopontocerebellar tracts
	"Locked-in syndrome"	Central pontine myelinolysis
Medulla	Weak pharyngeal muscles	CN IX
	Parasympathetic dysfunction	CN X
	Laryngeal muscle weakness	CN XI
	Poor and weak tongue movement	CN XII
	Ipsilateral Horner's syndrome	Medullary sympathetic pathway
	Vertigo	Vestibular nucleus
	Quadriplegia	Bilateral corticospinal tracts at decussation

of the internal auditory canal and spreads along the cerebello-pontine angle trapping the fifth cranial nerve and eventually compressing the pons.

Lesions in the brainstem often manifest as cerebellar, somatosensory, and motor symptoms plus cranial nerve dysfunction. The level of the lesion often can be determined by the affected cranial nerve and other key symptoms (Table 8.1). In assessing more precisely the location of intra-axial brainstem lesions, it is useful to delineate structures along two planes, longitudinal and cross sectional. The longitudinal plane is usually divided into the midbrain, pons, and medulla, and the cross-sectional divisions are usually medial and lateral. Review of a neuroanatomy textbook is helpful in localizing important tracts and cranial nerve nuclei within this pattern of division.

Blood supply to the brainstem and cerebellum comes from both vertebral arteries and the basilar artery (Fig. 8.1). There are many small penetrating arterioles that enter the brainstem from these major vessels. The arterioles generally supply one side of the medial brainstem (paramedian arteriole) or one lateral side (circumferential arteriole). Three arteries (superior cerebellar artery, anterior inferior cerebellar artery, and posterior inferior cerebellar artery) supply the cerebellum with blood and also may have branches to the brainstem.

A variety of diseases affect the brainstem but with a lower frequency than the same diseases affecting other brain regions. Brainstem tumors are most often astrocytic and slower growing than astrocytic tumors in the cortex. Bacterial abscesses are rare and most viruses causing encephalitis involve the brainstem less intensely. Hemorrhages involving the brainstem are uncommon. Ischemic strokes of the brainstem occur as lacunes or occlusions of penetrating brainstem arteries and are the most common brainstem disease. However, brainstem strokes are less common than hemispheric or basal ganglia strokes.

The cerebellum occupies about 10% of the brain volume but contains more neurons than

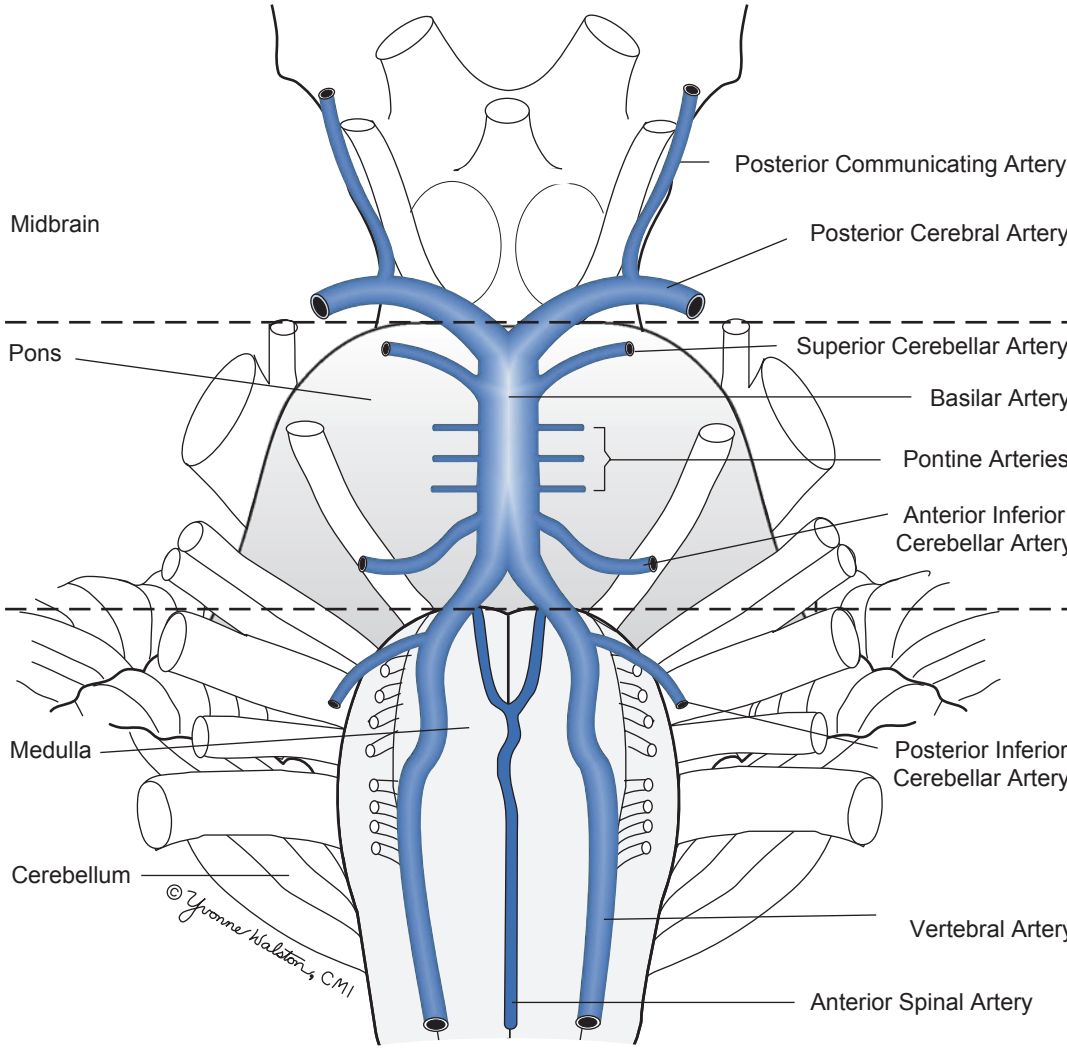

Fig. 8.1 Brainstem and cerebellar circulation

the entire rest of the brain. The cerebellum is divided into the three functional divisions of spinocerebellum, cerebrocerebellum, and flocculonodular lobe (Fig. 8.2). Each division in the cerebellar cortex sends Purkinje cell axons to specific deep cerebellar nuclei and has different functions (Table 8.2). Most input to the highly organized and redundant cerebellar cortex comes from many brainstem nuclei via excitatory mossy fibers that terminate on myriads of granule cells. These granule cell neurons then send inhibitory impulses to Purkinje cells. The inferior olive also sends excitatory input directly to Purkinje cells. Purkinje cells, the only output of the cerebellar cortex, send inhibitory impulses via a GABA neurotransmitter to neurons in the deep cerebellar nuclei that then send output to the brainstem and cerebral cortex.

Cerebellar neurons do not directly produce motor movements but act more as a comparator that compensates for errors in movement by comparing intention with performance and mak-

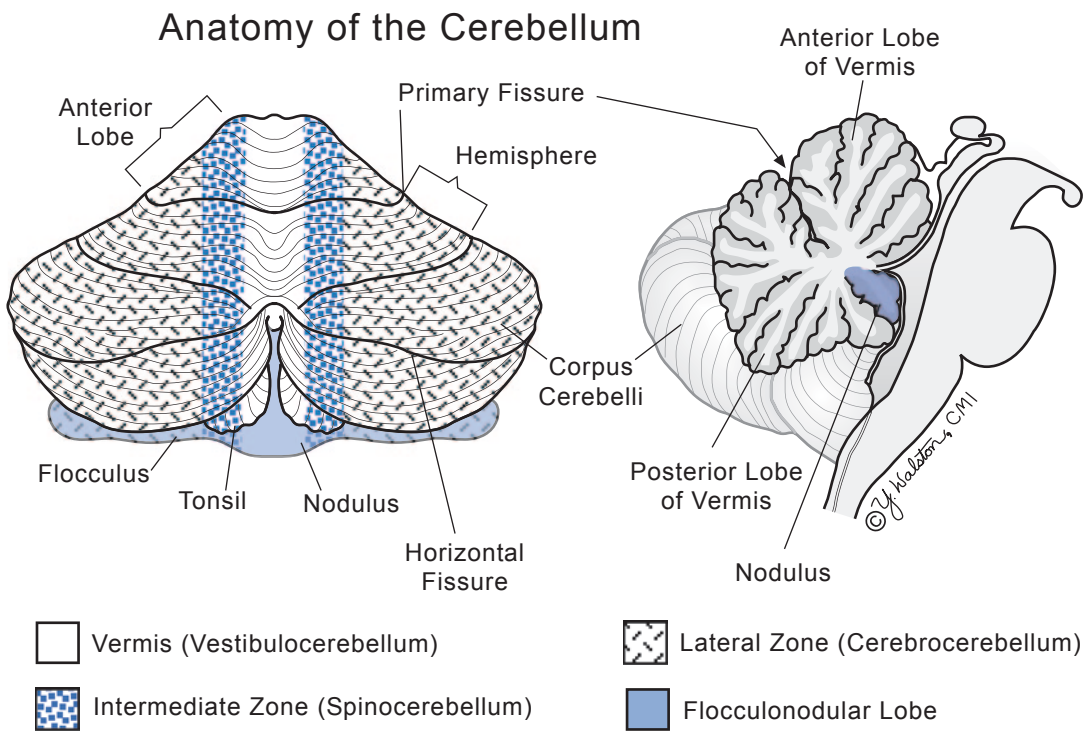

Fig. 8.2 Cerebellar divisions

Table 8.2 Cerebellar functions by location

Function	Cerebellar origin	Deep cerebellar nucleus	Cerebellar efferent connections
Adjust the ongoing movements of axial and proximal limb muscles	Spinocerebellum	Fastigial nucleus	Brainstem reticular formation, vestibular nuclei, and motor cortex
Adjust the ongoing movements of distal limb muscles	Intermediate spinocerebellum	Interposed deep nuclei	Red nucleus and motor cortex
Initiation, planning, and timing of motor movements	Cerebrocerebellum	Dentate nucleus	Red nucleus and premotor cortex
Axial control and vestibular reflexes	Flocculonodular lobe	Direct connection to brainstem	Brainstem vestibular nuclei

ing subtle adjustments. As such, patients with cerebellar diseases do not have weakness or sensory loss. Cerebellar clinical problems are expressed as impaired coordination, imbalance, and even vertigo (Table 8.3). Dysfunction of midline cerebellar structures (vermis of spinocerebellum) produces imbalance problems of midline body structures such as gait and truncal ataxia while cerebellar hemisphere dysfunction produces ataxia of limbs. Unlike the cerebral cortex, damage to one cerebellar hemisphere produces ipsilateral dysfunction.

Recently, converging evidence suggests that the cerebellum is also responsible for some aspects of cognitive and affective function, in addition to its well-known role in the motor system. Many functional imaging studies have demonstrated cerebellar activation in motor, language, and working memory tasks—and that there is a somatotopy to this activation. Whether this activation is completely unrelated to motor behavior (e.g., planning a future movement) is not entirely clear, but there does seem to be evi-

Table 8.3 Signs suggestive of cerebellar dysfunction and likely cerebellar localization

Vermis (midline cerebellum)
Gait ataxia
Clumsy, uncertain, irregular, staggering steps in walking with wide-based stance like "being drunk." Tendency to fall to involved side
Truncal ataxia
Inability to balance in sitting position at edge of table
Saccadic eye movement abnormalities
Conjugate eye movement rapidly to a target results in overshooting of eyes followed by over corrections until target is reached
Cerebellar hemisphere
Signs are ipsilateral to side of cerebellar lesion and more abnormal with fast limb movements than slow movements
Hypotonia
Diminished arm and leg muscle tone give a loose feeling when passively moving the limb
Dysdiadochokinesis
Irregular, uncoordinated rapid movements of hands or fingers. Often tested by asking patient to pat one palm alternately with the palm and dorsum of the opposite hand as rapidly as possible
Dysmetria
Inaccuracies in judging distance and target when moving limb to a target with eyes closed
Cerebellar tremor
Intention tremor develops when moving arm or leg that is perpendicular to the direction of the movement and often amplifies as the target is reached. Usually tested by asking patient to touch a target and then move quickly to his nose or to lift one heel and place it on the opposite knee and then move heel down the shin
Ataxic dysarthria
Poor coordination of articulation resulting in slow, explosive speech
Flocculonodular lobe
Nystagmus
Transient vertigo
Triggered by head or body movements from abnormal vestibulo-ocular reflex (reflex maintains eyes steady in space while head moves)
Postural and gait dysfunction
Vertigo, nausea, and vomiting
Seen only in acute lesions

dence that the areas of the cerebellum activity is task dependent.

A variety of diseases affect the cerebellum and include vascular events (ischemic and hemorrhagic strokes), tumors (meduloblastoma and childhood astrocytoma), toxins (alcohol, phenytoin), infections (chickenpox ataxia), and genetic disease (spinocerebellar ataxias, Friedreich ataxia). This chapter will focus on spinocerebellar ataxias due to a class of genetic diseases called triplet repeat nucleotide disorders that expresses most of the clinical cerebellar problems. Chapter 19 on neurologic complications of alcoholism discusses alcoholic cerebellar degeneration.

Central Pontine Myelinolysis or Osmotic Demyelination Syndrome

Introduction

Central pontine myelinolysis (CPM) is a demyelinating condition affecting the pons or outside of the pons (known as extrapontine myelinolysis). It occurs at times of severe osmotic disruption, such as during rapid correction of serum hyponatremia. The clinical spectrum can range from asymptomatic as an incidental finding on imaging or at autopsy to severe brainstem dysfunction and death. The incidence is difficult to establish as clinically unrecognized pathologic

lesions of CPM are often discovered at autopsy in patients with a history of chronic alcoholism or liver transplants. Large autopsy series report an incidence of about 0.25% in the general population with most cases not recognized premortem.

Pathophysiology

Neuropathological examination reveals abnormalities in the central pons, with destruction of myelin sheaths, loss of oligodendrocytes, and a lack of inflammation. Necrosis may develop in severe older lesions. CPM is also known as osmotic demyelination syndrome due to the hypothesis that osmotic stress is important in the pathophysiology. In the setting of hyponatremia, water moves into brain cells from the bloodstream causing intracellular edema. In order to restore osmotic equilibrium, organic and inorganic osmolytes are expelled from brain cells. If the hyponatremic state is corrected too quickly, the brain cells will not be able to acquire the inorganic and organic osmolytes at a fast enough rate to restore normal cell volume. Damage to the myelin sheath then ensues—but the exact pathological mechanism is unclear. Opening of the blood–brain barrier and introduction of injurious cytokines or complement have been suggested as mediators of damage in CPM. Others have considered impairment in potassium homeostasis leading to myelin destruction as an important step in CPM pathophysiology. It is unclear why the pons is particularly vulnerable to this damage but it could be due to the unique intermixing of gray (brainstem nuclei) and white matter (ascending and descending tracts) in that location.

Major Clinical Features

The initial presentation is often delirium with occasional seizures. There is often a period of lucidity that then is replaced by a range of symptoms from emotional ability to quadraplegia and bulbar dysfunction with dysphagia and dysarthria. Extrapontine symptoms may include Parkinsonism and ataxia. Conditions that may predispose to hyponatremia include alcoholism (40%), liver transplantation (10%), malnourishment, gastrointestinal disease, syndrome of inappropriate secretion of ADH, cancer, pregnancy, and a variety of medications including serotonin reuptake inhibitors (SSRIs).

Major Laboratory Findings

The MRI typically shows hypointense T1-weighted and bright lesions on T_2-weighted or FLAIR sequences, located in the pons in a characteristic *trident* or *batwing* distribution centrally that spares the ventrolateral pons and the corticospinal tracts. Lesions do not enhance with contrast. CPM lesions bilaterally involve the pons which distinguishes them from pontine strokes.

Principles of Management and Prognosis

Prevention of CPM is the goal. When evaluating a patient with hyponatremia (serum sodium levels below 135 mmol/L), several issues should be taken into consideration when calculating the rapidity of sodium correction. Weighing the patient's current clinical state with the underlying predisposing conditions, the chronicity of the hyponatremia and the volume status of the patient all should be considered. In general, the goal is to achieve sodium correction at a rate lower than 0.5 mmol/h or 10 mmol/24 h. Despite adequate preventative measures, CPM can still occur. In general, the treatment is supportive (e.g., antiseizure medications, ventilatory, and nutritional support as needed).

The prognosis of clinically identified CPM is considered poor. Studies suggest that about one-third of patients with CPM have a "good outcome," one-third have an "adequate outcome" and one-third have a "poor outcome that includes death and the locked-in-syndrome." Survivors may manifest paralysis and executive dysfunctioning and memory difficulties.

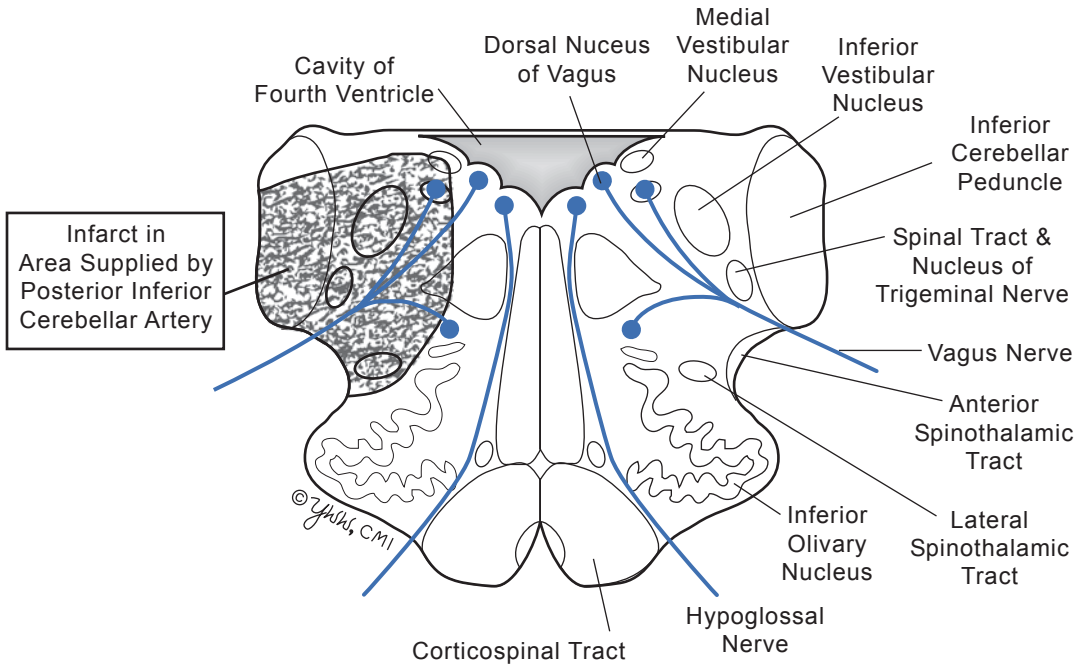

Fig. 8.3 Lateral medullary infarction

Lateral Medullary Infarction (Wallenberg's Syndrome)

Introduction

Most ischemic strokes involve the pons (55%) followed by the medulla (30%) and midbrain (15%). Lateral medullary infarction (LMI) is the classic stroke syndrome that dramatically demonstrates the multiple clinical signs that develop when there is damage to many important tracts and nuclei in the lateral medulla (Fig. 8.3).

Pathophysiology

The medulla receives its arterial blood supply from the vertebral artery via small branches that have considerable variability. The posterior inferior cerebellar artery (PICA) is a large artery that supplies blood both to the lateral medulla and to the posterior inferior aspect of the cerebellum. LMI can result from stenosis, thrombosis, embolus or dissection in the vertebral artery, or occlusion of the PICA or other small, unnamed, medullary arteries. Major risk factors include diabetes mellitus, neck trauma-producing vertebral artery dissection, and old age.

Major Clinical Features

Typically, patients have acute onset of symptoms (75%), and less commonly, some patients will develop symptoms that progress over hours to a day (25%). The symptoms will vary depending on how medial the infarction extends and whether the caudal or distal medulla is maximally affected. More than half of patients experience multiple signs and symptoms that include dizziness and vertigo (75%), nausea or, vomiting (60%), nystagmus (60%), skew deviation of vision (diplopia with targets diagonal to each other and not improved in any field of gaze), gait ataxia and ipsilateral limb ataxia are due to involvement of vestibular nuclei, inferior cerebellar peduncle, and/or vestibular nuclei-flocculonodular connections (70%). Patients

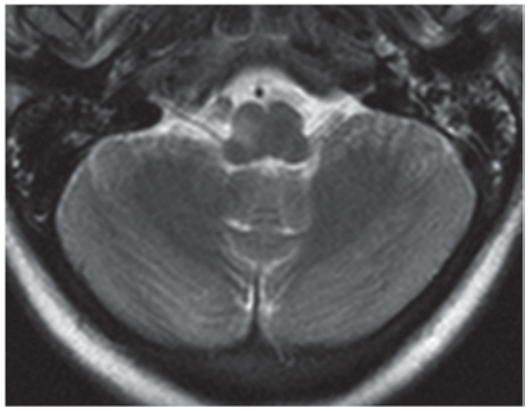

Fig. 8.4 Diffusion-weighted MRI of medulla showing acute infarct in lateral medulla (bright signal) in a 45-year-old woman with history of hypercholesterolemia and smoking. (Courtesy of Dr. Blaine Hart)

commonly complain of numbness and shooting pains of the ipsilateral side of the face and loss to pain and temperature on the contralateral side of the body from damage to the spinothalamic and descending trigeminal nerve tracts (90%). Dysphagia and dysarthria (75%) from paralysis of the ipsilateral palate, pharynx, and larynx muscles are due to damage to the nucleus ambiguous of the tenth cranial nerve. Horner's syndrome (70%) with ipsilateral ptosis, miosis (small reactive pupil), and loss of facial sweating occurs from damage to sympathetic tracts. Marked limb weakness is less common (25%) and implies corticospinal tract involvement from a large medullary infarction or hemorrhage affecting the ventral medulla.

Major Laboratory Findings

MRI, which is more sensitive than CT, demonstrates ischemic infarction in the lateral aspect of the dorsal medulla (Fig. 8.4) and a hemispheric cerebellar infarction in 20%. MRI may be normal in the hyperacute state but is able to confirm ischemia in the majority of patients. Magnetic resonance angiography (MRA) and vertebral arteriography may demonstrate stenosis or absence of blood flow in the PICA, vertebral, or basilar artery. In addition, vertrebral artery dissection is an important cause of LMI.

Principles of Management and Prognosis

Patients require hospitalization with attention to ability to swallow (50% will require an enterofeeding tube for several weeks). If marked vertigo, nausea, and vomiting are present, vestibular sedative drugs may be transiently required. Dysphagia, dysarthria, and vertigo usually improve over several weeks. Rehabilitation is needed to improve balance, coordination, and gait. Most patients will regain the ability to walk and function independently. To prevent subsequent strokes, patients benefit from controlling their vascular risk factors and using antiplatelet therapy.

Spinocerebellar Ataxias (SCAs)

Introduction

Cerebellar ataxia comprises a wide variety of different causes, making the diagnosis challenging as none are that common (Table 8.4). Most cases of cerebellar ataxia syndromes are sporadic, but rarely, they can have a known genetic cause. The majority of the inherited forms of spinocerebellar ataxia (SCA) are autosomal-dominant cerebellar ataxias (ADCAs). Although there are multiple pathologic mechanisms, the majority of these ADCAs (11 of the 18 currently assigned SCAs) share a common pathogenic mechanism—namely polyglutamine expansion. The clinical presentation is characterized by a progressive cerebellar ataxia with unsteady gait, clumsiness, and slurred speech. In addition, symptoms of cognitive abnormalities, other movement disorders, and visual disturbances can be present to a variable degree. In the European population, between 1 and 3 people per 100,000 will be affected by SCAs, with SCA3 being the most common but increases in some regions due to a founder effect of a particular SCA.

Table 8.4 Major causes of cerebellar ataxias

Genetic causes
Spinocerebellar ataxias (SCA 1–35+)
Degenerative
Multiple system atrophy
Atypical Creutzfeldt–Jakob disease
Toxins
Alcohol
Phenytoin
Lithium
Solvents
Heavy metals
Paraneoplastic cerebellar syndromes
Anti-Yo, anti-Hu, anti-Ri, anti-Ma, anti-CAD65
Infectious, autoimmune diseases
Mumps cerebellitis
Gluten ataxia
Miller–Fisher syndrome
Thyroiditis or hypothyroidism
Head trauma
Brain structural disease
Chiari malformation
Agenesis or hypoplasia of cerebellum
Neoplastic disorder
Cerebellar tumor

Common features of many polyglutamine SCA diseases include (1) onset in adulthood, (2) slow progression, (3) neuronal loss in the cerebellum, brainstem, and spinal cord, (4) instability and expansion of a trinucleotide repeat tract, (5) mutant protein aggregation or clumping in the nucleus of involved neurons, and (6) occurrence of anticipation or the tendency for disease onset to be more severe and occur at a younger age in the next generation. Trinucleotide repeat genetic diseases are recognized to cause a wide variety of diseases that involve the basal ganglia (Huntington's disease), muscle (myotonic muscular dystrophy), mental retardation (fragile X syndrome), motor neuron loss (spinobulbar muscular atrophy), and ataxia (Friedrich's ataxia, and SCAs). The expansion of the trinucleotide repeat part of the mutant gene may occur in non-coding regions (fragile X syndrome, Friedreich ataxia, and myotonic muscular dystrophy) or in coding regions (SCA, Huntington's disease) where the protein contains an expanded repeated amino acid.

Pathophysiology

The polyglutamine expansion SCAs have a highly polymorphic, unstable repeat expansion of DNA nucleotide bases cytosine, adenine, guanine (CAG). The nucleotides CAG encode the amino acid glutamine. Once the number of CAG repeats crosses a certain threshold of repeats (generally above 37–40 repeats), the expansion becomes pathological. Genetic *anticipation* refers to earlier age of onset and increased severity of symptoms in succeeding generations as seen in ADCAs. Due to the instability of the expansion, repeats can increase during paternal transmission to the mother. This instability, and therefore genetic anticipation, is more frequently seen with paternal transmission.

There are some common pathological mechanisms shared by the polyglutamine disorders—and this has implications for potential therapeutic strategies for these disorders. First, despite widespread expression of the proteins produced by the disease gene, targeted selective degeneration in the central nervous system is seen. Second, these disease proteins tend to misfold, coalesce, and form protein aggregates intracellularly producing intranuclear inclusions that can be identified on histologic examination. Despite these commonalities, in each of the polyglutamine disorders, different proteins are implicated, as well as different sites of vulnerability within the central nervous system depending on the particular disease involved.

Neuropathological changes in SCA 1, 2, 3 are fairly similar. Gross examination reveals atrophy of the cerebellum, pons, loss of the bulge of the inferior olive, and mild to moderate widening of sulci in the frontotemporal cortex region. Microscopically, there is severe loss of (1) Purkinje cells maximally in the vermis, (2) dentate neurons, (3) neurons in inferior olive, pontine nuclei, and nuclei basis pontis. There is moderate loss

of neurons in anterior horns, cranial nuclei 3, 10, and 12, and cholinergic system of the forebrain. Mild neuronal loss occurs in the cerebral cortex. Extensive atrophy of the superior, middle and inferior cerebellar peduncles, spinal cord posterior columns and spinocerebellar tracts, and corticospinal tract is present. Secondary gliosis develops in the cerebellar molecular layer, brainstem, and cerebral cortex.

Major Clinical Features

The clinical features of the ADCAs include progressive gait ataxia, clumsiness, and dysarthria—leading to eventual brainstem death. In general, symptoms begin in the third or fourth decade. The age of onset is largely dependent on the number of repeats. Gait ataxia is the common first symptom, although some patients may have visual complaints or episodic vertigo as a presenting complaint (~4%). Over time, spasticity may develop. The presence of spasticity may indicate SCA1, SCA7, or SCA3—all of which have spasticity as a prominent symptom. On the other hand, prominent eye movement abnormalities such as nystagmus, saccadic pursuit, and abnormal saccades indicate the presence of SCA6. Symptoms outside of the spinocerebellar axis, such as peripheral nerve involvement may be present as well (such as in SCA1). In the late stage of disease progression in the ADCAs, muscle atrophy, hypoactive deep tendon reflexes, loss of position sense, and variable degrees of oculomotor paralysis develop. Severe bulbar dysfunction with dysphagia and dysarthria occurs. Disease progression lasts 10–15 years with death resulting from aspiration and respiratory complications.

Major Laboratory Findings

Commercial testing is available for many of the ADCAs (as well as for many of the recessive ataxias as well). However, without a positive family history of ataxia, the likelihood of a positive genetic test result is quite low (see Table 8.1 for the many sporadic causes). Both trinucleotide repeat expansions and conventional mutations can be detected, commercially and in research lab settings.

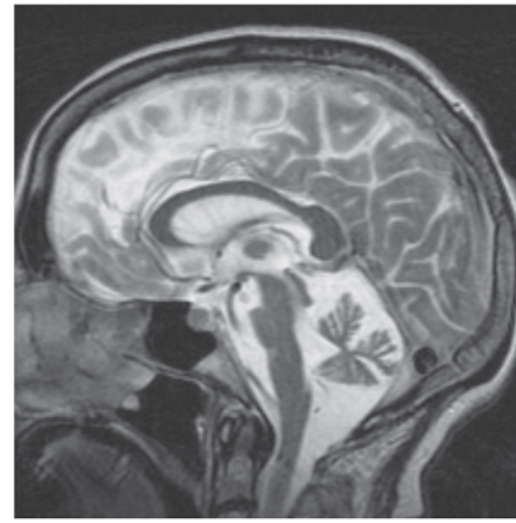

Fig. 8.5 T2-weighted sagittal MRI of brain showing marked atrophy of cerebellar vermis and pons in a 44-year-old man with a family history of spinocerebellar ataxia. (Courtesy of Dr. Blaine Hart)

MRI of the brain may show brainstem and cerebellar atrophy (Fig. 8.5). For the polyglutamine expansion ADCAs, the brainstem atrophy is typically greater than the cerebellar atrophy, whereas, for the conventional mutation ataxias, the atrophy is limited to the cerebellum.

Principles of Management and Prognosis

To date, no therapy is successful in delaying or halting disease progression. Therefore, management is supportive. Canes and walkers help prevent patients from falling and grab bars, raised toilet seats, ramps aid in safer ambulation. Wheelchairs are necessary when the gait ataxia and imbalance becomes severe. Speech therapy and computer-based communication devices help patients with marked dysarthria. Genetic counseling may be offered to patients of child-bearing age.

Video Legend

This video shows a 67 year-old woman with Multiple System Atrophy-Type Cerebellar

Segment 1: Cranial Nerve Exam
- Saccadic intrusions into fixation
- Dysmetric and slow saccades
- Impaired vestibulo-ocular reflex
- Scanning dysarthria

Segment 2: Cerebellar Exam
- Dysmetria on finger-to-nose
- Overshooting target on finger chase
- Dysmetria on heel-to-shin
- Limb rebound

Segment 3: Gait Exam
- Ataxic gait requiring use of walker

Recommended Reading

Kandel ER, Schwartz JH, Jessell JM. Principles of neural science, 5th edn. New York: McGraw-Hill Professional; 2012. (Good review of brainstem and cerebellar anatomy and physiology)

Querol-Pascual M. Clinical approach to brainstem lesions. Semin Ultrasound CT MRI. 2010;31:220–9. (Excellent brief review of brainstem locations for common brainstem clinical signs and symptoms)

Hurley RA, Filley CM, Taber KH. Central pontine myelinolysis: a metabolic disorder of myelin. J Neuropsychiatry Clin Neurosci. 2011;23(4):369–74. (Good review of the clinical manifestations and pathophysiology of CPM)

Kameda W, et al. Lateral and medial medullary infarction: a comparative analysis of 214 patients. Stroke. 2004;35:694–9. Comprehensive review of the features of medial vs. lateral medullary infarction with good anatomy-clinical correlations)

Durr A. Autosomal dominant cerebellar ataxias: polyglutamine expansions and beyond. Lancet Neurol. 2010;9:885–94. (Excellent review of clinical, pathological and genetic features of major SCAs)

Disorders of the Cerebrovascular System

9

A 65-year old previously healthy man who did not have a regular internist suddenly developed weakness and sensory loss in his right arm, leg, and face and also faced difficulty in speaking. He could understand his wife and knew what he wanted to say but could not get the words out. The episode lasted 20 min and spontaneously ended. He went to the emergency room (ER) where his neurologic examination was normal. He was diagnosed with a transient ischemic attack. The next day his echocardiogram was normal but the carotid artery Doppler ultrasound demonstrated that his left internal carotid artery narrowed by 85%. In addition, the ER also found him to have several risk factors for transient ischemic attack (TIA) including being overweight by 45 lbs, an elevated blood pressure of 160/108, and a hemoglobin A1C of 8.6%. The same day he met an internist to begin medical management for his hypertension, diabetes mellitus, and obesity plus a surgical referral to consider an elective carotid endarterectomy.

Overview

Stroke is a general term that implies damage to cerebral tissue from abnormalities of blood supply. In simple terms there may be insufficient blood supply to the brain (ischemic stroke or infarction), abnormal excess blood (hemorrhagic stroke or cerebral hemorrhage), or inadequate venous drainage of cerebral blood (venous stroke). Ischemic strokes represent 85% of all strokes, hemorrhagic strokes 14%, and venous strokes 1% (Table 9.1).

Stroke is the third leading cause of death in the USA. Each year 800,000 people in the USA develop stroke and 175,000 die. Fortunately, since 1960 the incidence of strokes in the USA has significantly fallen by 50% primarily due to better control of hypertension, diabetes mellitus, and smoking but still 4 million adults in the USA are found to have stroke with an overall stroke prevalence of 750 per 100,000.

Electronic supplementary material The online version of this chapter (doi: 10.1007/978-1-4939-2359-5_9) contains videos as supplementary material and can be accessed at http://link.springer.com/book/10.1007/978-1-4939-2359-5.

Ischemic Stroke

Introduction

Ischemic stroke occurs from lack of sufficient arterial blood flow in the territory of a specific cerebral artery to maintain neuronal viability. The stroke can be due to (1) intrinsic vascular occlusion (thrombus) that occurs in the neck portion of the internal carotid, vertebral artery, or a cerebral artery or (2) vascular occlusion with

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Table 9.1 Major stroke types[a]

Stroke type	Overall percentage (% of each category)
Ischemic	85%
Carotid artery circulation	(55%)
Vertebral/basilar artery circulation	(12%)
Lacune	(31%)
Other (vasculopathy, coagulopathy, sickle cell, hyperviscosity, vasculitis)	(2%)
Hemorrhagic	14%
Hypertensive hemorrhage	(50%)
Saccular aneurysm	(30%)
Amyloid angiopathy hemorrhage	(15%)
Arteriovenous malformation	(3%)
Other (infective aneurysm, cocaine, anticoagulants)	(2%)
Venous	1%
Thrombosis of cortical veins, deep cerebral veins, or dural sinuses	(100%)

[a]Excludes stroke due to head trauma and subdural hematomas (see Chap. 18 on Traumatic Brain Injury and Subdural Hematoma)

material originating elsewhere (embolism) such as a stenotic site of the internal carotid or vertebral artery or from the heart. The large majority of emboli are blood clots but occasionally they can be air, fat, or tissue fragments. Eighty percent of ischemic strokes involve the carotid artery territory or anterior circulation and 20% involve the vertebrobasilar artery or posterior circulation.

The cause of a stroke depends on the patient's age. In children, congenital heart disease with paradoxical embolism, Moyamoya disease, bacterial endocarditis, rheumatic fever, sickle cell anemia, and mitochondrial disorders should be considered. In young adults, estrogen-related stroke, migraine, vascular malformation, arteritis, hypercoagulation abnormalities, arterial dissections, and drug reactions from amphetamines, heroin, and cocaine may be seen. In middle age, hypertensive hemorrhage, ruptured saccular aneurysm, fibromuscular dysplasia and cardiogenic embolism often occur. The elderly often develop lacunar strokes, multi-infarct dementia, and atherosclerotic thrombotic strokes.

Table 9.2 lists the major modifiable and unmodifiable risk factors for stroke.

Pathophysiology

Cerebral ischemia occurs from inadequate cerebral blood flow to the brain area. Total lack of oxygen and glucose to all brain neurons, as in a 12 to 15 s cardiac arrest, suppresses electrical activity and causes loss of consciousness. Normally cerebral arterial blood flow is 50 mL/100 g brain/minute. When cerebral blood flow falls below 18 mL/100 g brain/minute, cerebral function falters but neurons may remain alive (Fig. 9.1). Thus, electrical activity ceases and sodium/potassium pumps begin to fail but the neurons are viable and can recover function if blood flow improves. In a stroke, this area of potential recovery is called an *ischemic penumbra*. Blood flow below 8 mL/100 g brain/minute results in neuronal death as early as 15 min after flow disruption. Neurons in the hippocampus and cerebellum are most sensitive to ischemia while neurons in the brainstem and spinal cord are the most resistant. Brain ischemia results in impaired energy metabolism with accumulation of calcium ions in the intracellular space, elevated lactate levels, acidosis, and production of free radicals. Cellular homeostasis is disrupted leading to neuronal death.

Stroke from occlusion of a specific cerebral artery causes a wedge-shaped infarction (Figs. 9.2 and 9.3). If a large artery occludes, such as the middle cerebral artery, the stroke may involve that entire vascular territory or portions may be spared depending on the degree of collateral circulation. In about 25% of ischemic strokes, there is rapid reperfusion of the ischemic territory from lysis of the embolic clot allowing blood to leak from damaged small arterioles, capillaries, and venules producing *hemorrhagic transformation* of varying degrees within the ischemic stroke.

Border zone or watershed infarctions are ischemic lesions that occur in characteristic locations at the junctions between two nonanastomosing arterial territories and constitute about 10% of ischemic infarctions. Hemodynamically, they usually develop from severe prolonged hypoperfusion of the watershed territory resulting from some combination of systemic hypotension, tight

Table 9.2 Risk factors for stroke

Risk factor	Increase in risk over normal age-matched population
Modifiable	
Hypertension	300–600 %
Diabetes mellitus	200–400 %
Smoking	150–300 %
Cocaine/Crack	200–500 %
Atrial fibrillation Untreated On warfarin	 300–500 % 50 %
Other heart abnormalities (mural thrombus, cardiomyopathy, acute myocardial infarction, mechanical heart valve, infective endocarditis)	200–600 %
Obesity	200 %
Serum lipid abnormalities	50 %
Asymptomatic carotid artery stenosis 60 to 74 % stenosis 75 to 94 % stenosis Greater than 95 % stenosis Total occlusion	(Five year increase) 10 % 14 % 10 % 5 %
Unmodifiable	
Advancing age	Relative rates double every decade after age 55 years
Male gender	25 %
Prior transient ischemic attack	400 %
Heredity (first degree relative with stroke)	100–400 % depending on cause

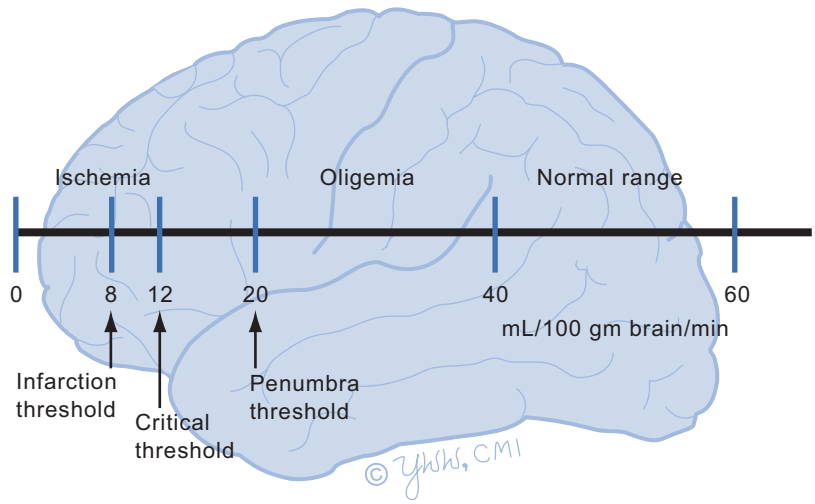

Fig. 9.1 Cerebral blood flow thresholds

stenosis or occlusion of extracranial or intracranial arteries, and microemboli that originate from the heart or the proximal stenotic artery lodging in distal intracranial arteries. The most common locations are between lenticulostriate and middle cerebral arteries and the middle and anterior cerebral arteries. The signs and symptoms produced are often mild, variable, and usually patients

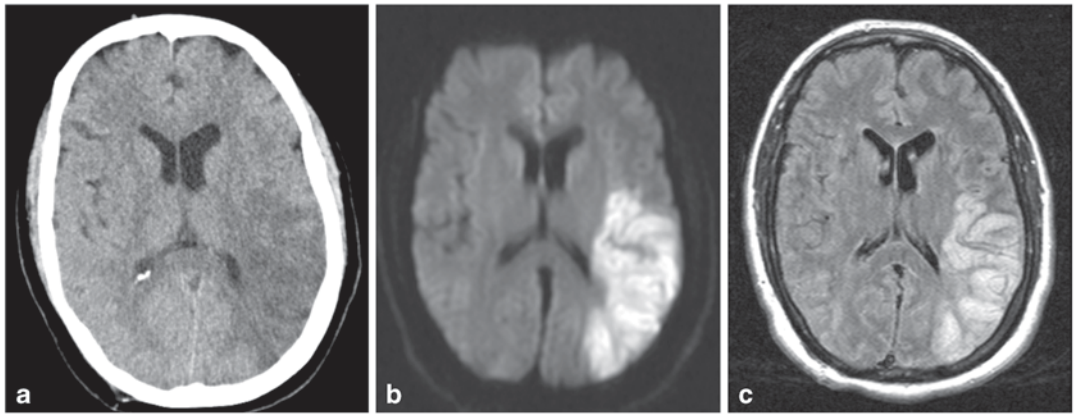

Fig. 9.2 Acute left middle cerebral artery wedge-shaped infarct shown by hypodensity on noncontrast head computed tomography (CT) (**a**), by bright signal on diffusion-weighted magnetic resonance imaging (MRI) (**b**) and by bright signal on T2 FLAIR MRI (**c**). (Courtesy of Blaine Hart, MD)

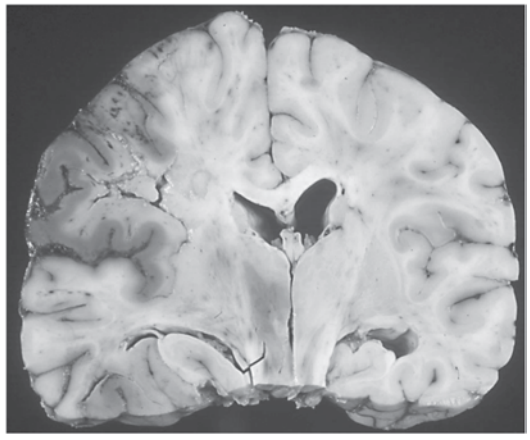

Fig. 9.3 Ischemic infarction, wedge-shaped pathologic specimen. (Courtesy of Mark Becher, MD)

make a good recovery. Exceptions are watershed brainstem infarctions involving branches of the basilar artery.

Microscopically, a large vessel ischemic stroke shows little visible changes until about 6 h later when swelling of neurons, astrocytes, and endothelial cells begins. Neurons first swell, then shrink, develop chromatolysis (nuclei become eccentric with hyperchromasia) and then die. Neutrophils are abundant after the first day. By second day microglia proliferate and become macrophages engulfing myelin breakdown products. Astrocytes proliferate, become reactive, and lay down glial fibers to produce gliosis. Neovascularity slowly develops and renourishes the damaged brain. Gradually over months the necrotic brain products are reabsorbed producing a glial lined cavity of variable size, seen on neuroimaging as encephalomalacia.

Lacunar ischemic strokes represent 25% of ischemic strokes and differ from large arterial strokes. They are small, less than 15 mm in diameter, and are primarily located in the basal ganglia, thalamus, brainstem, internal capsule, and centrum semiovale. Although many lacunes are silent producing with no symptoms, those that do cause clinical symptoms tend to be located at strategic sites where descending and ascending long tracts to and from the cortex are concentrated. Lacunes produce five well-recognized syndromes: pure motor hemiparesis (65%), sensorimotor stroke (20%), ataxic hemiparesis (9%), pure sensory stroke (5%), and dysarthria-clumsy-hand syndrome (1%). Acute lacunes are best recognized as small round lesions on magnetic resonance imaging (MRI) diffusion-weighted images. Older lacunes appear as hypointense small round cystic circles on T1-weighted MRI and must be distinguished from benign similar appearing vessels surrounded by a dilated Virchow–Robin space.

Lacunes are caused by arteriole microvascular occlusion of a single deep perforating artery less than 200 μ in diameter. The arterial pathology shows arteriolosclerotic or lipohyalinosis changes characterized by a disorganized occluded vessel wall, which has been replaced by connective tissue and surrounding macrophages. The predisposing factors for lacunes are unclear but advancing age and hypertension are the best recognized. The prognosis for good recovery is better than for major artery ischemic strokes. The rate of developing subsequent lacunes is 5% per year.

The mechanism of natural stroke recovery is incompletely understood. Possible mechanisms for motor recovery include: early recovery of motor neuronal excitability as blood flow increases; and later, (1) activation of partially spared corticospinal tract pathways; (2) alternate behavioral strategies to use limbs; (3) expansion or neuroplasticity of functional motor cortex within its existing normal domain; and (4) neuroplasticity of motor cortex within a new brain area. There is increasing evidence that the motor cortex is not fixed but plastic and can expand or shrink within the existing site based on clinical demand and can even move motor function to remote sites. However, movement of the motor cortex to a different gyrus likely occurs only in young children.

Major Clinical Features

Onset is sudden or the patient awakens from sleep with the completed stroke but rarely the stroke signs can progress over 1–2 days. Table 9.3 lists the common clinical features of lacunar, anterior circulation, and posterior circulation strokes while Fig. 9.4a, b show the location and distribution of the major arteries. Most cortical strokes are symptomatic but only one-third of lacunes are symptomatic. Overall in cortical ischemic strokes, the hemiparesis is severe in 60%, moderate in 20%, and mild in 20%. Broca's aphasia is more common than Wernicke's aphasia but in large left middle cerebral artery strokes, a global aphasia will be present (see Chap. 11 on disorders of higher cognitive function).

Major Laboratory Findings

Tests are performed to diagnose a stroke, identify its location and determine the cause and source. Computed tomography (CT) scans are excellent to detect a hemorrhagic stroke but often appear normal for 6 to 24 h following an acute ischemic stroke. Subtle effacement (loss of boundaries) of sulci is the earliest sign followed by development of a hypodense region due to development of cytotoxic and vasogenic edema. In general, the larger the stroke the earlier it becomes visible on neuroimaging. MRI is the most sensitive neuroimaging method to detect an ischemic stroke. While conventional MRI may appear normal for several hours, diffusion-weighted MRI will show an area of hyperintensity in the territory of the infarct within 4 h. Diffusion-weighted MRI scans are helpful to distinguish an acute stroke from older strokes that are not hyperintense. Within 8 h, edema from the infarction appears hyperintense on T2-weighted images and hypointense on T1-weighted images. MRI is sensitive for small lacunes and infarctions in the brainstem and cerebellum that may be missed by CT. In a patient with a lacunar stroke it is common to identify other older lacunes that were clinically silent.

Several tests are used to determine the cause of the stroke. Imaging of the extra- and intracranial vessels is done with either magnetic resonance angiography (MRA) or CT angiography (CTA) and can identify medium to large diameter stenotic or occluded arteries in the neck and head. Extracranial Doppler ultrasonography examination of the carotid artery in the neck also detects narrow or occluded vessels. Transthoracic or transesophageal echocardiogram can detect clots or masses within the heart, vegetations on heart valves, immobile cardiac wall segments, and cardiomegaly that point to a cardioembolic source. Cerebrospinal fluid (CSF) examination is seldom necessary but abnormal CSF can indicate a vasculitis or meningitis and CSF culture may determine the cause of the meningitis. A variety of blood tests can look for a coagulopathy or vasculopathy (see transient ischemia attack section for details).

Table 9.3 Clinical features of common strokes

Arterial territory of stroke	Clinical presentation[a]
Left middle cerebral artery (mid frontal and parietal lobes)	Aphasia, contralateral hemiparesis, contralateral hemisensory loss, homonymous hemianopia, dysphagia
Right middle cerebral artery (mid frontal and parietal lobe)	Contralateral hemiparesis, contralateral hemisensory loss, homonymous hemianopia, dysphagia, apraxia
Anterior cerebral artery (frontal pole and medial aspect of frontal and parietal lobes)	Contralateral leg weakness and sensory loss
Vertebral/basilar artery	
Wallenberg's syndrome from posterior inferior cerebellar artery (medulla and cerebellum)	Vertigo, nystagmus, dysphagia and dysarthria with ipsilateral Horner's (miosis, ptosis, and diminished sweating on face) diminished facial pain and temperature perception, limb ataxia and contralateral loss of trunk and limb pain and temperature
Mid basilar artery (pons and cerebellum)	Often involves bilateral branches producing signs that include facial weakness, quadraparesis, dysarthria, dysphagia, vertical and horizontal nystagmus, ptosis, skew deviation of vision, limb ataxia, and diminished level of consciousness Locked-in syndrome occasionally develops with complete loss of voluntary limb and face movement, retained consciousness and voluntary vertical eye movements
Top of basilar artery (midbrain, occipital lobes and temporal lobes)	Involves midbrain and posterior cerebral arteries producing disruption of voluntary vertical gaze, third nerve palsies, ataxia, somnolence, homonymous hemianopia or quadrantopia, and occasionally loss of recent memory
Lacunar stroke territory	
Internal capsule	Contralateral hemiparesis, hemisensory loss without aphasia or visual loss
Upper half brainstem/cerebellum	Combinations of ataxia, vertigo, diplopia, dysarthria, Horner's sign, contralateral sensory loss, ipsilateral facial weakness, ipsilateral facial sensory loss
Lower half brainstem	Contralateral hemiparesis without sensory loss (pure motor stroke)

[a] Clinical features may be less than described due to the arterial occlusion being only a branch and not the entire artery or there is good collateral circulation minimizing the size of the infarction

Principles of Management and Prognosis

Treatment goals of the acute ischemic stroke are to (1) minimize the size of the stroke, (2) maximize the extent of functional recovery, and (3) minimize the risk of subsequent strokes.

Patients with moderate to severe strokes require immediate hospitalization and monitoring, often in an intensive care unit. Myocardial injury associated with an acute stroke develops in 15% and occasionally leads to systemic hypotension, serious cardiac arrhythmias such as atrial fibrillation, and ventricular myocardial wall motion abnormalities with subsequent creation and discharge of new cardiac emboli. However, minor changes in the electrocardiogram (EKG) are common and often called "reversible stunned myocardium," presumably due to sympathetic relative hyperactivity and catecholamine release caused by the stroke.

Management of hypertension is controversial but the blood pressure should be lowered if the initial systolic blood pressure is very high (systolic >220 mm Hg or diastolic >105 mm Hg) or (>185 mm Hg/110 mm Hg if thrombolytics were given). In general, blood pressures up to 185 mm Hg systolic are not lowered by antihypertensives as studies demonstrated lowering moderate hypertension did not benefit outcome measures. Severe hypotension is detrimental as it lowers the cerebral perfusion pressure and should be corrected. Pulmonary complications including low pulse oximetry, secondary pneumonias, and pulmonary emboli develop in 20% during the

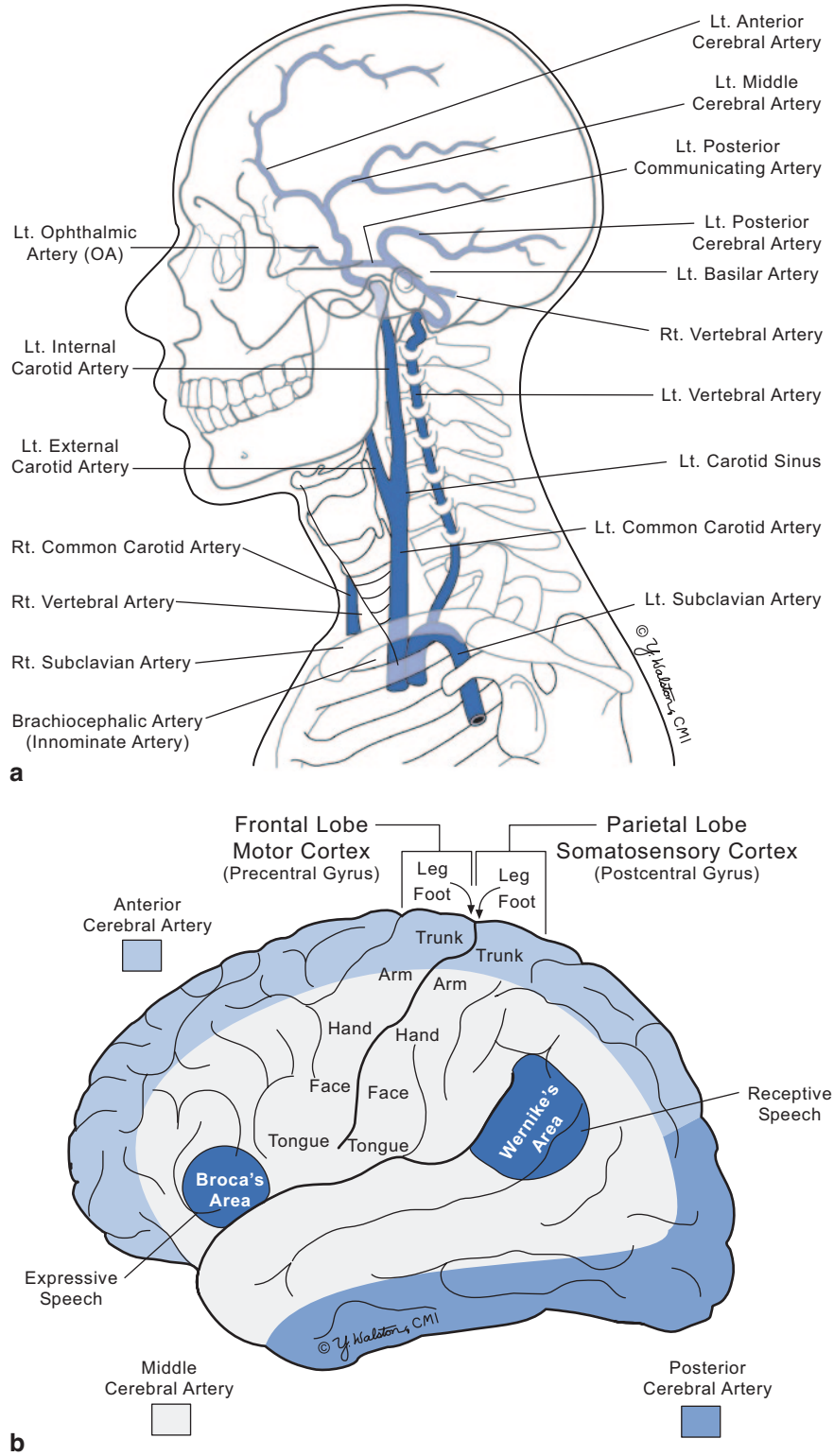

Fig. 9.4 Arterial supply of the brain. **a** Major vessels **b** Vascular territories

first week after a stroke and should be treated. Fever at the time of the acute stroke has a worse outcome but lowering the body temperature safely is difficult and currently not recommended. Patients with hyperglycemia at the time of the acute stroke are recognized to have poorer outcomes than normoglycemic patients, but studies to date have not demonstrated clear benefit from lowering the blood glucose with insulin.

Intravenous recombinant tissue plasminogen activator (rt-PA) alteplase is beneficial if given within 4.5 h of onset of the acute ischemic stroke in selected patients. The earlier the intravenous rt-PA is administered, the greater the benefit. The benefits are in reducing long-term disability and being independent when evaluated at 3 months (but not immediately after rt-PA administration). The major risk factors for rt-PA administration are diagnosis error, large size stroke, hypertension, hyperglycemia, and age above 80 years. To receive rt-PA, patients must meet strict entry criteria including (1) absence of blood on a CT scan, (2) presence of a small to moderate sized stroke, (3) no history of recent myocardial infarction, gastrointestinal bleeding, surgery, or anticoagulation, (4) no bleeding abnormality or elevated prothrombin time by an elevated *international normalized ratio* (INR) usually from taking warfarin, and (5) reliable onset of stroke symptoms within 4.5 h of rt-PA dose. Even if the criteria are met, rt-PA administration carries a 6.5% risk of hemorrhagic transformation of the stroke that occasionally can worsen outcome. When following the above criteria, only about 10% of patients with acute ischemic strokes meet the eligibility criteria and are administered rt-PA.

Patients should begin rehabilitation as soon as they are physically and mentally able to participate. Patients with Broca's aphasia benefit from speech therapy first to improve communication by gesturing and later by speaking. Patients with motor weakness require training in transferring, dressing, standing, and eventually walking. Since 20% of patients develop venous thrombosis in the paretic leg, subcutaneous heparin should be administered until the patient begins ambulating. Most major strokes cause dysphagia of both liquids and solids. Frequently a nasogastric feeding tube or gastrostomy is needed to maintain adequate nutrition until spontaneous recovery of swallowing occurs up to 2 months later. Patients lacking a good cough reflex are at a risk for aspiration pneumonia.

Natural recovery from most strokes occurs over 3–6 months. In general 70% of motor recovery occurs in the first month and 90% occurs by 3 months. Recovery of speech is slower with 90% recovery by 6 months. In hemiparetic patients, 80% walk again, but only 10% regain full use of the paretic hand. Factors associated with a good recovery include young age, mild stroke severity, high level of consciousness, previous independence, living with a partner, high frequency of social contacts, and positive mood. The latter factors suggest that patient motivation is important in recovery. Prevention of subsequent strokes is covered in the subsection on transient ischemic attacks.

Transient Ischemic Attack

Introduction

A transient ischemic attack (TIA) has a new definition: *A brief episode of neurologic dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than 1 h and without evidence of acute infarction*. This definition replaces the old one: The sudden onset of monocular visual loss or focal neurologic symptoms that stem from one vascular territory and completely clear within 24 h. The new definition recognizes that most TIAs last around 20 min and clinical symptoms are rapidly cleared but the MRI may still demonstrate that the patient actually experienced a small ischemic stroke.

The incidence of TIAs varies between studies and is complicated by many patients failing to report a TIA to their physician or that when a patient does see a physician, the TIA is over and the physician must rely on the patient's history. When actual TIAs were evaluated by physicians during the episode, only two-thirds were actually diagnosed as a TIA with the others being diagnosed as migraine auras, trauma, seizures,

and psychological events such as an acute anxiety or panic attack. A reasonable estimate is that 250,000 TIAs annually occur in the USA.

The significance of a TIA lies not in the event but that a TIA portends a future stroke. The 90 day risk of stroke after a TIA has been reported as high as 17%. Studies report that one-third of patients who develop a subsequent stroke do so within the next 2–7 days. A TIA also elevates the risk of acute cardiac disease (myocardial infarction, unstable angina, or ventricular arrhythmia) in the next few months.

Several risk factors are independently associated with a stroke following the TIA: age over 60 years, hypertension, elevated serum cholesterol, atrial fibrillation, high-grade carotid stenosis, diabetes mellitus, smoking, neurologic signs lasting longer than 1 h, heavy alcohol use; and obesity (Table 9.2). Many risk factors can be rapidly modified so that a prompt evaluation for these factors is needed.

Pathophysiology

Although incompletely understood, a TIA likely results from brief occlusion of a cerebral or central retinal artery by a platelet embolus that lodges in the artery and then rapidly breaks up or by a transient event that alters circulation dynamics and perfusion through a tightly stenotic artery. By definition, diffusion-weighted MRI scans are normal and no evidence of an infarction is found at autopsy.

Major Clinical Features

TIAs symptomatically fall into three large arterial territories; (1) ophthalmic artery, (2) branches of internal carotid cerebral arteries, or (3) vertebrobasilar artery. Transient monocular blindness or *amaurosis fugax* results from transient occlusion of the ophthalmic artery. This produces a painless, brief (minutes) sudden loss of sight involving all or part of the visual field of one eye. The visual loss is commonly described as a curtain drawn upward or downward over one eye that persists for minutes and then the curtain slowly reversing itself to restore vision. Permanent loss of vision is rare. Fundoscopic examination of retina is usually normal, although, occasionally tiny cholesterol emboli from a carotid artery plaque may be seen. Patients should not have bilateral visual loss or see lights flickering in the eye when it is closed. The latter suggests a migraine aura or retinal tear.

TIAs involving the middle cerebral artery are the most common presentation because that artery has the highest blood flow. Patients commonly present with sudden, painless onset of contralateral limb weakness (hemiparesis or monoparesis), and partial loss of touch and temperature sensation in the involved limbs. If the middle cerebral artery in the dominant hemisphere is affected, patients often develop an expressive or occasionally global aphasia.

TIAs involving the vertebrobasilar system most commonly produce a combination of hemiparesis, vertigo, ataxia, diplopia, dysarthria, and blurred vision in both eyes but rarely cause isolated vertigo or loss of consciousness.

Workup of a patient with a TIA to establish the cause should be performed as rapidly as possible due to the increased risk of future stroke.

Major Laboratory Findings

An MRI with diffusion-weighted imaging can rule out an acute ischemic or hemorrhagic infarction or other mimics of TIA. The most common important arterial lesion is stenosis (70–99%) of the internal carotid artery at the bifurcation from the common carotid artery on the side contralateral to the patient's symptoms. Dissection of the carotid arterial wall occasionally may be identified. The presence of atrial fibrillation or cardiomyopathy also carries a high risk for subsequent stroke. However, for many TIAs the cause is not found.

Principles of Management and Prognosis

Immediate management is to evaluate the patient for modifiable risk factors and improve them. The highest risk factors for subsequent stroke are the presence of cardiac thrombi, atrial fibrillation, or marked stenosis of the internal carotid artery. Thus immediate workup commonly involves an EKG looking for a myocardial infarction or atrial fibrillation. If there is a prior history of heart disease, a transthoracic echocardiogram looking for mural thrombi in the heart or valves or low ejection fraction of 20% or less is useful. There are several methods to evaluate the carotid artery for high-grade stenosis that include carotid duplex (current gold standard), magnetic resonance angiogram (MRA) of the head and neck, computed tomography angiogram (CTA) of the head and neck, and cerebral arteriogram. A stenosis of 70–99% identified on the symptomatic carotid artery should be considered for an elective and fairly rapid (within 2 weeks) carotid endarterectomy. In general, an elective surgical endarterectomy reduces the risk of a stroke over the next 5 years by 7%. However, there is an immediate risk of surgical complications that ranges from 3 to 6% even when performed by an experienced surgeon. Studies have shown that after the endarterectomy, failure to reduce modifiable stroke risk factors in the patient offers limited long-term benefit and a high rate of stenosis recurrence. In some patients, endovascular surgical placement of a carotid stent is being done but current outcome results are not superior to endarterectomy.

Reducing the blood pressure in patients with hypertension (systolic BP > 140 mm Hg or diastolic BP > 90 mm Hg) reduces the stroke risk by 30–40%. A number of other risk factors presented in Table 9.2 if found should be treated to lower risk of subsequent stroke. Lowering elevated blood, low-density lipoprotein cholesterol (LDL-C > 100 mg/dL) levels should be done. Patients should be encouraged to bring their weight down to the ideal level and to stop smoking. Evaluation for hypercoagulable state can be done by a series of blood tests in younger patients with stroke in whom no clear cause has been identified. Commonly ordered tests include screening for lupus anticoagulant, anticardiolipin antibodies, deficiency of proteins C and S, and antithrombin III and hemoglobin SS in African American patients. If atrial fibrillation is identified, patients should be considered for warfarin or the newer oral anticoagulant medications as these medications reduce the stroke risk by 40%.

Medical treatment for most patients involves administration of platelet aggregation inhibitors beginning with daily aspirin and advancing to clopidogrel or dipyridamole if the patient does not tolerate aspirin or continues to have TIAs. Use of daily low dose (80 mg) aspirin has been shown to reduce the risk of stroke by 20% in high-risk patients and 5% in the general population. Patients taking daily aspirin should not take Nonsteroidal antiinflammatory drugs (NSAIDs) more than twice a week as they interfere with the benefit of the aspirin.

Hemorrhagic Strokes

Overview

Intracranial hemorrhages occur in three intracranial spaces: intraparenchymal/ventricular, subarachnoid, and subdural/epidural. Subdural hematomas are discussed in the Chap. 18 on traumatic brain injury. The significance of blood in the subarachnoid space is not that it causes immediate clinical symptoms (headache, stiff neck, etc.) but that it often comes from a ruptured aneurysm that causes life-threatening parenchymal damage.

Spontaneous Intracerebral Hemorrhage

Introduction

Nontraumatic intracerebral hemorrhage (ICH) is bleeding into the brain parenchyma that may extend into the ventricles and rarely into the subarachnoid space. In the USA each year an estimated 45,000 people experience an ICH with an annual incidence of 15–20 cases per 100,000

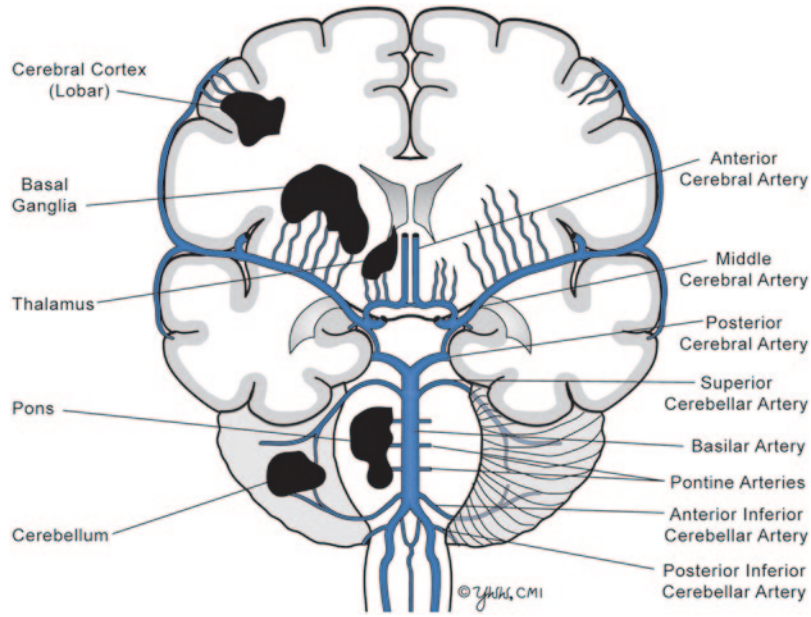

Fig. 9.5 Common sites of intracerebral hemorrhages

people. ICH is more common in men, African Americans and Japanese. Spontaneous intracerebral hemorrhages account for only 10% of all strokes but have the highest mortality rate.

Primary ICH represents 85% of cases. About 80% develop from spontaneous rupture of small arteries associated with hypertension and 20% from amyloid angiopathy. Secondary intracerebral hemorrhages occur from arteriovenous malformations, usage of sympathomimetic drugs such as methamphetamine, bleeding tumors, or impaired anticoagulation. Long-term anticoagulation results in a tenfold increase in risk of ICH and is becoming more common since anticoagulation is increasingly used in patients with atrial fibrillation.

Pathophysiology

Intracerebral hemorrhages (hematomas) most commonly occur in the cerebral lobes, basal ganglia, thalamus, pons and cerebellum (Fig. 9.3). The bleeding usually results from rupture of penetrating arteries originating from the basilar artery or the anterior, middle, or posterior cerebral artery. About 50% of ICH arise in the basal ganglia from lenticulostriate arteries and 10% occur in the thalamus (Fig. 9.5). However, smaller and subtle cerebral microbleeds resulting from leaky cortical and perforating vessels are being increasingly detected by MRI. Currently the cause of this vasculopathy is unclear.

The exact means by which ICH occurs is poorly understood but hypertension induces arteriosclerosis that results in fibroblast proliferation and deposition of lipids within the subintima of the artery. Involved arteries become both narrow and stiff as there is replacement of smooth muscle cells with collagen. These arteries then can either occlude causing infarction or tear causing a focal hemorrhage. In 10% of ICH small microaneurysms are found but for most patients no bleeding source is indentified.

Following vessel rupture, blood under arterial pressure rapidly flows into adjacent brain and often into ventricles. Intraventricular hemorrhage develops in almost half of patients with ICH. When blood enters ventricles, particularly the third ventricle, abrupt deterioration in consciousness develops. Clot formation often occurs which can lead to obstructive hydrocephalus and its consequences.

The cerebral bleeding often stops by tamponade within 30 min but CT studies show that 40% have expansion from the initial hemorrhage size.

In hemorrhages that expand, 75% have hematoma expansion within the first 6 h while the rest show expansion within the first 24 h. There is some evidence that slow bleeding from the ruptured vessel can continue for hours. The route of hematoma expansion is often along white matter tissue planes.

Red blood cell lysis occurs 6–8 days after the hemorrhage and is mediated by complement-activated membrane attack complexes. Release of hemoglobin and its byproducts are believed to be involved in neural toxicity. Macrophages invade the clot and phagocytose red blood cells and remove blood products over several months.

The surrounding compressed brain develops vasogenic edema from release and accumulation of osmotically active clot proteins and cytotoxic edema from compression of surrounding blood vessels producing secondary tissue ischemia. The edema begins in the first day, peaks in 5–7 days and persists for up to 2 weeks. Large areas of edema correlate with a poor outcome. Months later there is only a small cavity at the site of the original hemorrhage whose orange-stained walls contain hemosiderin-laden macrophages.

Cerebral amyloid angiopathy (CAA) is the second most common cause of ICH and develops mainly in adults over age 70 years. CAA affects primarily leptomeningeal and cortical vessels of neocortical regions, especially in the occipital cortex. CAA is uncommon in the thalamus, basal ganglia, and white matter, locations where hypertensive ICH commonly occurs. CAA is unrelated to a systemic disease but occurs from deposition of β-amyloid protein into the tunica media and adventitia of cortical arterioles and small arteries causing the vessel walls to initially thicken and then become thin from splitting of the arteriole walls. Some vessels develop fibrinoid necrosis and microaneurysms that are associated with hemorrhages. Vessels infiltrated with CAA can be histopathologically best seen with Congo-red, Thioflavin S, or anti-Aβ antibody stains.

As CAA vessels become more fragile, cortical lobar hemorrhages and microhemorrhages develop. In addition, amyloid deposition of vessels may initially thicken the walls predisposing to occlusions and microinfarctions that are commonly present. The source of the β-amyloid is unclear for CAA and the association with the amyloid plaques of Alzheimer's disease is uncertain and does not hold true for all patients.

Major Clinical Features

The most common hemorrhage locations are the putamen, thalamus, and caudate (60% of total). These patients may suddenly become aware of "something wrong" followed minutes later by progressive depression of consciousness, vomiting, headache, contralateral hemiparesis, and abnormal eye movements. Signs of a cerebral hemorrhage depend upon the lobe involved. When the hemorrhage invades the ventricles, patients rapidly developed a depressed level of consciousness. A cerebellar hemorrhage usually begins in the dentate nucleus with blood expansion into one cerebellar hemisphere producing headache, ipsilateral limb ataxia, vertigo, and vomiting without limb weakness. Patients with amyloid angiopathy often experience a lobar hemorrhage with signs depending on the lobe involved.

Major Laboratory Findings

The CT scan establishes the diagnosis by the presence of an acute ICH (Figs. 9.6 and 9.7). Secondary findings include surrounding cerebral edema, intraventricular hemorrhage, and findings of brain herniation (see Chap. 18 on traumatic brain injury and subdural hematoma for details). In 40%, repeat CT scans show expansion of the hematoma in the first 24 h. Cerebral angiography is occasionally needed to diagnose less common causes of ICH such as aneurysms, arteriovenous malformations, dural venous thromboses, and vasculitis.

Principles of Management and Prognosis

The goals of management are to improve survival from the acute hemorrhage, to identify the

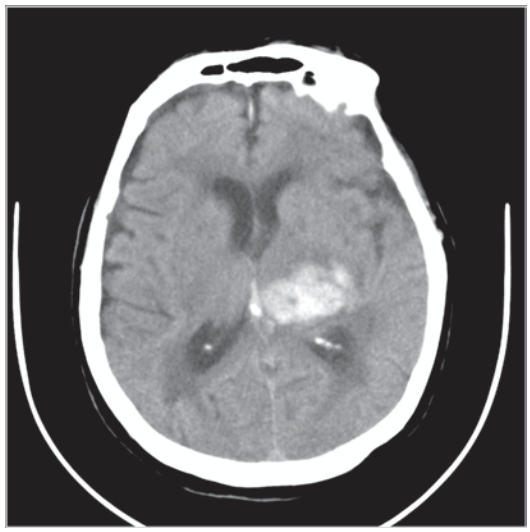

Fig. 9.6 Computed tomography (*CT*) scan of acute intracerebral hemorrhage in left thalamus due to hypertension. (Courtesy of Blaine Hart, MD)

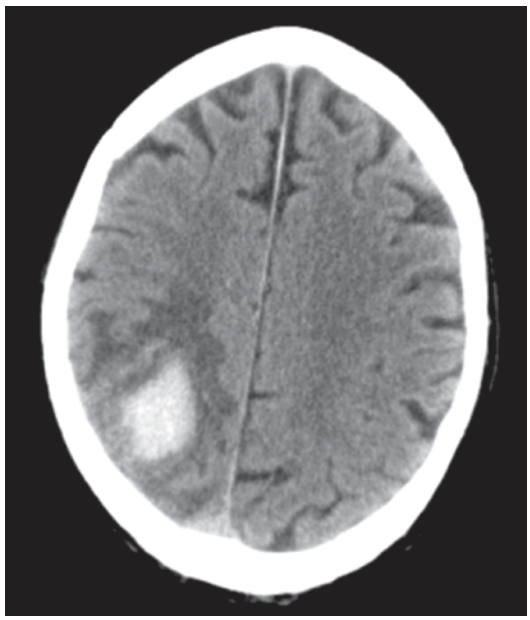

Fig. 9.7 Computed tomography (*CT*) scan of acute lobar intracerebral hemorrhage in right fronto-parietal lobe with surrounding vasogenic edema due to amyloid angiopathy in an 80-year old man. (Courtesy of Blaine Hart, MD)

etiology, and to prevent future bleeds. The acute management of an ICH is particularly challenging as the hemorrhage may cause transtentorial herniation. Patients often require early intubation and placement on a ventilator to control the airway, insure sufficient oxygenation, and to prevent tracheal aspiration. Frequent monitoring of vital signs and cardiac status are needed as patients often deteriorate in the first 24 h. Cardiac arrhythmias may develop that required treatment. Patients commonly have an elevated blood pressure when hospitalized. However, the optimal level of blood pressure is uncertain but very elevated systolic blood pressures above 220 mm Hg are usually reduced to less than 160/90 mm Hg. Hypotension always should be immediately corrected as it lowers intracerebral perfusion pressure.

Intravenous administration of recombinant factor VII (rFVIIa) has been tried to improve homeostasis and minimize hematoma expansion but is only considered in the setting of coagulopathy. Management of impending brain herniation is difficult. Mannitol or hypertonic saline is often tried but has not been very successful and corticosteroid administration is considered detrimental. Seizures develop in 15% during the first few weeks after hemorrhage. Patients require anticonvulsants as a generalized seizure raises intracranial pressure, which could increase the risk of brain herniation. However, prophylactic anticonvulsants are not currently recommended.

If the patient develops signs of brain herniation, repeat CT scans can determine if hematoma expansion or intraventricular hemorrhage occurred or there is obstructive hydrocephalus. Attempts to surgically remove the blood clot are controversial as limited evidence exists that surgery improves quality or duration of survival. However, a moderate to large (>3 cm) cerebellar hematoma is an exception and is a surgical emergency as removal of the hematoma carries a significant improvement in mortality and morbidity. Placement of a ventriculostomy or intraventricular shunt if hydrocephalus develops to remove ventricular blood does reduce intracranial pressure. Ventricular administration of rt-PA may be given to help break up ventricular clots that often block the shunt tubing.

Patients who survive the acute phase should be evaluated for the etiology of the bleed. This may require a cerebral arteriogram to diagnose an aneurysm or arteriovenous malformation and

MRI with gadolinium to identify a hemorrhagic tumor. Surgical removal of an arteriovenous malformation may be indicated if identified. Currently there is no easy method to diagnose cerebral amyloid angiopathy.

Rehabilitation of surviving patients aims at improving limb strength, gait, and speech. Control of the hypertension is essential. However, patients with a hypertensive hemorrhage seldom experience a second hemorrhage. Prevention of rebleeding in patients with amyloid angiopathy is presently impossible and patients have a recurrence rate of 10% per year. Rebleeding from arteriovenous malformations can occur at up to 18% chance per year.

Unfortunately, in over 25% of patients the mass from the blood clot and surrounding cerebral edema produces immensely increased intracranial pressure leading to secondary brain herniation and death within hours to a few days. The overall 1-year survival rate from an ICH is 35% but only 20% of survivors are independent at 6 months. In small hemorrhages, however, neurologic sequelae may be less severe compared to a similar sized ischemic stroke because neuronal tissue was compressed by the hemorrhage and therefore less destroyed.

Saccular Aneurysms and Subarachnoid Hemorrhage (SAH)

Introduction

SAH is the presence of blood in the meninges and CSF. Head trauma, the leading cause of SAH, is discussed in Chap. 18 on traumatic brain injury and subdural hematoma. Excluding trauma, the annual incidence of spontaneous SAH is 10 cases per 100,000 and accounts for 3% of all strokes. Aneurysm SAH is uncommon in infants and children, has a mean age of onset in the sixth decade and is less common in the elderly. Thus, the average patient with aneurysmal SAH is considerably younger than the patient with an ischemic stroke. Women outnumber men with a ratio of 3:2, and African Americans outnumber Caucasians with a ratio of 2:1.

At least 85% of SAH is due to rupture of a saccular (berry) or fusiform aneurysm and account for 30,000 individuals per year in the USA. Saccular aneurysms are outpouchings of midsized cerebral blood vessels while fusiform aneurysm are dilated elongated segments of the vessel. Saccular aneurysms rupture much more often than fusiform aneurysms. The remaining causes of aneurysms include vasculitis, superficial arteriovenous malformations of the brain and spinal cord, and mycotic aneurysms due to septic emboli that weaken the wall of the occluded arteriole.

Major risk factors for rupture of an aneurysm include hypertension, smoking, heavy alcohol consumption, cocaine, and a positive family history. Five percent of patients with SAH have a positive family history and first-degree relatives have a fivefold risk of SAH.

Pathophysiology

Autopsy studies estimate the prevalence of unruptured saccular aneurysms at 2%—with 30% of these patients having multiple aneurysms. The location of saccular aneurysms is mainly at the bifurcation of larger vessels or at sites where disturbances of blood flow are generated (Fig. 9.8). About 90% of aneurysms develop in anterior cerebral arteries that are branches of anterior part of the circle of Willis and 10% from posterior cerebral arteries that are branches of the vertebral arteries. The most common aneurysm locations are anterior communicating artery (40%), posterior communicating artery (20%), and bifurcation of the middle cerebral artery (15%). Except for a few hereditary diseases, patients with cerebral aneurysms do not have systemic aneurysms.

The pathophysiology by which saccular aneurysms develop is incompletely understood. Current evidence suggests the aneurysm is not congenital but develops into a mature aneurysm in adulthood since children seldom experience a ruptured aneurysm and autopsy studies of infants and children rarely find aneurysms. The origin of the aneurysm is just distal to a bifurcation where wall shear forces are high. The aneurysm wall is

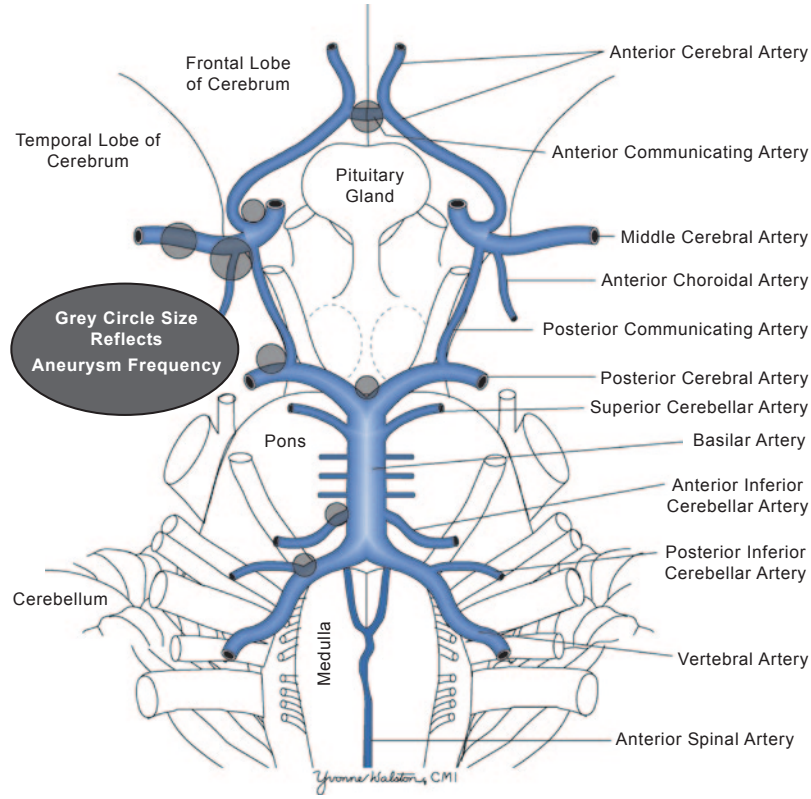

Fig. 9.8 Distribution of saccular aneurysms

characterized by reduction of collagenous fibers, atrophy of tunica media, and loss of internal elastic lamina in addition to the expected absence of external elastic lamina. The histologic appearance of the artery wall before and after the aneurysm is normal. The role of genetic factors in the pathogenesis is unclear.

The risk of bleeding from an aneurysm increases considerably by the size of the aneurysm. In general, the annual risk of rupture of a previously unruptured berry aneurysm is <0.5% for those less than 7–10 mm diameter, 1–3% for 10–24 mm diameter, and 8% for those larger than 24 mm. Patients with multiple aneurysms also are at higher risk of rupture.

Vasospasm often develops in arteries that are surrounded by collections of clotted subarachnoid blood producing narrowing of the lumen secondary to direct effect of blood on the adventitia. The distal cerebral ischemia territory may become infarcted if there is lack of sufficient blood supply from the parent artery and insufficient collateral blood flow. Arteries in chronic vasospasm can develop necrotic smooth muscle in the media with neutrophils infiltrating the adventitia.

Major Clinical Features

At the rupture of an aneurysm, arterial blood under high pressure flows in the subarachnoid space. The aneurysm rupture usually occurs when the patient is awake and not sleeping. The patient usually develops a sudden explosive headache, the cardinal feature, within seconds of a rupture. Patients may rapidly become unconscious but usually present to the emergency room with a severe headache, stiff neck, relative preservation of consciousness, and few or no localizing neurologic signs. However, in patients presenting to an emergency room with a severe sudden onset headache, less than 10% prove to have a SAH with the other 90% due to a migraine headache or meningitis. Vomiting is a presenting symptom

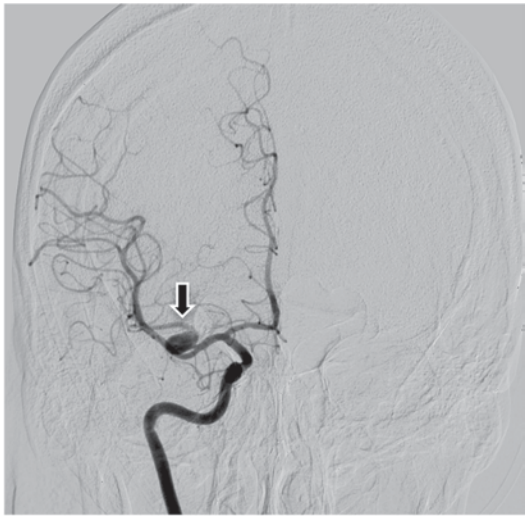

Fig. 9.9 : Cerebral angiogram of right carotid showing right middle cerebral artery saccular aneurysm (*arrow*). (Courtesy of Blaine Hart, MD)

in 70% of patients. Since the blood is in the subarachnoid space, the patient initially may have no focal neurologic signs or develop cranial nerve palsies including dilated pupils, disconjugate gaze, facial weakness, dysphagia, and dysarthria. Seizures occur in 10% of patients. Subhyloid intraocular hemorrhages develop in 15%. These hemorrhages are caused by a sustained increase in CSF pressure, with obstruction of the central retinal vein as it traverses the optic nerve sheath. Linear streaks of blood called flame-shaped hemorrhages appear in the preretinal or subhyloid layer usually near the optic disk.

Vasospasm commonly develops 5 to 15 days later producing a variety of focal neurologic signs that include hemiparesis, aphasia, and other neurologic signs depending on the artery in spasm. These signs develop from severe ischemia in the involved cerebral territory that may lead to infarctions.

Severe obstructive hydrocephalus often follows a SAH in about 15% from obstruction of cerebral CSF pathways and may require CSF shunting if it does not spontaneously subside. Occasional giant and fusiform aneurysms produce neurologic deficits by mass effect and may cause a third nerve palsy or other cranial nerve deficits (Fig. 9.9).

Major Laboratory Findings

The diagnosis of SAH is best made by CT, which is widely available, rapidly performed even in a restless patient, and identifies blood in the subarachnoid space over 90% of the time. The characteristic hyperdense appearance of extravasated blood in the basal cisterns is the most common finding (Fig. 9.10). Collections of extravasated blood elsewhere may suggest the site of the bleeding aneurysm. In 30% of patients, there is also an intraparenchymal hematoma due to rupture of the aneurysm directly into the brain.

CT best detects bloody CSF when there is a RBC concentration of greater than 0.5%. A lumbar puncture will detect fresh blood in the CSF as early as 1/2 h after the bleed and the early cell count shows the same number of RBCs in every tube. Centrifugation of the blood and comparison of supernatant color with water against a white background is similar. The CSF pressure is usually elevated. A lumbar puncture (LP) done after 8 h should show xanthochromia (yellow color) of the CSF supernatant establishing the diagnosis of SAH.

Several methods exist to identify the location of the aneurysm and whether other aneurysms coexist. The gold standard is four-vessel catheter angiography as it gives the best view of the aneurysm shape. However, an angiogram is time consuming, difficult to perform on a sick patient, and carries a complication rate of rebleeding in 2–5%. CTA using contrast media is becoming popular because it is faster, safer, and has a sensitivity of 95% for aneurysm greater than 4 mm. Because MR angiography is slower, technique dependent, and difficult to perform in a patient on a ventilator, it is less helpful.

Principles of Management and Prognosis

The goal is to maximize the quality of survival from the acute SAH, minimize the vasospasm, and to eliminate the aneurysm, thus preventing rebleeding.

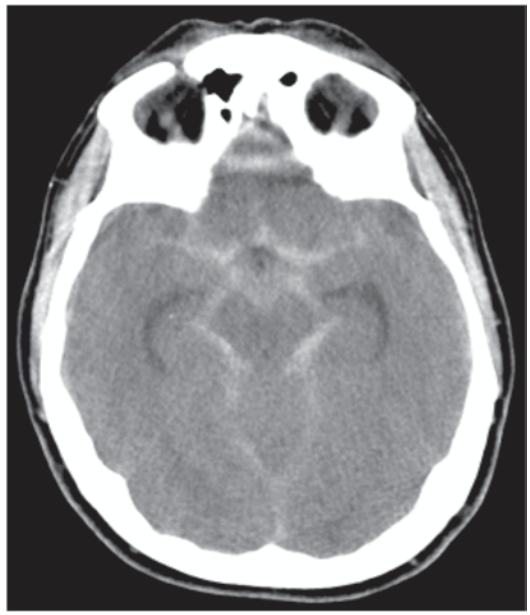

Fig. 9.10 Computed tomography (CT) scan of subarachnoid hemorrhage. (Courtesy of Blaine Hart, MD)

Table 9.4 General grading systems for ruptured saccular aneurysms. (Includes Hunt Hess and Botterell and Lougheed scales)

Grade	Clinical characteristics
1	Alert, minimal headache, slight neck stiffness and no neurologic deficit
2	Alert, moderate-severe headache, stiff neck, and no neurologic deficit other than cranial nerve palsy
3	Drowsiness, mild confusion with mild neurologic deficit
4	Semicoma, moderate-severe hemiparesis, possible early decerebrate rigidity
5	Deep coma, decerebrate rigidity, moribund

Patients are often classified as to severity and prognosis based on the Glasgow coma scale and other scales (Table 9.4). Patients should be placed in an intensive care unit as they often deteriorate during the first day. If mental status and breathing deteriorates, intubation and mechanical ventilation is required. The blood pressure should be carefully controlled. Pain should be controlled with narcotics.

Secondary cerebral ischemia from vasospasm develops in one-third of patients 5–15 days after bleed onset, may persist up to 2 weeks and can produce an infarction. Arterial vasospasm (reversible narrowing of a cerebral vessel) is often detected by CTA even in the absence of cerebral ischemia symptoms. Nevertheless, to minimize the effects of vasospasm, daily administration of a calcium channel blocker, nimodipine, from bleeding onset produces a modest reduction in secondary ischemia and improves outcome.

Rebleeding from the aneurysm is a serious problem. Rebleeding within 24 h of initial bleed occurs in 15%. After survival of 1 day, one-third of patients will rebleed over the next 4 weeks with the daily risk of bleeding being 1–2%. The optimal treatment approach depends on the clinical status of the patient and location and shape of the aneurysm. Aneurysms come in several forms: balloon-like with a narrow stalk; broad stalk; or cylindrical with no stalk. The surgeon is often faced with a dilemma. Operating on a comatose patient with vasospasm is technically difficult and carries a considerable surgical risk of death. However, waiting 1–2 weeks for the vasospasm to reduce and the patient to clinically improve carries the increased risk of the aneurysm rebleeding. In recent years, endovascular techniques enable placement of a detachable spring coil into the aneurysm via an arterial catheter with the goal of tightly packing the aneurysm with coils, effectively closing off blood flow into the aneurysm and thus preventing its rupture. Because endovascular surgery does not require a craniotomy and can be performed on sicker patients, outcomes of endovascularly-coiled patients have had better outcomes than direct surgical clipping in these sicker patients.

Unfortunately, the prognosis of a ruptured saccular aneurysm remains poor. Overall, 50% survive the first 30 days. Of those that survive, another half experience a diminished quality of life and are left with considerable neurologic sequelae that may include cognitive impairment and anosmia. Poor prognostic signs include grades 4 or 5 on the aneurysm grading scales, scores of 3–6 on Glasgow coma scale, presence of intracerebral hematoma, development of hydrocephalus, and rebleeding.

With more patients undergoing a cranial CT or MRI for other indications, patients are being identified with asymptomatic aneurysms. The question then arises as to the risk of future rupture

and whether to electively occlude the aneurysm by craniotomy or arterial endoscopy. While the patient makes the final decision, most experts recommend for aneurysms less than 7–10 mm diameter, periodic CTA to follow the aneurysm and elective surgical clipping if aneurysm expands in size.

Video Legend

This video shows a 53 year-old woman s/p right middle cerebral artery stroke.

Segment 1: Cranial Nerve Exam
- Upper motor neuron facial weakness with lower face affected and normal strength in eyelid and forehead muscles.
- With a central lesion, weakness of trapezius but preserved ipsilateral sternocleidomastoid strength due to bilateral innervation.

Segment 2: Motor Exam
- Pyramidal weakness: upper extremity with extensor > flexor weakness
- Pyramidal weakness: lower extremity with flexor > extensor weakness

Segment 3: Sensory Exam
- Extinction to double simultaneous sensory stimulation
- Extinction to double simultaneous visual stimulation

Segment 4: Reflex Exam
- Hyperreflexia of left upper extremity with clonus at finger flexors
- Hoffman's reflex showing flexion of thumb with "flicking" the terminal phalanx of middle finger
- Spontaneous Babinski sign

Segment 5: Gait Exam
- Stiff hemiparetic gait with extension at knee and hip

Recommended Reading

Davis SM, Donnan GA. Secondary prevention after ischemic stroke or transient ischemic attack. N Eng J Med 2012;366:1914–22. (Current review of methods to prevent strokes)

Furie KL, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack. Stroke 2011;42:227–6. (Current excellent guidelines from American Heart Association/American Stroke Association)

Arboix A, Marti-Vilalta JL. Lacunar stroke. Expert Rev Neurother 1009;9:179–96. (Comprehensive review of lacunar strokes)

Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. Ann Neurol 2011;70:871–80. (Good review of a complicated topic)

Quereshi AI, Mendelow AD, Hanley DF. Intracranial haemorrhage. Lancet 2009;373:1632–44. (Comprehensive review)

van Gijn J, Kerr RS, Rinkel GJE. Subarachnoid haemorrhage. Lancet 2007;36:306–18. (Good review with focus on aneurysms)

Connolly ES Jr, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage. Stroke 2012;43:1711–37. (Current excellent guidelines from American Heart Association/American Stroke Association)

Disorders of Myelin

10

A 27 year-old female administrative assistant developed acute monocular decreased vision in her left eye three years ago that spontaneously cleared over 6 weeks. Last week she developed the onset of left arm and leg clumsiness, moderate weakness and mild numbness over one day. Her physician found she had had normal mental status and a left relative afferent pupillary defect (Marcus Gunn pupil). The patient's pupils constricted less (therefore appeared to dilate) when a bright light was swung from the unaffected eye to the affected eye. A left hemiparesis was present along with very brisk left-sided deep tendon reflexes and a left Babinski sign. A T2-weighted MRI demonstrated 1 cm hyperintense oval lesion perpendicular to the right lateral ventricle, which enhanced with gadolinium, as well as two 1 cm hypodense lesions in the left parietal and frontal lobe white matter on T-1 weighted images. Her CSF demonstrated 3 WBC/mm^3, normal glucose, protein of 50 mg/dL, and 4 oligoclonal bands not seen in the serum. A diagnosis of relapsing remitting multiple sclerosis was made.

Myelin

Overview

Myelin is produced in the peripheral nervous system (PNS) by Schwann cells and in the central nervous system (CNS) by oligodendrocytes. Both cells are embryologically derived from the neural crest. Each Schwann cell myelinates a single 1-mm segment of a PNS axon while each oligodendrocyte myelinates as many as 60 CNS axon segments. At birth, PNS myelination is almost complete but CNS myelination continues after birth for over a decade. In the PNS, loss of Schwann cells triggers regeneration of new Schwann cells, which then can remyelinate the demyelinated axon. PNS remyelination is characterized by shorter length intervals of myelin that have fewer whorls of compact myelin. Nevertheless, remyelination often results in return of normal nerve function. Remyelination can occur in the CNS but does so to a far lesser extent.

Myelin serves several important functions. A key function is to house axons and to provide for the axons hollow tubular channels of extracellular matrix. In the PNS, unmyelinated axons are surrounded by Schwann cell cytoplasm but in the CNS oligodendrocytes do not wrap around unmyelinated axons. Myelin provides physical strength to the axon. Myelin serves to insulate the axon from environmental toxins and prevents ephaptic transmission (direct axon-to-axon electrical transmission without a synapse). Myelin allows saltatory conduction (action potential moves down a myelinated nerve by jumping from node of Ranvier to node of Ranvier) increasing nerve conduction velocity as much as 100-fold. An unmyelinated peripheral sensory nerve has a conduction velocity of 0.5 to 1.0 m/s. A myelinated peripheral motor nerve conducts at 60–80 m/s. Myelination allows more efficient impulse propagation requiring less energy. As such, myelinated axons can conduct at much faster frequencies for longer periods of time than unmyelinated axons.

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Myelin contains about 70% lipid and 30% protein compared to normal cell membranes that have only about 40% lipid. Some myelin proteins, such as myelin basic protein, myelin-associated glycoprotein, and myelin oligodendrocyte glycoprotein, are specific to myelin, can become immunogenetic, and may be the target in immune-mediated myelin damage.

Demyelinating diseases occur when the disease process primarily involves myelin sheaths, Schwann cells, or oligodendrocytes—with relative sparing of the underlying axon. A disease process such as a stroke that destroys both myelin and axons is not considered a demyelinating disease. The disease process may involve CNS myelin, PNS myelin or both. Causes of demyelinating disease include genetic (hereditary sensory neuropathies such as Charcot–Marie–Tooth neuropathy), toxic (diphtheric polyneuropathy), infectious (progressive multifocal leukoencephalopathy), immune-mediated (neuromyelitis optica), and unknown (multiple sclerosis).

There are four major mechanisms of demyelination: (1) death of oligodendrocyte or Schwann cell, (2) interference with myelin synthesis, (3) interference with myelin turnover, and (4) immune-mediated destruction of myelin.

Signs and symptoms of demyelination are due to dysfunction of the underlying axon. In general, the longer the myelinated nerve tract, the greater the probably that a demyelinating disease will disrupt its function. In the CNS, tracts commonly involved include the corticospinal tract (weakness, spasticity), spinothalamic tract (sensory loss), visual pathway (visual disturbance), and spinocerebellar pathways (ataxia). Of note, demyelinating diseases seldom produce the signs of gray matter disease, such as early dementia, aphasia, Parkinsonism, or seizures. In the PNS, motor and sensory (vibration sense)-myelinated nerves are often mildly involved. Similarly, the sensation of pain and temperature (unmyelinated axons) are seldom impaired. In general, genetic and toxic causes of demyelination usually produce symmetrical signs while immune-mediated and infectious causes of demyelination are asymmetrical.

Multiple Sclerosis

Introduction

Multiple sclerosis (MS) is an enigmatic, relapsing, and eventually a progressive disorder of CNS myelin. The classical definition of MS requires dissemination of CNS white matter lesions in time (multiple attacks) and space (involving different areas of CNS white matter). There is a female predominance of about 2:1. The disease usually begins in the third decade of life and is uncommon in children. About 3 million people are living with MS worldwide. In the USA, over 400,000 adults have the disorder with an estimated 200 new diagnoses each week. However, the prevalence varies widely from less than 1/100,000 to 30–80/100,000 adults around the world with higher prevalences occurring the further north or south one lives from the Equator. There is an unexplained familial aggregation of MS with monozygotic twins both developing MS in 34% but only in 4% if they are dizygotic twins.

Pathophysiology

The pathologic hallmark of MS, the demyelinated plaque, consists of a well-demarcated hypocellular area characterized by the loss of myelin, relative preservation of axons, and the formation of astrocytic, glial scars (Fig. 10.1). The mature lesions are usually oval and have a small- or medium-sized blood vessel near the center. Inflammatory cells (mainly B lymphocytes and macrophages) are typically perivascular in location, but also infiltrate the lesion. The pathogenesis of a MS lesion remains controversial. Many studies support a role for CD4+ T cells intermittently attacking the myelin sheath as the initiating event. However, other studies of very early MS lesions have reported that the initial myelin destruction develops from IgG+ macrophages interacting with complement-positive myelin via clathrin-mediated endocytosis in tissue depleted of oligodendrocytes. Prineas argues that the macrophage and microglial activity is best explained as a

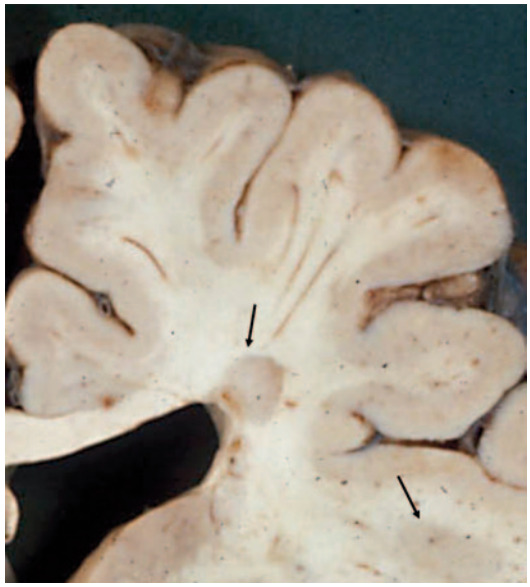

Fig 10.1 Pathologic specimen showing MS plaques (*arrows*) (Courtesy of Mario Kornfeld, MD)

scavenging reaction to the presence of dead myelin resulting from a loss of oligodendrocytes. However, what kills the oligodendrocytes remains unknown. Partial remyelination can subsequently develop called shadow plaques adjacent to the main plaque. New oligodendrocytes from dividing oligodendrocyte precursor cells produce short length thin new myelin segments but the new oligodendrocytes fail to invade the main demyelinated plaque to produce remyelination.

The main physiologic effect of demyelination is to impede saltatory electrical conduction of nerve impulses jumping from one node of Ranvier where sodium channels are concentrated to the next node. Normally, there are only rare sodium channels along the myelinated axon, so conduction does not proceed in the demyelinated axonal segment. Clinical recovery of the lost function develops because new sodium channels appear along the length of the demyelinated

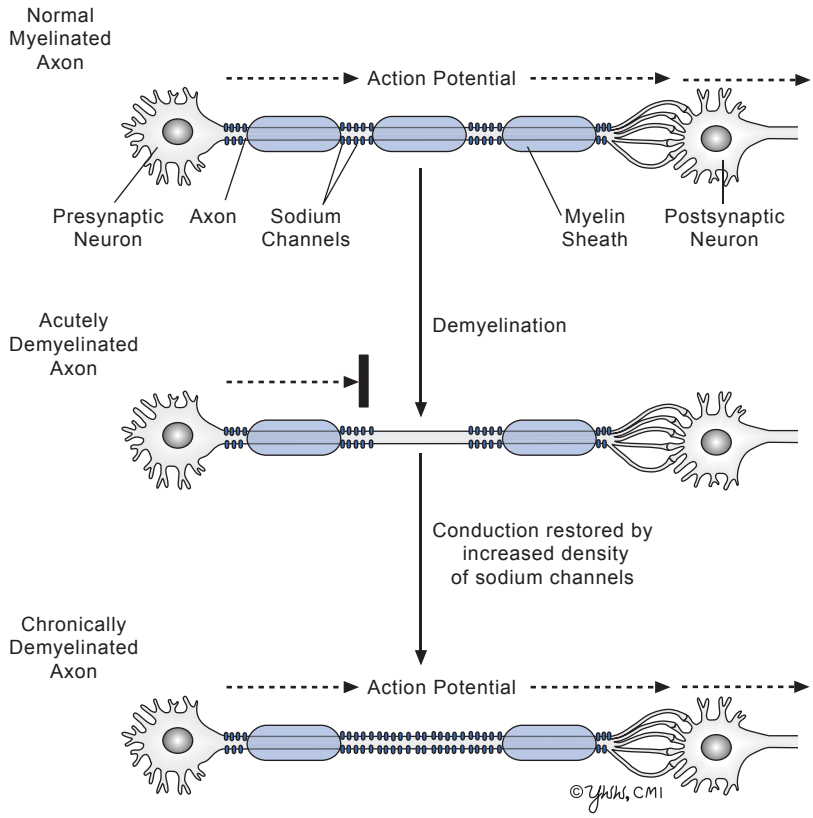

Fig 10.2 Axonal changes in acute and chronic demyelination

axon allowing continuous conduction to occur (Fig. 10.2). While the conduction velocity of the electrical signal becomes slower in the axon, the signal connects to its intended target allowing function to return. The functioning of the naked axon segment is sensitive to body temperature elevations as low as 0.5 °C, which results in conduction blockage. This accounts why patients often get a transient return of the symptoms when they develop a fever.

Over time, usually years, the plaque changes character. The relative abundance of naked axons disappears and marked gliosis develops, producing patches of hardened translucent tissue distributed randomly throughout the CNS neuroaxis along with secondary atrophy of the brain.

Plaques may occur anywhere in the CNS but not in the PNS. Common locations for plaques include the white matter of optic nerves, and white matter adjacent to lateral ventricles, corpus callosum, brainstem, cerebellum, and spinal cord. Lesions involve both hemispheres and distribute asymmetrically. Recent studies suggest that there may be several pathological forms of MS. The most common forms (>90%) appear to have primary damage to foci CNS myelin while the less common forms appear to have slower primary killing the oligodendrocytes without much inflammation and have a clinical history suggestive of primary progressive MS.

The cause of MS remains mysterious. Extensive searches for an infectious agent, specific myelin antigen, or genetic cause have yet to identify a likely etiology. Nevertheless, CD4 immune lymphocytes appear to play a role in the pathogenesis since most of the successful drugs to prevent MS attacks impair T cell functions.

Major Clinical Features

The clinical features and rate of MS progression vary considerably from patient to patient. Neuroimaging has shown that plaques often appear without producing clinical signs, suggesting that the demyelination does not stop axon conduction through the plaque, the plaque is in a silent brain area, or that there are alternate conduction pathways that maintain functional connectivity. In the early phase of MS, clinically apparent attacks develop about 0.3 times a year. The onset occurs over 1–3 days and does not have an identifiable trigger. Common clinical signs occur from damage to long CNS myelinated tracts. Thus, MS patients often develop hemiparesis or monoparesis (corticospinal tract), unilateral visual loss (optic nerve), sensory loss (posterior columns or spinothalamic tracts), ataxia (cerebellum or cerebellar pathways), and neurogenic bladder or paraparesis(spinal cord). Dementia, aphasia, and seizures (signs of grey matter disease) are uncommon.

Spontaneous clinical return of function usually occurs within a month. In the relapsing remitting form of MS, good or full return of function prevails but over time, attacks may leave some permanent dysfunction (Fig. 10.3). Return of clinical function occurs when the demyelinated portion of the axon converts from permitting only saltatory conduction to an axon segment that has continuous conduction (Fig. 10.3). Permanent loss of function is associated with loss of the underlying axons.

Major Laboratory Findings

There is no specific diagnostic test for multiple sclerosis. However, there are characteristic cerebrospinal fluid (CSF) changes that occur in most patients. The CSF usually shows a mild increase in total protein, an increased IgG synthesis rate (IgG index) and several oligoclonal bands seen in CSF but not blood. This indicates migration of B lymphocytes and plasmacytes from blood to brain plaques with subsequent local homogenous antibody production that then leaks into CSF. It is not known what antigen the MS antibody is directed against. The CSF may contain a small number of lymphocytes but should have a normal glucose level. Routine blood tests are normal.

MRI scans are sensitive, but not specific, indicators for myelin plaques. T2-weighted MRI lesions reflect inflammation, edema, demyelination, and gliosis. T1-weighted lesions ("black holes") often reflect marked axonal loss in the

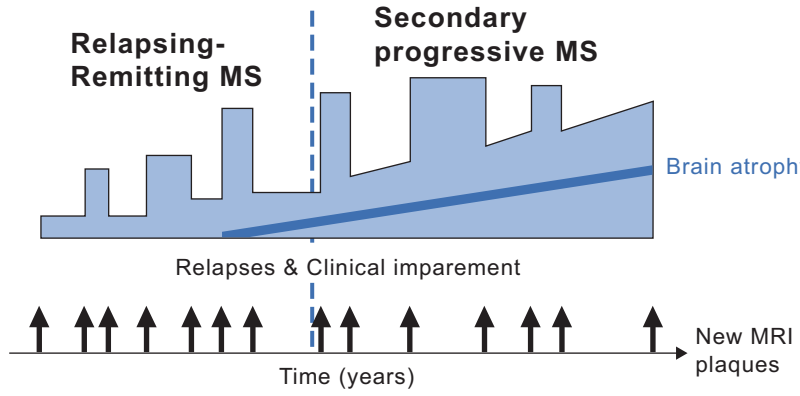

Fig 10.3 Natural history of MS

plaque (Fig. 10.4). Gadolinium-enhancing lesions on T1-weighted images suggest disruption in the blood–brain barrier from active inflammation and demyelination that can persist up to several months. Neuroimaging lesions are commonly seen as perpendicular ovals in the white matter around the lateral ventricles, corpus callosum, cerebellum, and spinal cord, and correlate with plaques found at autopsy.

MS is a clinical diagnosis with laboratory support. The definition of MS requires dissemination of CNS white matter lesions in time (multiple attacks) and space (involving different areas of CNS white matter). Since the advent of MRI neuroimaging, it is now possible to make the diagnosis after the first clinical attack (clinically isolated syndrome) by identifying more than one lesion at 2 or more characteristic sites in brain and finding a new MRI plaque on a follow-up MRI anytime afterwards. The clinical and neuroimaging diagnosis is supported by the presence of CSF oligoclonal bands and increased IgG synthesis. No other diagnosis for the clinical signs should be apparent such as neuromyelitis optica, CNS vasculitis, and systemic lupus erythematosus.

Principles of Management and Prognosis

Treatment of MS is divided into treatment of acute exacerbations, rehabilitation of the patient, and prevention of future plaques. Acute relapses are often treated with short courses of high-dose

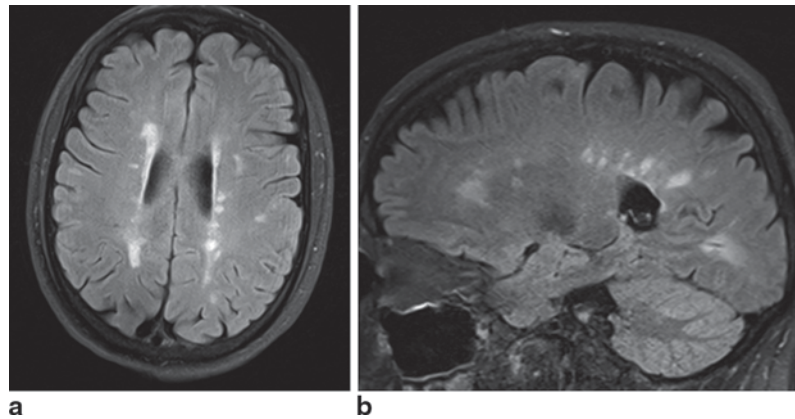

Fig 10.4 T2 FLAIR MRI scans in 35-year-old woman with MS showing **a** in axial view, bright lesions adjacent to the ventricles and **b** in sagittal view, bright lesions in corpus collosum (Courtesy of Blaine Hart, MD)

corticosteroids (IV methylprednisolone or oral prednisone). While spontaneous clinical recovery usually takes about 4 weeks, these drugs appear to shorten the time to recovery by 1–2 weeks. However, steroids do not improve the extent of recovery or change the course of disease. Chronic treatment with steroids has not been shown to prevent subsequent relapses.

There are several standard drugs that have proven efficacy in reducing the frequency of new lesions in relapsing remitting MS. Interferon beta-1b, interferon beta-1a, and glatiramer acetate all reduce the frequency of relapses by about 30%. Serial neuroimaging studies show these drugs reduce new T2-weighted lesions by about 60%. These drugs have shown some effect in delaying progression of disability. The mechanisms by which interferon and glatiramer acetate work are uncertain but studies suggest the drugs affect the immune-mediated attack on the white matter. Both the interferons and glatiramer acetate require daily or weekly injections, have a moderate number of local and systemic side effects, and have some expensive (about $ 10,000/year). It is currently unknown how long these drugs should be taken.

In the past few years, new drugs have been FDA approved for MS and several additional ones are in the pipeline. Natalizumab is a humanized monoclonal antibody that antagonizes α4-integrin of the adhesion molecule very late activating antigen (VLA-4) on leukocytes. Inhibition of VLA-4 is responsible for blockade of T cells across the blood–brain barrier. This drug is administered intravenously every 4 weeks and appears more effective than the standard anti-MS drugs. There is a 50–60% reduction in relapses and a 90% reduction in gadolinium-enhancing lesion on MRI compared to placebo. Unfortunately, natalizumab carries a small risk that is associated with progressive multifocal leukoencephalopathy (PML) that is usually fatal in individuals.

Fingolimod is an orally administered immunomodulator that becomes phosphorylated to act on the sphingosine-1-phosphate (SIP) receptor. The SIP receptor is responsible for lymphocytes release from lymphoid organs and thus reduces both CD4+ and CD8+ T lymphocytes in the blood. The drug also crosses the blood–brain barrier and reaches SIP receptors on oligodendrocytes, astrocytes, microglia, and neurons and thus may also have a direct neuroprotective effect on the acute plaque. Fingolimod appears to be superior to the standard anti-MS drugs reducing the annualized relapse rate from 0.33 for interferon to 0.16. Similar reductions in gadolinium-enhancing plaques were also shown. This drug has considerable potential systemic side effects requiring special monitoring when the drug is started.

A recent FDA approved drug for MS is teriflunomide, a selective inhibitor of *de novo* pyrimidine synthesis, which exerts a cytostatic effect on proliferating T and B lymphocytes in the periphery. It is particularly efficient in inhibiting T-cell dependent antibody production. In MS trials, the drug reduced the annualized relapse rate to 0.34 compared to 0.54 in the placebo group.

All new FDA-approved drugs for MS have shown superior efficacy in preventing both clinical relapses and new gadolinium-enhancing lesions on MRI. However, the long-term adverse effects of these drugs are unknown and their potential adverse effects are of some concern. The new drugs are very expensive (wholesale price of fingolimod is $ 50,000/year) and require considerable additional laboratory tests when administered. As such, many clinicians are reserving the newer drugs for patients in which the standard anti-MS drugs fail.

Rehabilitation aims at maximizing patient functioning. Patients may become depressed requiring counseling and antidepressant medication. Fatigue becomes a problem and is difficult to treat. Bladder spasticity with urinary incontinence may develop requiring treatment. Ataxia and spasticity affect gait, balance, and coordination interfering with activities of daily living and are difficult to treat.

After 5–15 years, relapsing-remitting patients often develop a slowly progressive illness called secondary progressive MS (Fig. 10.3). These patients enter a phase of slow steady or mildly fluctuating deterioration of neurologic function that is often attributed to the continued loss of axons

in the existing plaques, to the increasing number of lesions, and to generalized brain atrophy. Over 30 years, about half of MS patients will develop sufficient ataxia or spasticity to require a wheelchair and the average life expectancy is shortened by several years. However, about 20 % of patients have a benign clinical course their entire life.

Neuromyelitis Optica or Devic's Disease

Introduction

Neuromyelitis optica (NMO) or Devic's disease was first described by Eugene Devic in 1894 and was thought to be a variant of multiple sclerosis. In 1988, ten water-channel proteins called aquaporins were discovered, and in 2004, it was discovered that circulating IgG1 antibodies against the astrocyte water channel aquaporin 4 (AQP4) were responsible for NMO. NMO is not nearly as common as MS and represents about 1 % of the acquired causes of demyelinating diseases. However, its prevalence is highest in individuals of East Asian, and Native American descent where they represent 20–40 % of acquired demyelinating diseases. NMO has a mean onset of 39 years, about a decade later than MS, and occurs much more common in women.

Pathophysiology

Aquaporin monomers consist of six helical, membrane spanning domains that assemble as tetramers across cell membranes to enable water to enter and exit the cell. AQP4 is strongly expressed in the CNS, especially in astrocytes. What triggers the host production of antibodies to AQP4 is unknown but circulating antibody can enter the CSF and bind to AQP4 channels mainly in astrocytes of the spinal cord and the optic nerve. After binding, a complement cascade is initiated producing complement-mediated damage to astrocytes. Neutrophils and eosinophils then enter the lesion site and subsequently destroy neighboring oligodendrocytes. Microglia and macrophages enter the lesion resulting in continued damage to the denuded axons often resulting in axonal degeneration and secondary neuronal death. Necrotizing and cavitating lesions in the spinal cord or optic nerve are common. Reactive astrocytes finally cause gliosis of the lesion with permanent nerve damage. Thus, NMO is not a primary demyelinating disease of the spinal cord and optic nerve but results from a cascade of events that follow AQP4 antibody attaching to astrocyte AQP4 channels.

Some patients also have coexisting autoimmune disorders such as systemic lupus erythematosus, Sjögren's syndrome, and myasthenia gravis.

Major Clinical Features

In 80 %, the optic neuritis is bilateral and often characterized by a central scotoma and pain on eye movement. The optic disks usually are of normal appearance. The second key feature is a complete transverse myelitis usually developing in the cervical or thoracic spinal cord. Patients commonly develop pain in the neck and Lhermitte's sign plus a spastic paraplegia or tetraplegia and neurogenic bladder. Ascending sensory loss with numbness, tingling, and a sensory level are common. The optic neuritis and transverse myelitis commonly develop within a year of each other. Although NMO patients may show MRI lesions in the lower brainstem and hypothalamus, they are usually asymptomatic. Over 75 % of patients have a relapsing course with 90 % experiencing relapses within three years. In a few patients, the cervical transverse myelitis can advance into the medulla producing severe and often fatal brainstem signs.

Major Laboratory Features

A variety of serum or CSF antibody tests to detect IgG antibody to aquaporin 4 (AQP4) exist with most tests having a sensitivity of at least 75 % and greater than 90 % specificity.

The cervical or thoracic MRI with contrast typically demonstrates a centrally placed lesion occupying more than half the cord area and in-

volving the grey matter (Fig. 10.5). Contiguous T2-hyperintense lesions span three or more vertebral segments longitudinally and are associated with cord edema and gadolinium enhancement on T1-weighted images.

CSF in the acute attack typically demonstrates a CSF pleocytosis of greater than 50 WBC/mm^3. Oligoclonal bands and increased IgG synthesis are rarely found, which distinguishes NMO from MS.

Since 2006, revised criteria for the diagnosis requires myelitis and optic neuritis and at least 2 of 3 supporting criteria: (1) laboratory evidence of serum AQP4-IgG1 antibodies, (2) MRI demonstrating contiguous spinal cord lesions extending over 3 segments, and (3) brain MRI non-diagnostic for multiple sclerosis. Supporting evidence includes the lack of CSF oligoclonal bands.

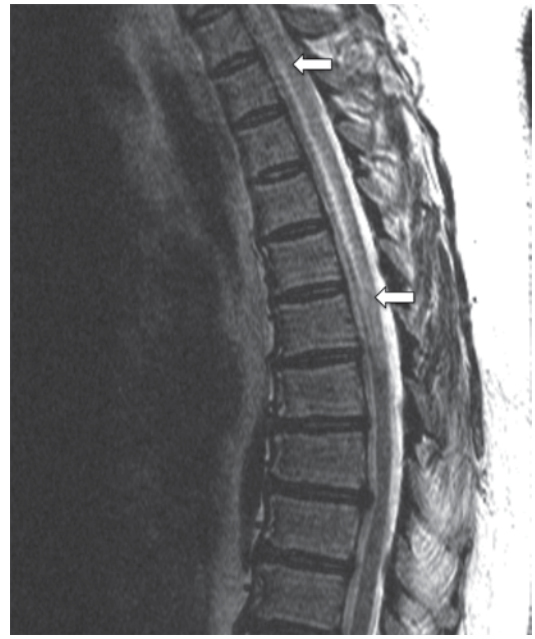

Fig 10.5 Sagittal T2 MRI of cervical and thoracic spine showing abnormal T2 (bright) signal extending for almost 5 vertebral levels (indicated by *white arrows*) in a 56-year-old woman with neuromyelitis optica (Courtesy of Blaine Hart, MD)

Principles of Management and Prognosis

First-line treatment for an acute attack is with high-dose corticosteroids. If patients do not respond, plasmapheresis is given. About 80% of patients show clinical improvement. To prevent relapses, chronic therapy has not been fully established but may include oral steroids plus azathioprine or mycophenolate mofetil. Some patients are now given rituximab, a monoclonal anti-CD 20 antibody, which eliminates pre-B and mature B lymphocytes and lowers the patient's titer to AQP4 antibodies. Standard multiple sclerosis drugs such as interferons and copaxone are not helpful.

Because the spinal cord and optic nerve damage is often permanent, recovery is limited.

Guillain–Barré Syndrome

Introduction

Guillain–Barré syndrome (GBS) is an acute monophasic disease involving only myelinated nerves in the peripheral nervous system. With the dramatic decline in paralytic poliomyelitis following the introduction of the polio vaccine, GBS has become the major cause of acute neuromuscular paralysis. The annual incidence of GBS in the USA and Europe is about 1–2 cases per 100,000 persons. GBS can affect all ages but the incidence increases with advancing age. Males slightly predominate. Patients with partial immunosuppression are at an increased risk for GBS.

The most common form (>90% in the USA) called acute inflammatory demyelinating polyneuropathy (AIDP) appears to be due to an immune-mediated attack of peripheral myelin. Acute motor axonal neuropathy (AMAN) is clinically more common (30%) in Asia and South America.

Pathophysiology

GBS occurs in the setting of an antecedent illness in about 60% of patients. Upper respiratory and

gastroenterologic infections are frequent with the most common being viruses (cytomegalovirus, Epstein–Barr, and human immunodeficiency virus) and bacteria (*Campylobacter jejuni*). It is proposed that via molecular mimicry, the patient develops an immune response against the infecting agent that cross-reacts with antigens on the patient's peripheral nerve myelin or axons.

In AIDP, the nerve damage results from lymphocytic immune responses against peripheral nerve myelin. What initiates the episode is unclear but antibodies against myelin that have been poorly identified may initiate the entire event. The pathology shows patchy lymphocytic infiltrates, particularly around venules and capillaries within the endoneurium, and macrophages around the myelinated nerves. Hematogenous macrophages adhere to nerve fibers where they penetrate the Schwann cell basal lamina extending processes that amputate myelin lamellae and the "strip" myelin away from the axon. This process produces segmental demyelination. The most heavily affected part of the nerve is the proximal root. Multiple peripheral nerves are involved in a uniform and generally symmetrical fashion. Clinical recovery begins weeks later when the demyelination stimulates abundant Schwann cell proliferation with subsequent remyelination of the naked axonal segment. Remyelination produces short-length myelin segments that are thinner than the original myelin.

In AMAN, antibodies (especially those associated with *Campylobacter jejuni* infection) appear to attack axon antigens located at the internodal axolemma. The most commonly identified antibodies are against gangliosides, particularly against GM1, GM1b, GD1a, and GalNac-GD1a antigens. Current evidence points to an anti-ganglioside antibody attack at the node of Ranvier axolemma leading to a membrane attack complex with complement causing detachment of paranodal myelin followed by macrophage invasion to clear the myelin sheath. Axonal degeneration may also occur leading to Wallerian degeneration along with the segmental demyelination and sparse lymphocytic infiltration.

In an uncommon variant of AMAN called Miller–Fisher syndrome (ataxia, areflexia, and ophthalmoparesis), the responsible antigen appears to be a ganglioside GQ1b-like epitope that is shared by *C. jejuni* and paranodal regions of cranial nerves, especially 3, 4, and 6.

Major Clinical Features

About two-third of patients report an antecedent upper respiratory infection, diarrhea, or rarely a recent vaccination in the few weeks before weakness onset. Flaccid weakness is the hallmark of GBS. Leg weakness is often the earliest sign but usually the weakness involves all extremities. The weakness is both proximal and distal, and a quarter of patients also involves motor cranial nerves producing facial weakness and trouble swallowing and chewing. Diffuse paresthesias and dysesthesias are common but objective numbness is rare. About 50 % of patients experience a reduced vital capacity and about 25 % require ventilator assistance. The weakness progresses over 1–3 weeks and then plateaus. Clinical involvement of the myelinated autonomic nerve system is common and may be life-threatening with complex supraventricular tachycardias, abrupt bradycardia, and bouts of hypertension or hypotension. Most patients become areflexic during the first week even if weakness is minor. Mild diminished vibration and position sense in the feet are common because these sensory fibers are myelinated but loss of touch, pain, and temperature rarely occurs since these fibers are unmyelinated. Loss of bladder or bowel control is uncommon. Mentation remains normal.

In most cases, the diagnosis is based on typical clinical signs as there is no pathognomonic test for GBS. For atypical cases, the differential diagnosis includes acute intermittent porphyria, poliomyelitis, West Nile viral myelitis, hypokalemia, myasthenia gravis, botulism, lead poisoning, tick paralysis, diphtheric polyneuropathy, and critical illness neuropathy.

Major Laboratory Findings

Major blood tests are normal. The CSF becomes abnormal during the first week. CSF protein elevates to the levels of 100–400 mg/dl but CSF IgG

synthesis does not increase and oligoclonal bands do not develop. The CSF has a normal glucose level and normal white blood cell count. Neuroimaging of the spinal cord should be normal.

Nerve conduction studies become abnormal in AIDP by the end of the first week. Mean values for compound motor action potential (CMAP) amplitude following nerve stimulation reduce to about 25–50% of normal implying conduction blockage in the majority of motor axons. The motor nerve conduction velocity reduces to 50–70% of normal after several weeks reflecting slow conduction velocity across areas of segmental demyelination. Variable evidence of muscle denervation may be found on electromyography beginning after 2–3 weeks. In AMAN, the motor nerve conduction velocity does not fall markedly but the amplitude of the CMAP does. There is widespread evidence of muscle denervation from axonal destruction and Wallerian degeneration.

Features strongly supportive of the diagnosis of GBS include progression of symptoms over days to 3 weeks, relative symmetry of the weakness, areflexia, minimal sensory signs, bilateral weakness of the facial muscles (if bulbar signs present), autonomic dysfunction, elevated CSF protein without pleocytosis, and typical nerve electrodiagnostic abnormalities. Features that make diagnosis unlikely include fever at onset, asymmetrical limb weakness, severe sensory abnormalities, persistent bladder and bowel dysfunction, or CSF pleocytosis, especially with neutrophils.

Principles of Management and Prognosis

The key to successful management is excellent nursing care. Patients usually require hospitalization and placement in a critical care setting. About one-fourth of patients require a ventilator, so careful monitoring of vital capacity and oxygen saturation is important. Cardiac monitoring is recommended because patients may be prone to severe arrhythmias. A nasogastric feeding tube may be needed for feeding.

Plasmapheresis or human immune globulin is beneficial if given early in the course of GBS. Both equally shorten the time to recovery and likely prevent progression of disease to more severe stages. In contrast, the use of corticosteroids is not beneficial. During recovery, physical therapy often improves function.

The weakness progresses over the first 1–3 weeks with subsequent stabilization and recovery. In mild cases of AIDP, the motor recovery can occur over a few weeks. For AIDP patients who cannot walk, ambulation often takes 4–6 months but in severe cases, recovery may continue for up to 2 years. In AIDP, about 85% of patients are fully recovered and 15% are left with minor sequelae such as loss of reflexes. In AMAN, up to half the patient are left with neurologic sequelae. Death following cardiac arrhythmias or infectious complications still occurs in 3% of patients with GBS. Poor prognostic factors include old age, placement on respirator, bulbar motor weakness, secondary pulmonary infections, and presence of axonal damage. Treatment for Miller–Fisher syndrome is seldom needed as spontaneous recovery usually occurs within a few months.

Acute Disseminated Encephalomyelitis

Introduction

Acute disseminated encephalomyelitis (ADEM) is a complex monophasic illness that often follows a recent infection and occasionally a vaccination. It is much more common in children than adults. Unfortunately, there is no unique laboratory or neuroimaging test to make the diagnosis. Thus, no consensus exists for specific criteria to make the diagnosis and no major therapeutic trials have been done. While many variants of ADEM have been described, this account focuses only on the most common presentation.

The annual incidence is estimated at between 0.3 and 0.8 per 100,000 with a median age of 6.5 years. Ninety percent of cases are associated with a preceding upper respiratory tract, GI illness, or

exanthema, but 5% have been associated with a variety of vaccinations administered within the previous three weeks.

Pathogenesis

The pathogenesis is poorly understood but thought to represent a single immune attack against CNS myelin but not against peripheral nervous system myelin. The target of the immune attack is unknown but thought to be a component of the myelin sheath. This hypothesis is based on experimental studies of experimental allergic encephalitis (EAE) where immunization of an animal with myelin components triggers a monophasic encephalomyelitis attack that appears similar to ADEM.

The best-characterized cases of ADEM are those following common childhood infections such as measles (rubeola), chickenpox (varicella), rubella, and influenza. The most common post-infection ADEM association is measles with an incidence of one per 1000 infections. Clinically, these patients experience severe ADEM with fatalities up to 20%. To date, there has been no evidence of rubeola virus being identified in the CNS of fatal cases arguing that the ADEM represents an aberrant immune response to the virus rather than a primary infection. In the last 10 years, especially in Asia, influenza viral infection of children and occasional adults has triggered a severe ADEM encephalopathy associated with seizures. Again, there has been very minimal evidence that influenza virus is present in the CNS of fatal cases.

The current hypothesis is based on molecular mimicry in which a component of the infectious agent shares antigens with a component of CNS myelin producing an immune attack against both the infectious agent and CNS myelin. Available brain pathology supports this theory. Brain biopsies have shown areas of edema, acute inflammation, demyelination, and adjacent venules with perivascular lymphocytes and macrophages. Involved axons are relatively spared. In autopsies, all lesions are of the same histologic age.

Current childhood vaccines including the seasonal influenza vaccines and the rabies vaccine prepared in cell culture are carefully monitored by the Centers for Disease Control and epidemiologically have not been associated with ADEM.

Major Clinical Features

Systemic symptoms of fever, headache, malaise, and myalgia often precede the encephalopathy by a few days. The patient then develops an abrupt encephalopathy characterized by many of the following neurologic signs: obtundation to coma, unilateral or bilateral long track signs, acute hemiparesis, ataxia, cranial nerve palsies, visual impairment, aphasia, and seizures. If the basal ganglia are involved, tremors and chorea may be seen. The neurologic signs may progress over a few days.

Major Laboratory Findings

MRI scans are abnormal over 95% of the time. Most scans demonstrate multiple, bilateral, asymmetrical lesions from one to several centimeters in diameter that are best seen on T2-weighted or fluid-attenuated inversion-recovery images (Fig. 10.6). MRI lesions may be seen in the thalamus and basal ganglia, which are often symmetrical. Incomplete gadolinium enhancement of T1-weighted lesions commonly occurs in the lesion periphery. MRI lesions are commonly seen in cerebral white matter and in the brainstem but spinal cord lesions may also develop. Hemorrhages and necrosis in the edematous lesions are uncommon. Follow-up MRI scans weeks to months later usually demonstrate disappearance of the lesions but occasionally show persistence of smaller lesions.

The CSF exam is needed to rule out an infectious etiology and often shows a mild lymphocytic pleocytosis (mean 50 WBC/mm^3), normal glucose level, slightly elevated protein level for the patient's age, and only rarely oligoclonal bands. Infectious agents should never be isolated or identified by polymerase chain reaction tests.

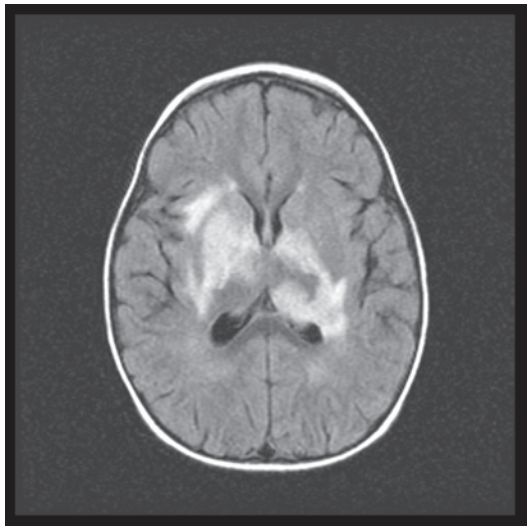

Fig 10.6 Axial T2 FLAIR MRI showing bright lesions consistent with acute disseminated encephalomyelitis (ADEM) in a 3-year-old who presented with chorea and difficulty walking 3 weeks after a viral illness (Courtesy of Blaine Hart, MD)

With no specific diagnostic tests available, exact criteria for the diagnosis are difficult and clinically based on the following features: (1) acute clinical onset, (2) poly-symptomatic clinical presentation that includes encephalopathy, (3) MRI showing multifocal characteristic lesions are of the same MRI age, which are large (> 1 cm), hyperintense and located in white matter of cerebrum, brainstem, cerebellum, spinal cord, thalamus, or basal ganglia, (4) lack of history of previous demyelinating events, and (5) no other cause for the lesions and encephalopathy such as neuromyelitis optica, multiple sclerosis, brain abscesses, or tumors. Supporting findings include young age below 10 years, mild CSF pleocytosis without oligoclonal bands, and symmetrical lesions in the thalamus or basal ganglia.

Principles of Management and Prognosis

Patients with ADEM need to be hospitalized usually in an intensive care unit but usually not placed in isolation. If the coma or respiratory involvement is severe, intubation with ventilation may be required.

While no careful controlled studies have been done, most patients are given high doses of corticosteroids for several days with a slow taper. Plasma exchanges have also been reported to be beneficial. Recovery takes 1–6 months and is excellent in 75 % and good in 90 %. Poor prognostic factors include severe encephalopathy with coma requiring intubation, old age, and spinal cord involvement.

Recommended Reading

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Pelletier D, Hafler DA. Fingolimod for multiple sclerosis. N Engl J Med. 2012;366:339–47. *(Nice review of the first oral anti-MS drug and its current indications)*.

Nandhagopal R, Al-Asmi A, Gujjar AR. Neuromyelitis optica: an overview. Postgrad Med J 2010;86:153–9. *(Clear review of the clinical, pathological neuroimaging, and management plus a good review of the role aquaporin 4 antibodies in the pathogenesis)*.

Yuki N, Hartung H-P. Guillain-Barre Syndrome. N Engl J Med 2012;366:2294–304. *(Nice review of the clinical features, proposed mechanisms of immunopathogenesis, treatment and prognosis of GBS)*.

Tenembaum S, Chitnis T, Ness J, et al. Acute disseminated encephalomyelitis. Neurology 2007;68(suppl2): S23–36. *(Reviews epidemiology, clinical features, neuroimaging, and treatment of ADEM)*.

Disorders of Higher Cortical Function

11

Kathleen Y. Haaland

An 82-year-old woman who lives alone is brought home by the police after being found confused and unable to get back home. Her son is contacted, stays with her, and brings her to the neurologist for evaluation. The patient is very friendly and denies any concerns. Her son reports that she has been forgetful for the past year. In the past 6 months, he has been doing her monthly bills as he was concerned that she might forget to pay them. The neurologist performs a neurologic exam, which is normal with the exception of an MMSE of 17/30. CT of the head showed moderate cortical atrophy. She had normal laboratory workup. She was diagnosed with Alzheimer's disease and started on daily donepezil.

Localization of Function

Neurologists have always been fascinated by how the brain controls complex functions, such as language or memory. How do we remember what we did last night or what we did 20 years ago, and what areas of the brain are responsible for such abilities? Historically, our knowledge of such brain–behavior relationships was based upon careful behavioral observations, which were related to the area of brain damage at autopsy. This approach was most famously used by Paul Broca who observed in 1860 that the left inferior frontal convolution was responsible for expressive language and damage to that area was associated with Broca's aphasia. Later, in 1926 Wernicke described the significant auditory comprehension deficits and fluent speech, which was called Wernicke's aphasia and was associated with damage to the left superior temporal gyrus.

Localization of higher order functions in the brain has been lauded and criticized at different times in history. Phrenology is a good example of localization gone wrong. It was initially developed by Gall in 1796. Proponents believed that bumps on the head reflected the size of the underlying brain tissue, which in turn influenced the mental faculties of the individual. This theory has been discredited. Nonetheless, its central assumption that different areas in the brain were associated with different mental faculties is similar to current notions of functional localization of the brain. This was an important advance because it contradicted the views of the day, which emphasized that behavior could be best understood in a religious or philosophical context, rather than a biological context.

The nineteenth and early twentieth centuries were dominated by using pathology from individual brain damaged patients to identify the neuroanatomical correlates of syndromes such as Broca's and Wernicke's aphasia.Neuroimaging has now made it possible to examine these neuroanatomical correlates in vivo.Both structural neuroimaging (CT and MRI) and functional neuroimag-

Electronic supplementary material The online version of this chapter (doi: 10.1007/978-1-4939-2359-5_11) contains videos as supplementary material and can be accessed at http://link.springer.com/book/10.1007/978-1-4939-2359-5.

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ing (e.g., functional MRI, electroencephalography, magnetoencephalography) are now being used to better characterize the neural structures that are important for complex behaviors.What is very clear is that it is not single areas in the cerebral cortex that are solely responsible for these behaviors, but rather neural circuits that include single or multiple cortical regions as well as subcortical structures.While damage in different parts of the circuit may produce somewhat different deficits in a particular complex behavior, the critical point is that damage in any of the areas comprising the circuit can produce impairment of the behavior.

General Neuroanatomical Considerations

The cerebral cortex is subdivided into three types of areas based upon their neuroanatomical interconnections and cellular structure. Fig. 11.1 shows the primary cortex, secondary association cortex, and tertiary association cortex. Primary sensory cortex includes the auditory, visual, or somatosensory cortex. It is characterized by direct connection to different parts of the thalamus, precise topographic mapping, and responsibility for less complex behaviors when compared to the secondary and tertiary association cortex. For example, while cells in the primary visual cortex may be sensitive to a line of a particular orientation and in a particular location in the visual field, cells in secondary association cortex may be sensitive to a line of the same orientation but in a greater number of locations in the visual field, and cells in tertiary association cortex may be sensitive to a particular object.

Tertiary association cortex is a particularly important node for complex behaviors. While secondary association cortex receives projections primarily from its associated primary sensory cortex, the tertiary association cortex is multimodal and receives projections from multiple sensory regions. These tertiary regions include the superior and inferior parietal areas and prefrontal cortex, and they are important for complex perception and higher order abilities, such as language, complex spatial skills, and executive functions (e.g., problem solving, planning).

The limbic system includes the limbic lobe (subcallosal area, cingulate gyrus, parahippocampus, uncus, and hippocampal formation),

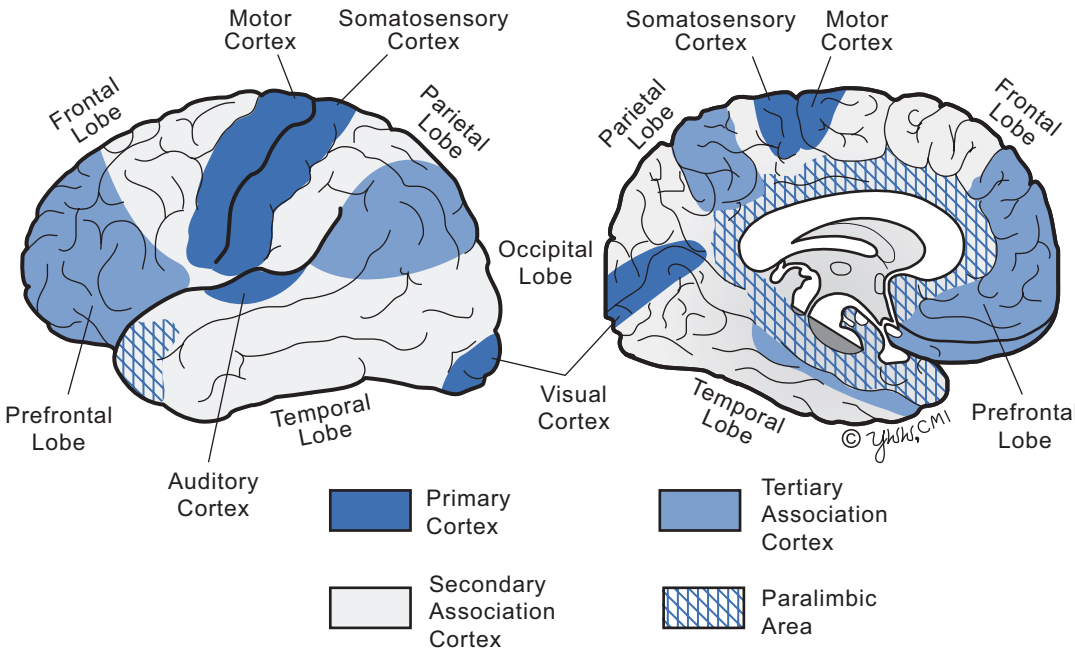

Fig. 11.1 Primary, secondary, and tertiary multimodal association cortices, and paralimbic regions

Table 11.1 Deficits after damage to particular tertiary association areas in the left or right hemisphere

Left hemisphere functions	Right hemisphere functions
Frontal, parietal, and temporal lobes	
Aphasia: auditory comprehension, [a]speech, [a]reading, [a]writing	[a]Speech (prosody), [a]reading and [a]writing due to perceptual/spatial deficits
Parietal lobe	
Limb apraxia: deficit in what common objects are used for or deficit in the spatial and temporal characteristics of a gesture	Dressing apraxia: difficulty dressing for spatial reasons, such as inability to identify top or bottom, left or right of garment
[a]Constructional apraxia: minor impairment copying or drawing of geometric forms or three-dimensional constructions due to errors of detail	[a]Constructional apraxia: more severe impairment copying or drawing geometric forms or three-dimensional constructions due to errors of spatial relationships (Gestalt of design); see Fig. 11.3 for examples
	Left hemineglect: inattention to the left hemispace and/or left side of body despite intact visual fields, somatosensory functions, and motor skills; see Fig. 11.4 for visual neglect
Medial temporal lobe-memory	
Verbal learning and memory	Nonverbal visual learning and memory
Frontal lobes: dysexecutive syndrome	
Initiation of verbal information, such as rapidly naming words beginning with a particular letter	Initiation of nonverbal information, such as rapidly drawing unique designs
Judgment, sense of purpose, planning, problem solving, cognitive flexibility, simultaneous processing, response inhibition, mental tracking	

[a]Present after damage to either hemisphere, but deficit after left hemisphere damage is usually associated with language impairment and after right hemisphere damage is associated with spatial impairment

many nuclei of the nucleus accumbens, the hypothalamus, mammillary bodies, the amygdala, and the cingulate gyrus (Fig. 11.1). The major arterial supply comes from the anterior and posterior cerebral arteries and anterior choroidal artery. The two major functions of the limbic system are emotion and memory, which is heavily dependent on circuits that include the hippocampus.

The Influence of Hemispheric Asymmetries

There is strong evidence that the left hemisphere of the brain is dominant for language, especially in right-handers. About 99% of right-handers and 70% of left-handers are left hemisphere dominant for language. Therefore, handedness is important information to obtain from patients in order to guide the focus of the examination. These findings show that the left and right hemispheres are often important for different higher order functions, such as language. However, it is also common for a complex task to be impaired after damage in tertiary association cortex of the left or right hemisphere even in right-handers, but the reason for the deficit is different (See Table 11.1). For example, deficits can be seen after right hemisphere damage on language tasks, such as speaking. However, expressive language abnormalities after left hemisphere damage are associated with impaired language (e.g., impaired word finding) and after right hemisphere damage are associated with impairment in the melody or prosody of speech. Table 11.1 summarizes the most important hemispheric differences in higher order cognitive functions.

Neurobehavioral Syndromes

Aphasia

Language impairment or aphasia is seen most frequently with damage to the lateral surface of the left hemisphere. There are several types of aphasia that are differentiated by their patterns

Table 11.2 Aphasia types, descriptions, and lesion location in left hemisphere

Type	Spontaneous speech	Auditory comprehension	Repetition	Area of damage
Broca's, Expressive, Nonfluent	*Nonfluent*	Intact	*Impaired*	Posterior inferior frontal
Wernicke's, Receptive, Fluent	Fluent	*Impaired*	*Impaired*	Superior temporal gyrus
Global, Expressive & Receptive	Nonfluent	Impaired	Impaired	Posterior frontal and temporal
Anomic, word finding problems	Nonfluent due to word finding problems	Intact	Intact	Not localizing

Italicized impairments highlight most critical characteristics for each aphasia type

of deficits in expressive language, auditory comprehension, and naming (see Table 11.2) and the area of brain damage. Fig. 11.2 depicts the location for Broca's, Wernicke's, Global, and anomic aphasia, the four most important and most frequent types of aphasia.

Broca's aphasia is known as nonfluent or expressive aphasia. It is characterized by nonfluent expressive language that is agrammatic or telegraphic, such that language is dominated by subjects and verbs but not modifiers or conjunctions. Expressive language is hesitant in mild cases and minimal in more severe cases with relatively intact auditory comprehension. Associated hemiparesis is common given the proximity of Broca's area to the motor cortex, and because these patients' auditory comprehension is intact, they usually keep trying to self-correct errors with little success. They also can become quite frustrated with their inability to speak normally despite repeated tries. While damage to Broca's area in the inferior third frontal convolution of the left hemisphere (Brodmann Area 44) is emphasized, neuroimaging suggests that more widespread suprasylvian damage back to the inferior parietal cortex is more common for Broca's aphasia.

Wernicke's aphasia is known as fluent aphasia or receptive aphasia. It is characterized by

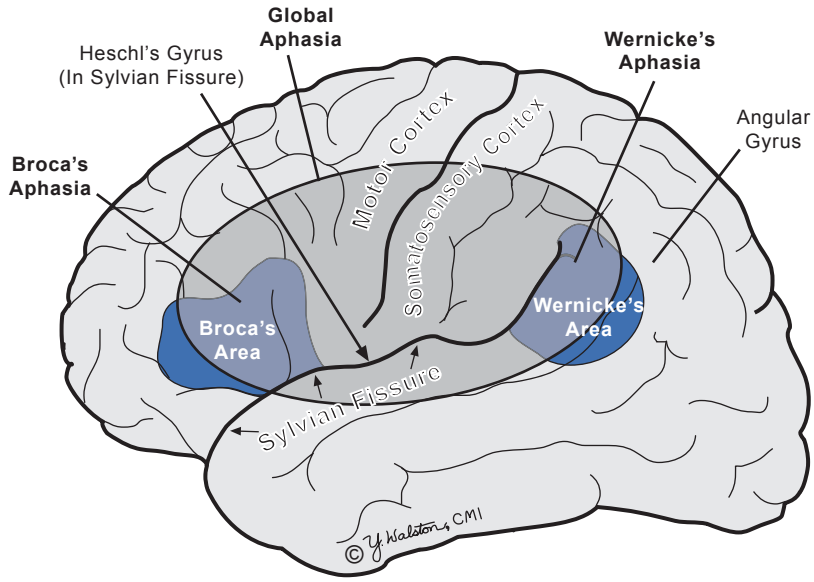

Fig. 11.2 Location of brain lesions causing different types of aphasia (left hemisphere)

severely impaired auditory comprehension with fluent expressive language that is often not appropriate for the situation due to comprehension deficits. Paraphasic errors are common, and these patients are sometimes described as having a jargon aphasia when their expressive language is dominated by phonemic paraphasic errors ('spoot' for spoon), semantic paraphasic errors ('fork' for spoon), and neologisms (output that is not real words). Because of severe comprehension deficits, these patients have difficulty monitoring the accuracy of their communication, so they are typically less frustrated than the patient with Broca's aphasia; they do not seem to appreciate that the listener cannot understand them. Wernicke's aphasia is associated with damage to the left superior temporal gyrus.

Global aphasia is defined by the same impairments seen in both Broca's and Wernicke's aphasia with nonfluent expressive language and impaired auditory comprehension. This type of aphasia is related to damage that encompasses Broca's and Wernicke's area.

Anomic aphasia is characterized by impaired word finding with intact understanding and grammatically accurate expressive language. Verbal output is characterized by circumlocution, use of somewhat inappropriate words for the context, and halting conversation as a result. Naming difficulties are related to damage in any of the central language areas (see gray circle in Fig. 11.2), so it is not helpful for inferring focal damage within this network. Anomic aphasia is the most common type of aphasia that is the outcome of recovery from Broca's or Wernicke's aphasia after stroke.

Apraxia

There are many syndromes that are labeled apraxia including limb apraxia, constructional apraxia, and dressing apraxia. The initial assumption was that all types of apraxia were reflective of problems with complex movement. However, while that is true of limb apraxia, constructional and dressing apraxia primarily reflect visuospatial or perceptual problems.

Limb apraxia is a deficit in skilled movement that cannot be attributed to weakness, akinesia, abnormal tone or posture, movement disorders (e.g., tremor), deafferentation, or poor comprehension. It is more common after left hemisphere damage, especially in the parietal lobe, and it is seen in both arms even with left hemisphere damage only. Limb apraxia is assessed by asking patients to perform object-use movements (e.g., brush teeth) to verbal command, to imitation, and with object present. Imitation is especially important to rule out the possibility that the deficits are related to auditory comprehension deficits. Spatiotemporal deficits (e.g., patient with ideomotor apraxia makes jerky vertical movements rather than smooth horizontal movements to imitate sawing or using index finger as toothbrush) and sequencing deficits to assess the patient's understanding of object functions (e.g., patients with ideational apraxia try to light the candle before striking the match).

Constructional apraxia is most common after right parietal damage. In addition, as the design complexity increases, the planning abilities of the frontal lobes become more influential. Constructional abilities are typically assessed by asking the patient to draw to command or copy a design (See Fig. 11.3a and b). Asking patients to draw the state and the location of several cities can also identify impairment in spatial relationships, which is often associated with getting lost and difficulty map reading. Regardless of the method of examination, it is best to vary item complexity (e.g., square, diamond inside a square, clock). Clock drawing is an example of a more complex design, and planning problems are evidenced by poor organization of the placement of the numbers around the clock face. Constructional apraxia can be worsened by hemispatial neglect with a tendency to not paying attention to the left side of space (see Fig. 11.4). Clock drawing to command is also sensitive to constructional apraxia, but Fig. 11.5 shows an example of impaired clock drawing that reflects impaired planning rather than constructional apraxia due to visuospatial deficits.

Dressing apraxia is defined as difficulty dressing, which is most commonly associated with

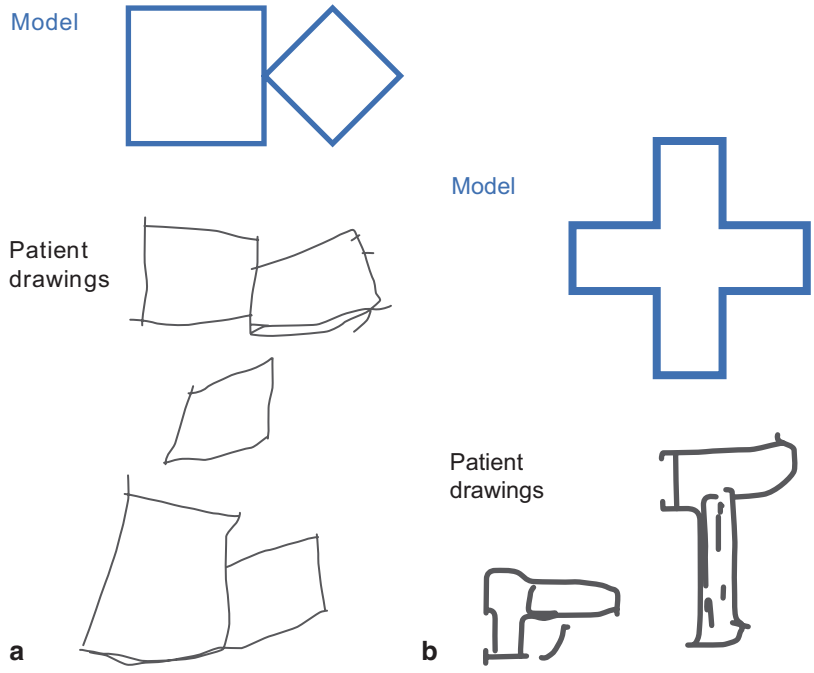

Fig. 11.3 Drawings copied by a patient with right parietal damage to illustrate the fact that **a** the patient could draw the two parts of the design, but could not accurately capture the spatial relationship between the two figures and **b** could not accurately copy a cross even with several attempts

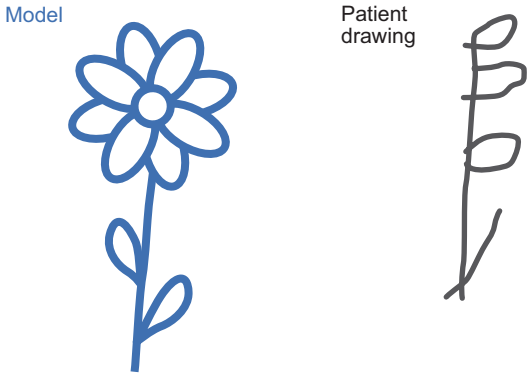

Fig. 11.4 Illustration of hemispatial neglect in a patient without visual field cut. The left side of the drawing is omitted reflecting hemispatial neglect, and the right side of the drawing illustrates visuospatial deficits

spatial problems. For example, such patients have difficulty differentiating the top or bottom of a garment and the right or left sleeve as well as putting the correct arm in the correct sleeve. This problem is most commonly associated with right hemisphere damage, especially of the parietal lobe.

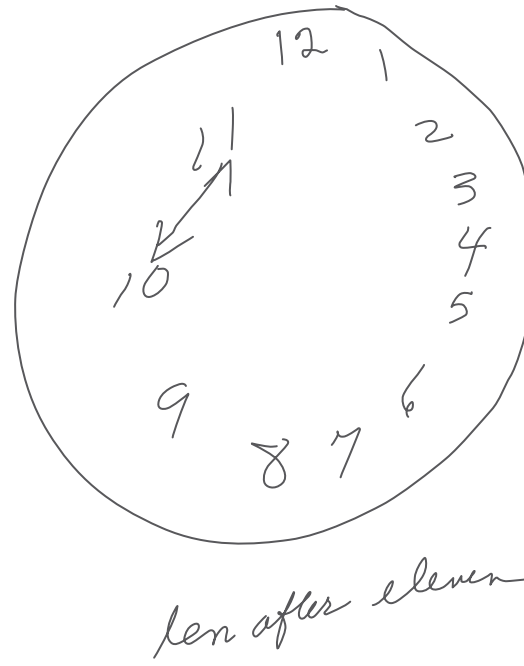

Fig. 11.5 Clock drawing. Reflects impaired executive function including poor planning and writing the time below the drawing ("ten after eleven") before concretely placing the hands at the 10 and the 11 rather than at the 10 and the 2

Amnesia

Memory and learning are particularly dependent on the medial temporal lobes and hippocampus, but the hippocampus is part of a larger network that is important for different aspects of memory, such as initial learning, storage, and retrieval of information. Damage to the left medial temporal lobe, especially the hippocampus, classically produces intact initial learning but impaired storage of new verbal information as evidenced by intact immediate recall but impaired delayed recall or rapid forgetting, a characteristic of early Alzheimer's disease. In order to be sure that deficits in delayed recall are due to impaired storage of the new information and not due to impaired retrieval, the patient is asked to recognize the list words from words that were not presented. Impaired recognition of the target word suggests that the patient has not stored the word. Intact recognition despite poor recall is indicative of impaired retrieval, which is more common after damage to the frontal lobes. Remote memory (e.g., autobiographical information from the past, knowledge of TV shows, or sports teams from the past) is less frequently impaired after neurologic disease likely because such information is stored in multiple places in the nervous system. However, when there is widespread brain damage, such as with advanced Alzheimer's disease, remote memory is eventually affected.

While verbal memory deficits are most common after left temporal lobe damage, and nonverbal memory deficits are most common after right temporal lobe damage, bilateral lesions produce particularly devastating memory deficits. These lesions may involve the hippocampal formation, dorsomedial nuclei of the thalami, or the mammillary bodies. The most common diseases that produce devastating memory loss are Wernicke–Korsakoff syndrome, anoxia due to cardiac arrest, and advanced Alzheimer's disease.

Dysexecutive Syndrome or "Frontal Lobe Syndrome"

The prefrontal lobes, which are the anterior to premotor cortex, encompass about 30% of human cortical volume, about 17% of chimpanzee cortical volume, and less than 5% of cat cortical volume. These volumetric differences suggest that the frontal lobes are important for many of our unique human characteristics. Interestingly, from a historical perspective, the functions of the frontal lobes were not obvious; they do not control simple day-to-day behaviors, such as hearing, seeing, or moving.

The prefrontal association cortex, located anterior to the motor and premotor frontal cortex, is supplied by branches of the anterior and middle cerebral arteries. See Table 11.1 for the functions of the frontal lobe. Clinical dysfunction usually occurs when the damage is fairly large and involves both prefrontal cortices. Thus, surgical removal of a considerable area of one prefrontal cortex leaves subtle deficits generally only detected with detailed neuropsychological evaluation. In contrast, severe head trauma causing bilateral prefrontal lobe damage can produce significant signs and symptoms.

Damage to the prefrontal cortex can produce such reflexes as grasp, snout, suck, and rooting. These reflexes are normal in the newborn, but disappear by about 4 months of age, presumably due to myelination of inhibitory pathways from the prefrontal cortex (see Chap. 2, Neurologic Exam, for details).

The dysexecutive syndrome is most commonly associated with bilateral frontal lobe damage. Damage to the lateral prefrontal regions produces deficits in higher level cognitive processing, such as flexible problem solving, organization and planning, mental manipulation of information (digits or months of the year backwards), and word retrieval. These patients may lack spontaneity and often lack awareness of their deficits and their implications. See Fig. 11.5 as an example of how poor planning can influence clock drawing. If orbitofrontal parts of the prefrontal lobes are damaged, which is common after moderate to severe traumatic brain injury, impulsivity characterized by inability to inhibit inappropriate social responses (e.g., fighting), and poor decision making (e.g., poor financial management) are common. Families often report personality change. Poor response inhibition has also been reported with damage to medial parts of

the prefrontal lobes, important for making risk-benefit analyses, and damage to these regions is associated with personality change including increased anger.

Neurologic Changes of Normal Aging

The number of adults over age 85 will increase from about 12% in 2000 to 24% in 2050. Therefore, the diagnosis of dementia is becoming even more important, and in order to accurately diagnose dementia, the cognitive changes associated with normal aging must first be understood. In the past 30–40 years, studies have identified neurologic changes that occur with normal aging independent of any neurologic diagnosis. In general, cognitive functioning peaks in the middle of our second decade and slowly declines, after that with accelerated decline during the fifth decade. There is a slow loss of many neurologic functions with normal aging, but the loss is subtle, allowing some individuals to continue to function normally into the 90s. However, about 50% of adults over age 85 require assistance for daily living, with both neurologic and nonneurologic reasons for their lack of independence.

Cognition

There is an age-related decline in (1) mental processing speed, (2) new learning, (3) retrieval of old and new information, and (4) executive functions. However, fund of general information actually increases into the 60s likely due to increased experience. The elderly require more time to process information, although their answer is usually correct. Memory studies find that, compared with young adults, the elderly show deficits in the initial learning of new information, but they do not forget the information more rapidly. Their memory problems are associated with decreased new learning rather than increased forgetfulness. The difficulty in initial learning is related to many factors including greater distractibility, poor use of memory strategies that enhance learning, and poorer retrieval.

Neuropathological Reasons for Normal Aging

Neurophysiological explanations for changes with normal aging are multifactorial and include occasional abnormalities that are seen in diagnosed dementias (such as neurofibrillary tangles or minor vascular insults), loss of synapses, neuronal shrinkage, and changes in neural networks. These changes reduce neural efficiency and are particularly common in the hippocampus and prefrontal lobes.

Other Age-Related Issues

Sensory losses include changes in vision, hearing, and somatosensory functions. There is a mild progressive loss of vibratory and position sense, mainly in the feet, due to a progressive loss of distal peripheral nerve axons. The result is balance problems, especially with the eyes closed. The ankle jerk is diminished. However, pathologic reflexes, such as clonus, Babinski signs, or grasp reflexes, are not part of the normal aging process.

There is also a progressive decline in muscle bulk and strength, speed, and coordination of movement. Muscle wasting is most noticeable in intrinsic hand muscles. Grip strength declines in 85% of individuals over age 60, which is out of proportion to loss of muscle bulk. Changes of gait with advancing age include a wider-based walking stance, shorter steps, mild loss of accompanying arm swing, and slightly stooped posture.

Mild Cognitive Impairment (MCI)

There has been a significant controversy associated with the borderland between normal aging and dementia. Terms such as malignant senescent forgetfulness, late life forgetfulness, questionable dementia, and mild cognitive impairment have been used, and MCI is the most commonly used term. It is used to describe the patient whose global cognition functioning is normal or near normal but who has subjective complaints (self-

or family report) or objective evidence of isolated cognitive deficits (i.e., 1.5 SD below age- and education-matched peers) that cannot be related to other causes, such as depression or medications. However, in contrast to the patient with dementia, patients with MCI do not demonstrate cognitive deficits in more than one cognitive domain and do not report significant problems with daily functioning. When compared to normal adults and those with Alzheimer's disease, MCI is associated with intermediate hippocampal atrophy, intermediate changes in brain metabolites, and the same frequency of a genetic variation seen with Alzheimer's disease (apolipoprotein E allelic frequencies). Depending on the pattern of cognitive impairment, amnestic and multidomain MCI have been identified. Long-term studies of individuals with MCI find 12% per year develop frank dementia compared with 1% for age-matched controls. However, a team of experts is required to make this diagnosis because it is based upon subtle distinctions, and the risks (e.g., inaccurate diagnosis that can cause significant, unnecessary stress) and benefits (e.g., getting estate in order, early treatment) are important to keep in mind.

Dementia

As defined by a group of experts in 2011, dementia is defined by a decline in cognitive abilities that reduces normal daily functioning, and cannot be explained by delirium or psychiatric disorder; cognitive deficits must be confirmed by mental status exam or by neuropsychological evaluation when deficits are subtle, and deficits must be present in two or more areas of cognition. Dementia is the fourth most common cause of death in the USA. About 4 million Americans have dementia and another 3 million have mild cognitive impairment. In one study, dementia prevalence was about 14% after the age of 71, and it increased with age, from 5% between ages 71 and 79 to 37% after age 90. In most cases dementia is progressive, as in Alzheimer's Disease, but it can be static, as from hypoxia due to cardiac arrest. Unfortunately, the vast majority of causes are not reversible.

There is no single pathophysiologic mechanism that produces all types of dementia, but the final outcome is loss of neurons in one or more of the multimodal or tertiary association cortical regions. The neuronal loss can occur abruptly due to anoxia from a cardiac arrest, stroke, loss of brain nutrients due to hypoxemia or hypoglycemia, acute exposure to neurotoxins, head trauma, or CNS infections. Progressive decline can be due to neurodegeneration, chronic exposure to neurotoxins, vitamin deficiencies, CNS infections, serial cerebral infarcts, and chronic systemic or metabolic encephalopathies (See Table 11.3).

The character of the dementia is dependent on the parts of the brain that are affected. The most common complaint is memory decline, but careful evaluation of mental status can determine if the memory complaints are due to impaired attention, mental tracking, or retrieval, which can produce memory problems. Table 11.4 lists the major tests that should be obtained in patients being worked up for dementia. In the early stages of dementia, objective neuropsychological tests can demonstrate abnormalities even when mental status screening does not partly because neuropsychological examination is more detailed and uses normative data that allow comparison of the individual patient's performance with a group of normal individuals with similar education. As the dementia progresses, diagnosis is easier because deficits are less subtle and neuroimaging abnormalities may be present depending on the etiology of the dementia.

Although treatments for dementia have been disappointing, it may be that earlier detection prior to clinical diagnosis and prior to such significant neuropathology could result in more successful treatment even with the currently available treatments. In addition, early detection will allow us to test new treatments more optimally in the future. This research is attempting to identify biomarkers, such as amyloid deposition, tau proteins, which are linked to neuropathological abnormalities such as neurofibrillary tangles, brain atrophy, changes in neural activation, and genetic differences. These findings, in concert with clinical information, are also helping to identify dif-

Table 11.3 Major causes of dementia in the USA

Neurodegenerative and neurogenetic diseases
Alzheimer's disease (60%)
Alzheimer's disease plus other causes (especially multi-infarct dementia) (15%)
Dementia with Lewy bodies (10%)
Down's syndrome
Tauopathies (such as progressive supranuclear palsy, corticobasal degeneration)
Huntington's disease
Hepatolenticular degeneration (Wilson's disease)
Cerebrovascular disease
Multi-infarct dementia
Subacute arteriosclerotic encephalopathy (Binswanger's disease)
CNS *vasculitis*
Traumatic brain injury
Infectious disease
Creutzfeldt–Jakob disease
Sequelae of viral encephalitis (such as herpes simplex encephalitis)
Neurosyphilis
HIV infection (AIDS dementia)
Systemic metabolic encephalopathies
Hypothyroidism
Hepatic encephalopathy
Vitamin deficiencies (B_1 and B_{12})
Hypoxic disorders (such as cardiac arrest, chronic obstructive pulmonary disease)
Toxic encephalopathies
Heavy metals (such as lead, arsenic, mercury)
Alcoholism
Carbon monoxide
Immune disorders
Systemic lupus erythematosus
Paraneoplastic syndromes
Psychiatric disorders
Depression

Bold represents common causes with () being their approximate incidence
Italics represent causes that may be reversible

ferent types of dementia, which are characterized by different patterns of cognitive deficits, and location and type of pathology. While this chapter will focus on Alzheimer's disease because it is the most common dementia diagnosis, other types of dementia include vascular dementia, frontotemporal dementia including primary progressive aphasia, Lewy body dementia, and corticobasal degeneration.

Table 11.4 Laboratory workup for patient with dementia

Blood tests
Complete blood count
Electrolytes
Glucose
Calcium
Creatinine
Liver function studies
Thyroid stimulating hormone
Syphilis serology (RPR and FTA-ABS if RPR positive)
Vitamin B_{12} level
Special tests (such as ceruloplasm level for suspected Wilson's disease)
Neuroimaging
MRI (to evaluate for CNS masses, hydrocephalus, multiple infarctions, infection)
CT if patient poorly cooperative
Neuropsychological Evaluation
Quantification of various cognitive functions with normative standards
Provides pattern of cognitive deficits and abilities to aid in diagnosis
Provides comparison of patient's performance with individuals of the same age and education
Allows diagnosis of more subtle cognitive problems earlier
Particularly useful for early diagnosis of mild cognitive impairment or early dementia, especially in higher functioning individuals

Alzheimer's Disease

The diagnosis of Alzheimer's disease from a group of experts in 2011 required (1) all criteria for dementia described above with insidious onset, clear history of cognitive deterioration, and the most common initial presentation of memory deficits followed by nonamnestic deficits, such as impaired language or executive functions. This diagnosis is not made when there are other potential medical explanations, including substantial cerebrovascular disease, other types of dementia (e.g., Lewy body dementia, FTD, primary progressive aphasia), or medications. That is why a workup for Alzheimer's disease must be thorough to rule out these other explanations.

Alzheimer's disease accounts for about 60% of dementia in the elderly. Its prevalence in the USA in 1999 for those over age 60 was estimated at 2.44 million, and 360,000 Americans are diagnosed with Alzheimer's each year. At this rate, by 2050 there will be 13.2 million Americans with Alzheimer's, which, especially considering the aging population, could easily overwhelm our healthcare system. The sheer numbers mean that all medical specialties will take care of patients with Alzheimer's disease.

Pathophysiology

The hallmark pathology of Alzheimer's is an excess of neuritic plaques and neurofibrillary tangles in the cerebral cortex relative to healthy age-matched controls. Neuritic plaques consist of a central core of B-amyloid protein surrounded by a ring of astrocytes, microglia, and dystrophic neurites. The dystrophic neurones often contain abnormal paired helical filaments. Neurofibrillary tangles are abnormal accumulations in the neuronal cell body and dendrites of paired helical filaments of abnormally hyperphosphorylated tau proteins that can be seen by electron microscopy or by light microscopy after silver staining. Neurofibrillary tangles have been most consistently correlated with the progression of cognitive deficits in AD. They are seen initially in the temporal lobes, especially in the regions around the hippocampus with inclusion of the frontal and parietal lobes as the dementia progresses. This progression of pathology in AD is consistent with the initial presentation of memory deficits (dependent on the medial temporal lobes and hippocampus) and progression to impaired executive functions (dependent on the frontal lobes), and spatial and language abilities (dependent on the parietal lobes).

Additional histological feature of AD are loss of cortical neurons producing cerebral atrophy with enlarged ventricles (hydrocephalus ex vacuo), marked reductions in the density of cortical synapses, and granulovascular degeneration in hippocampal neurons. Neuronal loss in the nucleus basalis accounts for the loss of cholinergic neurons and their cortical axons.

The pathogenic mechanisms that produce these histological changes are incompletely understood. Current evidence points to the accumulation of an abnormal amyloid protein as being central to the cerebral damage. However, the link between amyloid deposition, the proliferation of tau proteins, and the increasing numbers of neurofibrillary tangles (which best correlate with the cognitive deficits of AD) is not known. The B-amyloid gene encodes a large protein, amyloid precursor protein that is normally inserted into neuronal membranes with a B-amyloid fragment of 40–42 amino acids located outside the cell. In AD, the B-amyloid fragment is abnormally cleaved, producing a B-amyloid peptide that is poorly catabolized, which accumulates locally and is toxic to neurons.

The presence of the apolipoprotein (Apo) E4 allele increases AD susceptibility. Of the three forms, E2, E3, and E4, only E4 increases the likelihood of late-onset AD while E2 appears to decrease the risk. Greater changes in the brain, including increased neurofibrillary tangles and neuritic plaques, and depletion of cholinergic markers, are associated with the presence of the APOE E4 allele. However, more than 45% of those with late-onset AD do not carry the E4 allele showing that while it has promise, its current clinical utility is questionable. Other risk factors for developing AD are increasing age, significant head trauma, low folate and vitamin B_{12} levels, and elevated homocysteine levels. Some risk factors such as fewer years of formal education, low income, and lower occupational status appear to work by decreasing the patient's cognitive reserve, which may result in poorer ability to compensate using intact neural circuitry.

Major Clinical Features

Table 11.5 lists common early and late clinical features of AD. Patients with early AD present with impaired recent memory with relatively intact remote memory. They may also have mild

Table 11.5 Common Features of Alzheimer's Disease

Early AD	Late AD
Deficits in two or more cognitive areas and deficits in daily functioning	
Progressive decline in recent memory with intact remote memory	Global cognitive deficits with impaired remote memory
Progressive decline in executive functioning	Loss of judgment and insight
Normal expressive language and gait	Unpredictable behavioral changes, such as anger
Mild to moderate atrophy of the medial temporal lobes on neuroimaging	More widespread, marked atrophy on neuroimaging with hydrocephalus ex vacuo
Normal routine cerebrospinal fluid	Terminal apathy and withdrawal from social situations, leading to virtual 'mutism'

executive function deficits characterized by difficulty solving problems or mentally manipulating information, and they may be depressed related to their frustration with poorer memory and fear of a progressive dementia. Functional deficits must be present to make a diagnosis of dementia, and it is common for these individuals to have some financial difficulties, problems remembering their medications, or getting lost. More basic activities of daily living, such as toileting, are intact. Some patients also experience unexpected periods of agitation, anger, and abnormal sexual activity. As the disease progresses, more basic activities of daily living become impaired, cognitive deficits become more global, and patient becomes less aware of deficits and their implications. Although difficulty coming up with a needed word in conversation is impaired relatively early, global language function is relatively intact even later in the disease's progression, such that the AD patient can carry out simple "cocktail party" conversations yet cannot discuss current events. As the disease progresses, patients lose the ability to recognize family and close friends, have meaningful conversations, and keep track of time and place.

After the diagnosis of AD, survival time varies and ranges from about 7 years in those diagnosed in their 60s to 3 years in those diagnosed in their 90s.

Vascular Dementia

Nearly 10% of AD is associated with vascular dementia related to widespread white matter changes related to microvascular ischemia or large vessel strokes. Historically, vascular dementia was defined by stepwise progression (presumably related to large vessel strokes that are clinically identifiable), but the identification of microvascular changes has changed that clinical picture. Even though the microvascular changes are related to ischemic events, they are so small that they are not identifiable as an "event," and they accumulate over time and do not produce a report of stepwise progression.

Major Laboratory Findings

No laboratory test establishes the diagnosis of AD. A definite diagnosis is based on characteristic neuritic plaques and neurofibrillary tangles seen on brain autopsy. However, clinical diagnosis is now quite accurate. Routine blood and CSF tests are normal. Neuroimaging usually demonstrates symmetrical brain atrophy that is out of proportion for age with an accompanying hydrocephalous ex vacuo of the third and lateral ventricles (Fig. 11.5). EEG shows a diffuse slowing of background activity that is nonspecific. PET/SPECT scans demonstrate hypometabolism and reduced blood flow to temporal and parietal lobes.

Principles of Management and Prognosis

There is no method to stop or reverse the progression of AD. However, cholinesterase inhibitors may produce modest transient improvements in cognition and may reduce behavioral outbursts.

Low doses of psychoactive medications may be required to treat patients who have frequent outbursts of anger or agitation.

The first step in management is to provide accurate information to patient and family when the diagnosis is made acknowledging that it is difficult to predict the rate of progression in an individual patient. These discussions can be difficult, especially because 7 of 10 AD patients live at home and typically rely on family members for their care, and 90 % of demented patients will require custodial care at some point. Management options should be discussed and include type of supervision necessary and future options as dementia worsens (e.g., day care, home healthcare, group home, nursing home), recommendations regarding safety (e.g., driving, medication management), and legal issues (e.g., identification of someone to advise or control financial issues and healthcare decisions). These issues can be particularly difficult because AD is usually associated with lack of awareness of deficits and their implications. So, the patient often does not understand restrictions, such as not driving. A balance between the patient's needs and the caregiver's needs is critical. Ideally, consultation should be available when problems arise. Providing community resources for information and help as well as books about managing the demented patient is important. The caregiver may also need mental health intervention because depression is not uncommon.

Rules of Thumb for Mental Status Examination

Medical and psychosocial history, ideally obtained from the patient and a collateral, is critical to help you generate reasonable differential diagnoses; useful issues to consider are as follows: (1) in order to separate problems with memory storage and retrieval find out if they eventually remember what they forgot because retrieval problems are more common with normal aging, not dementia, (2) find out if old memories from the far past are worse than day-to-day memories. It is uncommon for neurologic disease to produce equal or greater remote memory problems, and psychiatric diagnoses need to be considered. (3) Specify the onset of problems, whether there was a precipitating event, if the problems are progressive or static, and estimate the amount of loss (if you were at 100 % before you started having problems, where are you now? This helps you get the patient's perception of the severity of the problem). (4) When patients come for an evaluation for cognitive complaints, it is very common for them to be worried about AD. Ask them so you can be sure to rule in or rule out dementia when making your final diagnosis. Reassuring someone who is unnecessarily worried about dementia can have very positive impact because worry decreases cognitive efficiency. Neuropsychological evaluation can help you reliably determine if the pattern and degree of cognitive performance is consistent with normal aging or with MCI or dementia.

Video Legend

This video shows a 35 year-old man s/p gunshot wound to left cerebral hemisphere

Segment 1: Language Exam
- Nonfluent or expressive aphasia
- Impaired auditory comprehension with multistep commands
- Telegraphic speech
- Intact repetition
- Circumlocution

Segment 2: Praxis Exam
- No limb apraxia

Recommended Reading

Devinsky O, D'Esposito M. Neurology of cognitive and behavioral disorders. Oxford: Oxford University Press; 2003. (This book details a broad range of neurobehavioral syndromes with case studies).

Cummings JL, Trimble MR. Concise guide to neuropsychiatry and behavioral neurology. Washington DC: American Psychiatric Publishing; 2008. (This book covers neuropsychiatry and behavioral neurology, including frontal lobe syndromes and the dementias, in order to enhance the clinical workup of such patients).

Disorders of the Extrapyramidal System

12

A 59-year-old man makes an appointment with a neurologist for tremor. He has noted difficulty with a tremor in both of his hands. It interferes with drinking from a cup and his handwriting has become very difficult for him to read. He also finds it embarrassing when he is trying to sign a check at the store. He has started having a glass of wine before going out to dinner as his tremor does not seem to bother him as much after drinking the wine. His neurological exam reveals normal language and cranial nerve function. He has normal strength and tone. He does have a high-frequency, small amplitude tremor in both hands that is seen on posture and with action. There is no tremor at rest. His gait is normal. On handwriting examination, he has a tremulous spiral. After history and examination, he is diagnosed with essential tremor. As the patient finds the symptoms intrusive, he is started on symptomatic medications to reduce the tremor.

Overview

The human motor system controls both voluntary and involuntary movements. The pyramidal motor system generates voluntary movement through the premotor and motor cortices and transmits those commands via the corticospinal tract—making up the medullary pyramids. Voluntary movements are facilitated through the extrapyramidal system (e.g., *does not pass through the pyramids*), where a process—likely *surround inhibition*—enforces wanted movement and suppresses unwanted movement (See Fig. 12.1). Based primarily in the basal ganglia, the extrapyramidal motor system also controls involuntary movement. While surround inhibition has been shown to be an active physiologic process that likely plays a role in the execution of skilled movement, the exact anatomic substrates that produce the surround inhibition and how it is altered in the generation of disordered movement is not known.

Movement disorders or extrapyramidal disorders are diseases characterized by excessive or abnormal movements in conscious patients. Damage to or presumed dysfunction of the basal ganglia and their brainstem and cerebellar connections is implicated in the etiology of these diseases. The abnormal movements may be the only manifestation of a disease process or part of a constellation of deficits in others. Movement disorders are characterized by either excessive (*hyperkinetic*) or reduced (*hypokinetic*) activity. Parkinson's disease is the classic hypokinetic movement disorder with reduced voluntary and involuntary movement. Chorea, tremor, myoclonus, and tics represent hyperki-

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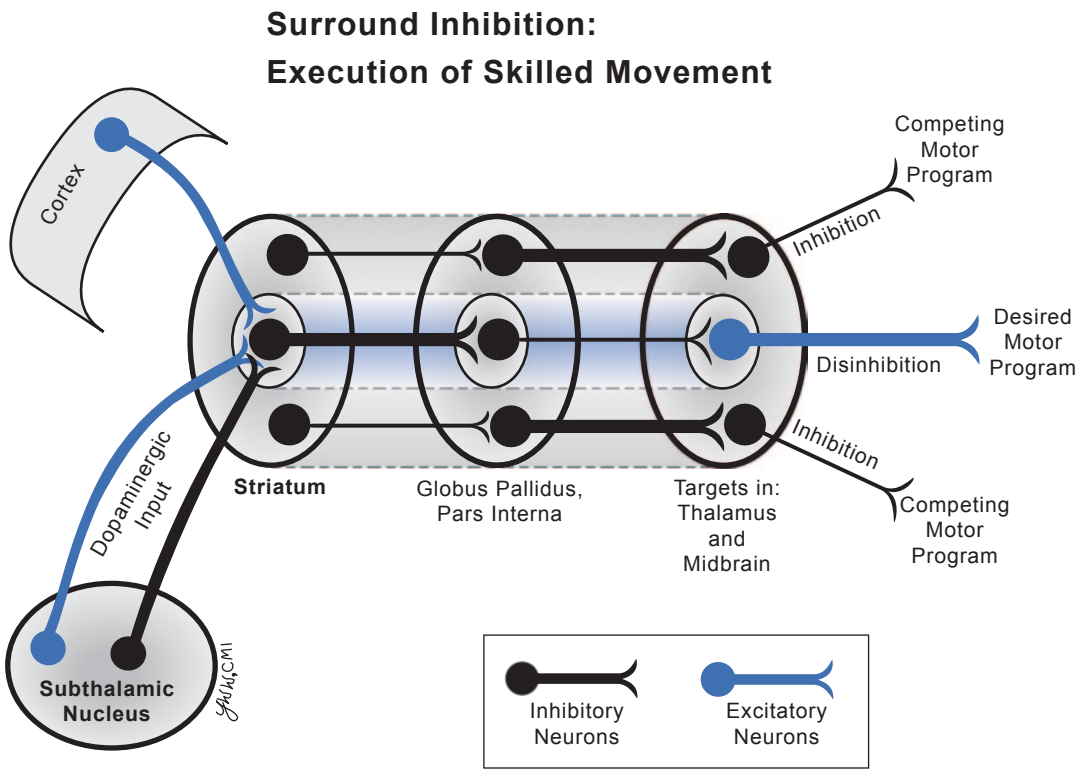

Fig. 12.1 Illustration of *surround inhibition*. The brain produces the desired motor pattern while simultaneously creating a surround inhibition of competing motor movements

netic movement disorders, which cause extra involuntary movement and sometimes interfere with normal voluntary movement as well.

In this chapter, we will first cover definitions of hyperkinetic movement disorders, followed by examples of common movement disorders (Essential tremor, Parkinson's disease and Huntington disease).

Hyperkinetic Movement Disorders

When observing a patient with a hyperkinetic disorder, a neurologist notes the topography, symmetry or asymmetry, velocity, task-specificity or posture-specificity of the movement. In addition, the neurologist questions the patient regarding how the movement interferes with voluntary movement, and whether the movement is suppressible, precipitated by any factors, and/or ameliorated by any interventions.

Chorea Irregular, unpredictable, brief, involuntary jerking movements involving shifting muscles or muscle groups involving the arms, hands, legs, tongue or trunk.

Dystonia Sustained muscle contractions causing twisting, repetitive movements or abnormal posture. In adults, dystonia is focal in presentation, affecting the neck, the eyes, the jaw or a limb. In children, dystonia can present focally and then generalize over time. The contractions can be painful and may be disabling.

Athetosis Distal, slow, writhing form of dystonia. It can be seen in combination with chorea.

Ballismus Uncontrollable, proximal, flinging movements of a limb that is often due to a lesion in the subthalamic nucleus.

Tics Abrupt, brief, repetitive, stereotypical movements of face, tongue and limbs or vocalizations that may be briefly voluntarily sup-

Table 12.1 Tremor type by clinical presentation

Tremor type (other common names)	Characteristics (examples)
Rest tremor (pill-rolling tremor)	Present at rest with limb supported against gravity
	• Low-frequency (3–5 Hz), medium to high amplitude (parkinsonian tremor)
Action tremor (postural tremor)	Present when voluntarily maintaining a limb still against gravity such as holding arms outstretched
	Usually bilateral but may be asymmetric
	Low to medium amplitude and medium to high frequency (4–8 Hz)
	Present during voluntary movements such as writing or eating (essential tremor, enhanced physiologic tremor)
Intention tremor (cerebellar tremor)	Present during voluntary movement and often perpendicular to direction of movement
	Medium amplitude and low frequency
	Often amplifies when limb approaches the target or near the face
	Interferes with coordination (cerebellar-type tremor as seen in finger-to-nose movements)

pressed but is often then followed by a burst of tics when the suppression is removed.

Myoclonus Sudden, shock-like movements or a pause in movement. The movements can be restricted to a specific muscle or group of muscles or may be multifocal occurring at the same or different times. Myoclonus can be generated in the motor cortex, subcortical areas, brainstem (reticular myoclonus), or spinal cord (propriospinal myoclonus). Many healthy individuals experience myoclonus on falling asleep in the form of a *hypnic jerk*.

Tremor A tremor is an involuntary oscillation of a body part caused by alternating contractions of reciprocally innervated muscles. Physiologic tremor in present in the limbs but usually is not bothersome. Stimulants or anxiety can enhance a physiologic tremor causing it to be visible and sometimes intrusive. Current evidence suggests that tremors come from alterations in a complex central oscillatory cycle that involves neurons in the basal ganglia, brainstem, and sometimes the cerebellum. Tremors are classified by frequency, their relationship to movement, and location (Table 12.1).

Essential Tremor

Introduction

Essential tremor is the most common movement disorder with an estimated 10 million Americans affected. Essential tremor can begin at any age but is more prevalent with increasing age. It is estimated that 4–5% of people from age 40 to 60 years have essential tremor. Over the age of 60 years, the incidence rate increases and is estimated at 6–9%. Although activities of daily living such as feeding, drinking, and writing may be difficult, only a small percentage of patients with essential tremor seek medical attention. Essential tremor can be misdiagnosed as Parkinson disease—likewise in a young patient (under 40 years), other rare causes of tremor should be excluded such as Wilson's disease and medical conditions such as hyperthyroidism.

Pathophysiology

In the majority of patients with essential tremor, there is a positive family history. Genetic studies have identified several genes suggesting that multiple etiologies may account for essential tremor. At present, the actual pathophysiology of how sporadic or genetic cases develop the tremor is unknown, as structural lesions have not been recognized. There is evidence that the generators of essential tremor are widespread in the brain—including the motor cortex, thalamus, cerebellum, and brainstem, such as the inferior olivary nucleus. These are the same centers that control voluntary movement through a thalamocortical relay, and it is hypothesized that the bidirectional nature of the thalamocortical loops could provide

the substrate for oscillatory activity to become established—leading to tremor instead of normal voluntary movement.

Major Clinical Features

The characteristic history is one of slowly progressive bilateral tremors of the hands that began in middle age. The tremor is of medium to high frequency, of low amplitude, sustained and is present immediately with arms outstretched (postural tremor), and absent at rest. The tremor severity can range from socially embarrassing to interfering with activities of daily living such as writing and drinking. Occasionally, the tremor also may involve the head, legs, or voice. Patients relate that the tremor worsens with anxiety, coffee, and some medications. About half of patients endorse a history of their tremor transiently improving after drinking alcohol. Patients with essential tremor could have mild gait imbalance and subtle cognitive changes, but in general, the tremor is the predominant symptom. Weakness, sensory loss, or changes in deep tendon reflexes do not occur in essential tremor. Patients should not have features of Parkinson disease. The clinical diagnosis is made based on the history and exam.

Several drugs that may worsen essential tremor or exaggerate a physiologic tremor include stimulants, lithium, levothyroxine, beta-adrenergic bronchodilators, valproate, prednisone, caffeine, and selective serotonin-reuptake inhibitors (SSRI).

Major Laboratory Findings

No laboratory test is diagnostic. Routine blood tests are normal, and neuroimaging of the spinal cord and brain is normal.

Principles of Management and Prognosis

Patients with mild symptoms usually do not require treatment once they are reassured that they do not have Parkinson disease and that the tremor rarely becomes incapacitating. Many patients find that a small amount of alcohol (glass of wine or beer) suppresses the tremor for hours and is useful when entertaining friends. For patients with severe essential tremor or whose occupation is impaired by the tremor, propanolol and primidone have been successful in reducing the tremor severity. Other agents with evidence of efficacy in treating essential tremor include topiramate and gabapentin. In severe tremor, surgical implantation of electrical stimulators in the thalamus or stereotactic thalamotomy may be indicated.

Parkinson's Disease

Introduction

Parkinson's disease (PD) affects more than one million Americans, and each year 50,000–60,000 people are diagnosed with the disease. The direct annual cost in the USA is over $ 10 million. Both sexes are equally involved and the incidence climbs exponentially with increasing age to 7% above age 70 years. Idiopathic PD usually begins above age 50 while patients with young-onset PD can have onset of symptoms as early as age 21–40 years. A subset of those patients with young-onset PD may have a genetic form of the disease. PD has a dramatic impact on quality of life and a marked reduction in life expectancy.

The cardinal symptoms of PD are designated by the abbreviation **TRAP**: resting **T**remor, cogwheel **R**igidity, **A**kinesia or bradykinesia (slowed and small amplitude movements), and **P**ostural instability with gait changes. PD often causes a stooped posture and shuffling gait that are readily apparent even at a distance (Fig. 12.2). PD refers to the primary idiopathic form and represents two thirds of all Parkinsonism. Parkinsonism is the secondary form and refers to the above clinical and biochemical features that develop from specific causes such as repeated head trauma (boxing), infections of the upper midbrain, medications that affect dopamine transmission, or CNS diseases that damage the nigrostriatal pathway and other brain areas.

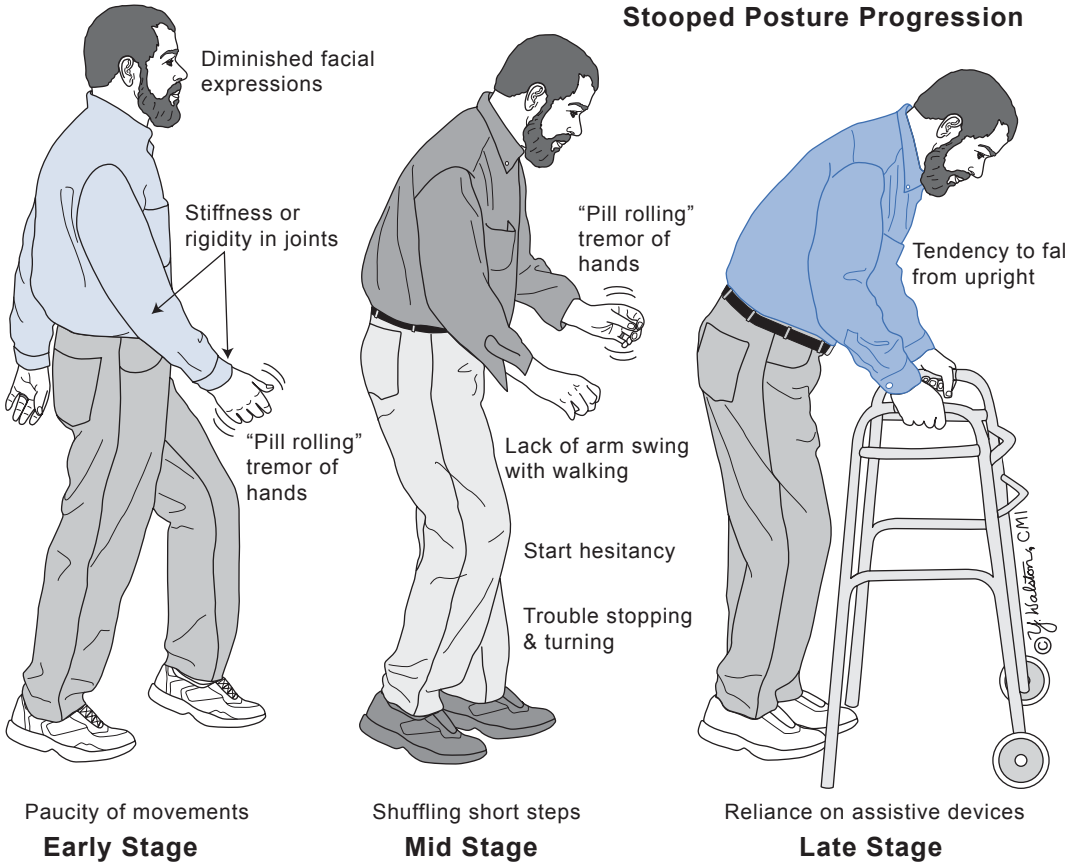

Fig. 12.2 Postural and gait changes in the progression of Parkinson's disease

Pathophysiology

Idiopathic PD results from the slowly progressive death of CNS dopaminergic neurons, although what triggers the demise of these specific neurons is not known. Current theories include exposure to environment neurotoxins, abnormal mitochondrial function, abnormal oxidative metabolism, and generation of misfolded alpha-synuclein protein (such as a prion) that is toxic. Evidence suggests that the death of dopaminergic neurons begins a decade before symptom onset. The motor symptoms of PD manifest when approximately 60–80% of the melanin-containing pigmented dopaminergic neurons in the pars compacta of the substantia nigra are not able to produce enough dopamine to facilitate normal voluntary and involuntary through the extrapyramidal pathway.

Grossly, there is loss of pigmentation in the substantia nigra and other dopaminergic nuclei such as locus ceruleus (Fig. 12.3). Microscopically, there is loss of small pigmented neurons in the substantia nigra and eosinophilic, cytoplasmic inclusion bodies surrounded by a clear halo (Lewy bodies) in remaining neurons that contain aggregations of neurofilaments and alpha-synuclein protein attached to ubiquitin.

Substantia nigra dopaminergic neurons project to the ipsilateral striatum (caudate nucleus and putamen). Dopamine release from substantia nigra neurons stimulates D1 receptors and inhibits D2 receptors resulting in the striatum sending impulses to the motor cortex (called the basal ganglia-thalamocortical motor circuit) in a direct excitatory pathway via thalamic nuclei. Concomitant inhibitory impulses to the motor cortex in a polysynaptic indirect pathway via globus pal-

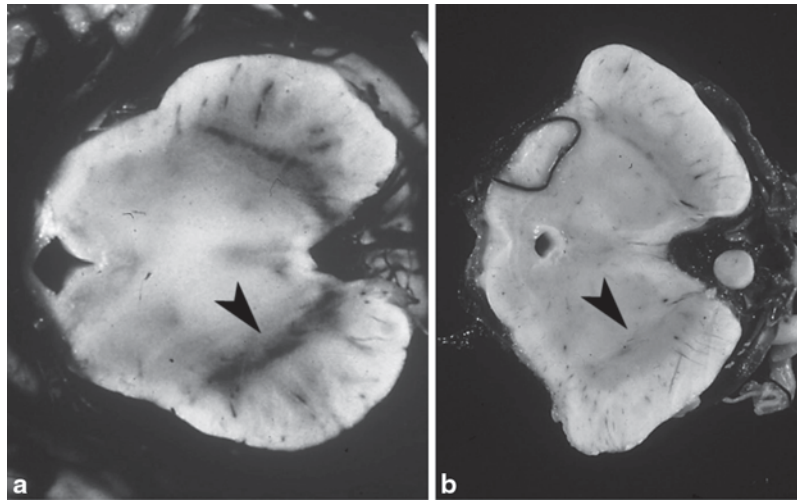

Fig. 12.3 Gross brain specimen of midbrain of **a** Healthy subject and. **b** Patient with Parkinson's disease, showing loss of pigmentation in the substantia nigra (*arrow*). (Courtesy of Dr. Mario Kornfeld)

lidus externa, subthalamic nucleus, and thalamic nuclei are also sent. Loss of dopaminergic nigral cells leads to striatal dopamine depletion and overall less motor cortex excitation. The loss of excitatory stimulation decreases excitatory activity of the direct pathway to the motor cortex and increases inhibitory activity of the indirect pathway to the motor cortex. As yet incompletely understood, the increased inhibitory input to the motor cortex causes bradykinesia.

Using the surround inhibition model of the basal ganglia, the loss of substantia nigra input to the striatum would cause loss of inhibition of competing motor movements (Fig. 12.1). For example, when a normal individual flexes their arm, the biceps fires (desired movement) and the triceps is inhibited (surround inhibition). In the patient with PD, flexion of the arm fires both the biceps (desired movement) and triceps (loss of surround inhibition) resulting in bradykinesia. The tremor of PD is felt to be secondary to interruption of the CNS oscillatory pathway in the globus pallidus and thalamus.

Five percent of PD is due to autosomal-dominant mutation in the *parkin* gene and occasionally in the *alpha-synuclein* gene. The role of alpha-synuclein in the pathogenesis of PD is receiving attention since alpha-synuclein is normally abundant in neurons and presynaptic terminals, as well as in Lewy bodies. The *parkin* gene product appears to be involved in identifying proteins such as alpha-synuclein for degradation via the ubiquitin pathway.

Major Clinical Features

The diagnosis of Parkinson's disease is usually made by the presence of asymmetrical bradykinesia in the limbs, cogwheel rigidity (of the wrist or elbow), resting limb tremor, and a good response to levodopa. Approximately 70 % of patients will have tremor at some point in their disease course. Only half of those patients will have a tremor that is responsive to levodopa. Rigidity is a constant resistance to passive muscle stretching in both flexors and extensors throughout range of motion due to the stretching force inducing some antagonistic motor units to fire. In Parkinson disease, the rigidity is constant regardless of the speed of the passive muscle stretch. Spasticity is different and is dependent on the speed of the movement. In addition, flexion and extension or rotation of wrist or elbow often elicits a ratchet-like feeling (*cogwheel rigidity*).

The disabling feature of PD is bradykinesia. One patient described early bradykinesia as walking in a swimming pool with water up to his neck and advanced bradykinesia as walking in a swimming pool filled with molasses. Thus, patients spend enormous amounts of energy and time performing routine activities of daily living.

Everything "slows down" in the patient with PD. Limb and chewing movements are slow; gait is slow, shuffling, difficult to initiate, and often with a stooped posture; standing balance is impaired from slow corrective steps to maintain balance so falling is common; spontaneous facial expression is minimal (masked facies); gut peristalsis is slow and constipation is common, and mental activities are slower than normal so there is less spontaneous speech and delayed answers (*bradyphrenia*) to questions spoken in a soft, dysarthric voice. In many patients, cognitive problems such as executive dysfunction and memory loss will develop. About 40% of patients also develop dementia that may be due to dementia with Lewy bodies or the coexistence of two common diseases of elderly, Alzheimer disease and PD.

Major Laboratory Findings

Routine blood and CSF studies are normal. Conventional neuroimaging is seldom helpful in diagnosing PD or distinguishing it from other causes of parkinsonism. Isoflupam I123 is a radioactive compound that mainly binds to the dopamine transporter of nigrostriatal neuronal presynaptic terminals in the caudate and putamen. During a DaTscan, isoflupam is intravenously injected into a patient and the brain is studied using single photon emission computed tomography (SPECT). PD patients have depleted dopamine transporter, compared to the healthy state, so the SPECT image of the striatum is smaller than in normal subjects. This technology is not widely available currently, and the expertise in interpreting the scan results is variable from center to center. Given these limitations, the diagnosis of PD remains largely clinical.

Principles of Management and Prognosis

Since no treatment halts disease progression of Parkinson's disease, management aims at minimizing the symptoms and maximizing patient functioning and safety. Presently, there is a controversy whether drugs such as monoamine oxidase inhibitors such as selegiline and rasagiline are "neuroprotective" and slow the rate of early disease progression.

The mainstay of early treatment is providing additional dopamine or dopamine agonists to the striatum. Dopamine cannot cross the blood–brain barrier and causes considerable systemic nausea and hypotension by stimulating peripheral dopamine pathways. Levodopa was found to cross the blood–brain barrier and to be converted in brain to dopamine by the enzyme dopa-decarboxylase. To minimize systemic conversion of levodopa to dopamine, the dopa-decarboxylase inhibitor, carbidopa, is added to levodopa. Carbidopa does not cross the blood–brain barrier, so CNS conversion of levodopa is unaffected. Levodopa is converted to dopamine within the dopamine neuron cell body and transported via axoplasmic flow to the nerve terminal. Levodopa is also converted to dopamine at the distant presynaptic nerve terminal where it is taken up and stored by the nerve terminal. Dopamine agonists, such as pramipexole, cross the blood–brain barrier to act directly upon D1 or D2 postsynaptic terminals in the striatum (Fig. 12.4).

Levodopa is the most potent of all anti-parkinson drugs and is particularly helpful in reducing bradykinesia. Controversy exists as to whether its early usage may accelerate the time to developing levodopa complications but the weight of evidence suggests there is not a neurotoxic effect. Nevertheless, many neurologists adopt a "dopamine-sparing" approach and may use exercise, dopamine agonists, and medications such as monoamine oxidase inhibitors. If these do not provide enough symptomatic benefit, then levodopa is employed.

In early PD, complete relief of the bradykinesia is achieved with levodopa and carbidopa

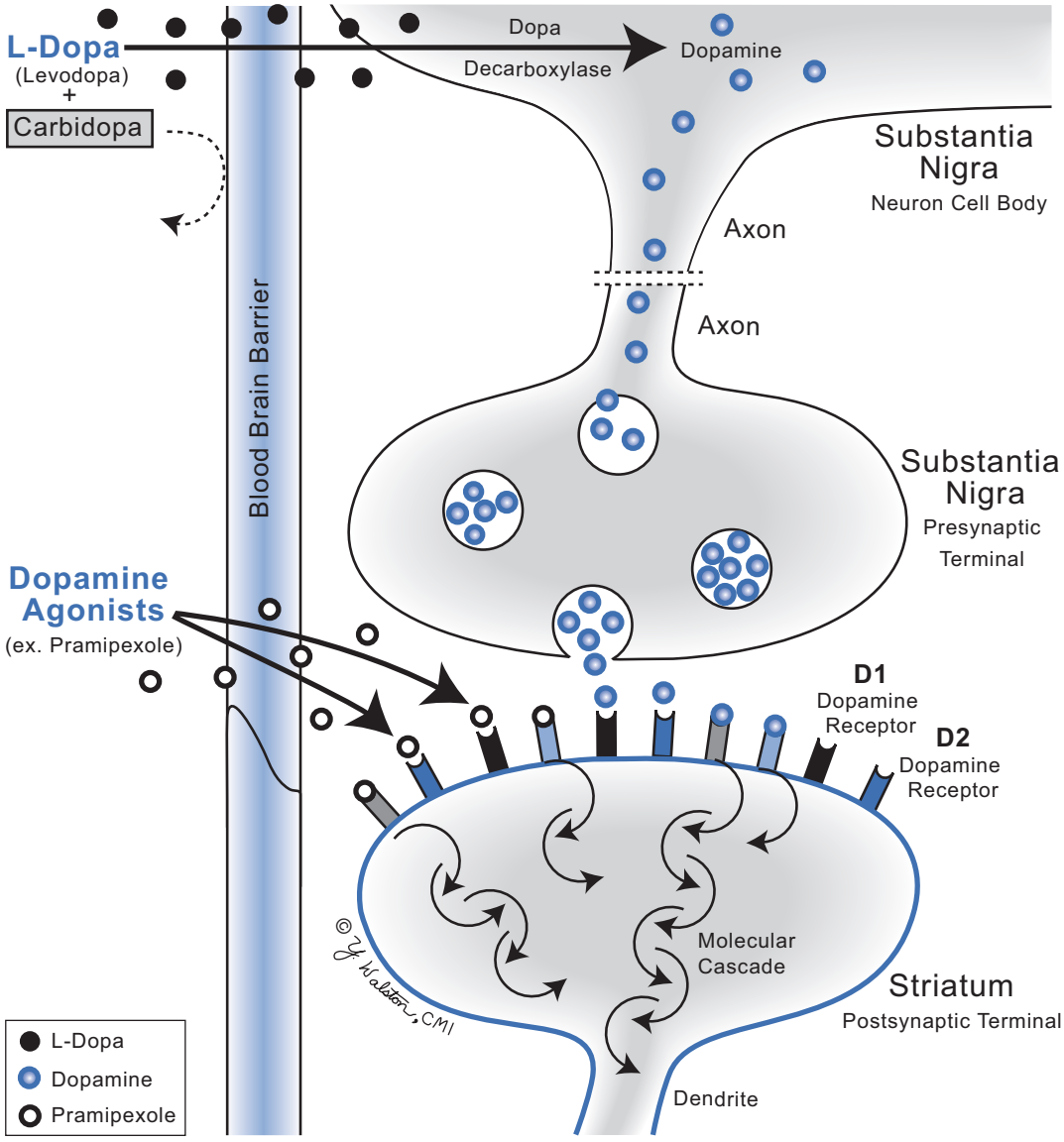

Fig. 12.4 Dopaminergic therapy for Parkinson's disease

in low doses three times a day or from a slow release formulation given once to twice daily. Anticholinergic drugs may help the tremor but have considerable side effects in the elderly including constipation, urinary retention, confusion, memory loss, and hallucinations.

After about 5 years of disease duration, it becomes increasingly difficult to achieve and maintain ideal CNS levels of dopamine. Patients often develop dyskinesias 1–2 h after taking levodopa medication that is felt to represent excessively elevated CNS drug levels that stimulate non-essential dopamine pathways. Patients experience involuntary movements of their arms, legs, and face in an irregular fashion during a time when their bradykinesia is minimal. The levodopa

level then rapidly falls below optimal CNS levels producing freezing spells or "off" periods where they can hardly move. It is felt that "on-off" phenomena represent disease-related loss of dopamine-buffering capacity and storage capacity by striatal dopamine nerve terminals. As the disease progresses, it is not uncommon for patients to experience hallucinations that are often visual, occur in evenings, and may or may not be frightening. Dopamine agonists may be given to smooth out the "on-off" phenomena in the intermediate stage. Unfortunately in the advanced stage, dopamine agonists are less successful and have a similar side effect profile.

When patients have developed motor complications, such as dyskinesia and motor fluctuations, and require very frequent dosing of levodopa to improve symptoms, they are considered for surgical treatment. Early surgical treatments for PD were ablative such as thalamotomy and pallidotomy. They were effective at improving tremor and sometimes other features of the disease but due to side effects were limited to unilateral procedures. Stimulation of these same nuclei with electrical impulses was found to be effective at reducing Parkinsonian symptoms and due to the "nonlesional" nature of this procedure, bilateral interventions could be tolerated. Deep brain stimulation of the globus pallidum interna and the subthalamic nuclei is FDA approved for the treatment of advanced PD. The procedures are not without some risk related to the nature of brain surgery but do provide improvement in Parkinson symptoms with a reduction in the amount of levodopa required for up to a decade (the longest period of follow-up studied thus far).

The goal of transplantation is to replace neuronal circuitry lost by death of substantia nigra neurons with dopamine neurons from fetal mesencephalon or adult adrenal medulla. Studies of patients receiving transplantation of fetal mesencephalon into the striatum have demonstrated survival of the dopamine neurons and even the formation of some synapses to striatal neurons. However, clinical benefit to the patient has been minimal presumably because the transplanted dopamine neurons do not spontaneously fire and release dopamine into synapses to stimulate the striatal neurons. Current experimental approaches in addition to transplantation include growth factor delivered directly to the striatum and gene therapy.

Education of the patient and family about PD is important as this is a slowly progressive illness. Patients should be taught to avoid sofa-like seats since arising from a sturdy captain's chair with arms is easier, to use bars in the bathroom to minimize falls, and eventually to use walkers to improve balance while walking. A hip fracture in a patient with Parkinson disease is serious. There is a slow recovery and a 25 % mortality risk. There is very good evidence that exercise yields important benefits for patients with PD. Exercise has been shown to reduce fall risk and to improve balance. There is also a suggestion of a neuroprotective effect of exercise on the disease process itself.

Huntington's Disease

Introduction

Huntington's disease (HD) is an autosomal-dominant neurodegenerative disease with high penetrance characterized by progressive chorea, cognitive decline, and behavioral disturbances that usually begin in mid-life. The original description came from Dr. George Huntington, a family physician, who in 1872 accurately described the clinical and genetic features of HD from his observations of three generations of illness in a family living in Long Island, New York.

HD is found around the world with the prevalence of 1/10,000–1/20,000 in the Caucasian population. In the USA, about 25,000 individuals have HD and another 60,000 carry the abnormal gene but have not manifest symptoms yet. As an autosomal-dominant disorder, men and women are equally affected and there is a high degree of penetrance in individuals who live to middle age. The average age of onset is between 30 and 50 years, although it can manifest in children as juvenile Huntington's disease.

Pathophysiology

All cases of HD develop from an abnormal extended the length of triplet-repeating cytosine–adenine–guanine (CAG) DNA bases in the *HD* gene. The normal length of the trinucleotide repeats is polymorphic and ranges from 10 to 26 units producing a string of 10–26 polyglutamine amino acids in the normal Huntingtin protein. The length of the CAG trinucleotide repeats is not constant, and healthy offspring normally gain or lose up to 6 repeats. However, CAG repeat lengths longer than 36 units give rise to HD. There is an inverse correlation between the length of the CAG repeats and the age of disease onset. Individuals with repeat lengths of greater than 55 develop juvenile HD with onset before age 20 years. Men with HD often have sperm containing an *HD* gene with many more CAG repeats than in their own somatic cell *HD* gene. Thus, the next generation displays the phenomenon of anticipation, resulting in an increasing trinucleotide repeat length and earlier onset of symptoms.

Huntingtin protein is a large protein (>3000 amino acids) that is expressed widely in neural and non-neural tissues and whose normal function is currently unknown. The amino acid sequence is not related to other proteins but shows a high degree of evolutionary conservation. Studies in animals and man show the gene is essential in fetal development as loss of both gene copies leads to fetal death. However, fetuses containing HD protein molecules with abnormal polyglutamine length have normal fetal and childhood development. Thus, current evidence suggests the pathogenesis of HD is mediated by a "gain of function" of the Huntingtin protein. In this construct, the normal Huntingtin protein functions remain intact but a new function is detrimental to the neuron. In the end, the abnormal Huntingtin protein somehow causes premature death of selected neuronal populations.

The striking pathology in HD is atrophy of the caudate nucleus and putamen (together called the striatum). This is easily visible on gross inspection of the brain (Fig. 12.5) and can be seen on neuroimaging. The neuronal cell loss is primarily from death of medium-sized spiny neurons that account for 80% of striatal neurons. There is a relative preservation of large spiny neurons. Microscopically, intranuclear inclusions that contain fragments of Huntingtin protein are commonly seen in the striatum and there is a secondary gliosis that accompanies the neuronal loss. Medium spiny neurons are inhibitory and release gamma-aminobutyric acid (GABA) as their main neurotransmitter. Medium spiny neurons that have D2 receptors and project to the globus pallidus externa die earlier than those with D1 receptors that project to the substantia nigra and globus

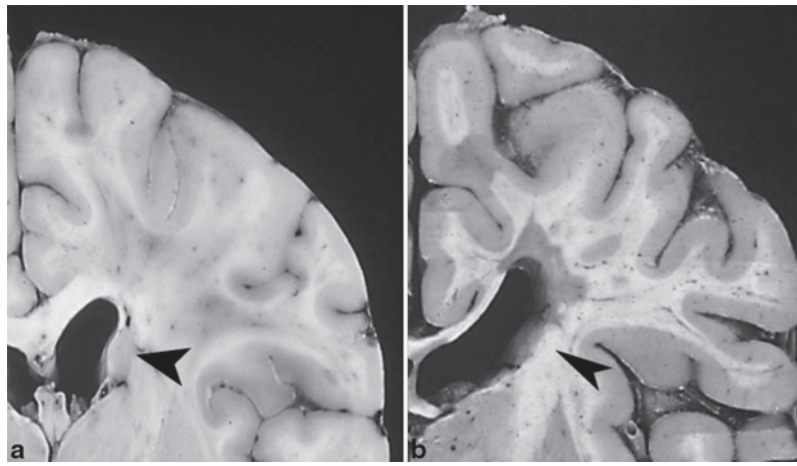

Fig. 12.5 Coronal section of pathologic specimen showing. **a** Healthy subject, protrusion of caudate head into lateral ventricle. **b** Patient with Huntington's chorea, caudate atrophy with resulting dilatation of lateral ventricle (Courtesy of Dr. Mario Kornfeld)

pallidus interna. This unequal pattern of neuronal death is thought to be responsible for adult HD patients experiencing chorea rather than Parkinsonism. In juvenile HD, both neuronal populations die early and these patients express more signs of Parkinsonism—also called the Westphal variant of HD. PET studies demonstrate that hypometabolism in the striatum begins prior to observable atrophy and before the onset of clinical symptoms. In addition to striatal neuronal loss, there is a moderate loss (10–50%) of neurons in many basal ganglia nuclei and the prefrontal cerebral cortex.

Major Clinical Features

The mean age of the onset of HD is 40 years, but some patients do not develop signs until past age 60 years. The clinical features are progressive disorders of movement, cognition, and behavior. Irregular, unpredictable, brief, involuntary jerking movements involving shifting muscles or muscle groups involving the arms, hands, legs, tongue, or trunk characterize chorea, the defining movement disorder of HD. Chorea worsens over the course of the disease in terms of frequency, becoming constant, and of severity. Early in the disease, patients frequently appear fidgety and mask the involuntary limb movement by incorporating the involuntary jerk into a semi-purposeful movement called a parakinesia. Voluntary rapid eye movements from one target to another (saccadic eye movements) become difficult to initiate and quite slow. The inability to sustain a constant voluntary muscle contraction, called motor impersistence, manifests as trouble extending their tongues for any period of time and maintaining a steady handshake without varying contraction strengths (milkmaid's grip). In the early stage of the disease, patients often have normal activities of daily living and may continue to be employed. As the disease worsens, stiffness and slowness can appear such as in dystonic symptoms (such as rigidity involuntary muscle contractions) and Parkinsonism may appear. Dysarthria develops with hypophonic irregular speech that becomes unintelligible. At this stage, the patient depends on others for help. Dysphagia appears late and often contributes to the death of the patient.

A global progressive decline in cognitive capabilities begins before or after the onset of chorea, and only a few patients continue to have only mild cognitive loss. The cognitive decline is characterized by loss of executive functions with the inability to plan, sequence, and execute complex tasks, forgetfulness from loss of recent memory, slow response times, and poor concentration. The IQ score falls and dementia is present in most patients. Aphasia, apraxia, and agnosia are uncommon but impaired visuospatial abilities develop in the late stage.

Behavioral problems often begin with personality changes manifesting as irritability, compulsivity, apathy, and anxiety that may appear years before the chorea. Depression develops in one-third of patients and may lead to suicide. Psychosis is uncommon (5%).

Juvenile HD has an onset of less than 20 years and is characterized by more prominent Parkinsonism, especially bradykinesia. Patients have marked rigidity, severe mental deterioration, prominent motor and cerebellar signs, dysarthria, myoclonus, tics, and dysphagia. Juvenile HD progresses faster than adult HD.

Major Laboratory Findings

Routine blood and CSF tests are unremarkable. Neuroimaging studies demonstrate atrophy of the caudate and may show atrophy of the putamen. The progressive caudate atrophy parallels the loss of cognitive function and putaminal atrophy with motor decline. Neuropsychiatric tests demonstrate many abnormalities but none are diagnostic.

The clinical diagnosis is usually made based on (1) onset in mid-life with typical chorea, cognitive loss, and behavioral changes, (2) positive family history, and (3) neuroimaging demonstrating caudate atrophy. The definite diagnosis is made by demonstrating abnormally long CAG trinucleotide repeat lengths (>36) in the *HD* gene (chromosomal locus 4p16) with genetic testing. This commercial test is useful in establishing the

diagnosis in atypical cases, symptomatic individuals without a positive family history, individuals at risk for the illness, and prenatal screening. For predictive testing to be performed, there should be (1) multidisciplinary supportive counseling before and after testing, (2) clear informed consent, and (3) confidential reporting. In general, predictive tests should not be done on minors.

Principles of Management and Prognosis

Since no treatment is available to cure or slow disease progression, medical management aims at maximizing the quality of life as long as possible. The motor manifestations of HD, specifically the chorea, are treated with dopamine receptor-blocking or depleting medications. Typical and atypical neuroleptics, which block dopamine receptors, are commonly used. Tetrabenazine (a dopamine-depleting and dopamine receptor-blocking medication) is also used to reduce chorea. Tetrabenazine can have significant side effects of depression and suicidality as well as parkinsonism. It is imperative that patients on this medication have frequent and careful screens for worsening of mood, suicidality, and new motor impairment. Depression should be diagnosed early and actively treated with antidepressants. Psychosis and severe agitation can be treated with neuroleptic medication and mood-stabilizing medications. There is no treatment for the cognitive decline. Patients and their families/caregivers benefit from access to a multidisciplinary clinic that specializes in the care of these patients.

HD severely shortens lifespan. The mean duration from diagnosis to death is 20 years with a range from 10 to 25 years with death typically occurring at a mean age of 55 years. Individuals with juvenile HD tend to have an even shorter life span with more rapid progression of their disease.

Video Legend

This video shows a 66 year-old woman with Essential Tremor

Segment 1: Motor Exam
- Low amplitude, high frequency postural/action tremor
- Absence of rest tremor
- Absence of bradykinesia
- Head/Neck tremor present

Segment 2: Cerebellar Exam
- No intention tremor

Segment 3: Handwriting Example
- Tremor on handwriting and Archimedes spiral

This video shows a 70 year-old man with Parkinson disease

Segment 1: Cranial Nerve Exam
- Hypometric saccades
- Hypophonia

Segment 2: Motor Exam
- Bradykinesia
- No tremor with DBS

Segment 3: Gait Exam
- Shortened stride length
- En bloc turn

Recommended Reading

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Roos RA. Huntington's disease: a clinical review. Orphanet J Rare Dis. 2010;5(10):40. doi:10.1186/1750-1172-5-40. *(A succinct review of Huntington's disease from symptoms to genetic counseling)*

Zeuner KE, Deuschl G. An update on tremors. Curr Opin Neurol. 2012;25(4):475–82. (Good review of Essential tremor as well as less common tremors)

Infections of the Nervous System

13

A 68-year-old man is present with a 2 day history of low-grade fever and 1 day of increasing confusion and headache. His wife tells you he has poorly controlled type 2 diabetes, chronic obstructive pulmonary disease from chronic smoking, and osteoarthritis. On examination, his temperature is 100 °F and he has normal oxygen saturation on room air. He is confused but knows his name and recognizes his wife. He has no focal neurologic findings but his neck is stiff in all directions. A lumbar puncture demonstrates an opening pressure of 200 mm H_20, 450 WBC/mm^3 with a predominance of neutrophils, glucose of 26 mg/dL, protein of 130 mg/dL, and Gram stain of CSF sediment demonstrates Gram-positive diplococci. A diagnosis of acute bacterial meningitis is made.

Overview

Viruses, bacteria, fungi, and parasites cause central nervous system (CNS) infections but bacteria and viruses are the most common agents. After entering the body via the gastrointestinal (GI) tract, respiratory tract, or following skin inoculation (animal or insect bites), the infectious organism sets up the initial site of replication in the GI tract, respiratory tract, or subcutaneous/muscle/vascular tissue. Most organisms reach the CNS by way of the blood stream, but occasionally, organisms reach the brain via peripheral nerves or by direct entry through adjacent bone from skull fractures or infected mastoid and air sinuses.

In spite of the many infections we develop during our lifetimes, organisms rarely reach the CNS. Important protective systems include the reticuloendothelial system (which nonspecifically and efficiently removes microorganisms from the blood), cellular and humoral immune responses (which destroy specific microorganisms in the blood and sites of infection), and the blood–brain barrier. The CNS evolved differently from other systemic organs and did not develop a sensitive immune surveillance system. The brain lacks lymphatic channels or lymph nodes. Instead, a blood–brain barrier has developed to prevent infectious organisms from entering the CNS. When intact, the blood–brain barrier not only prevents entry of infectious organisms but also maintains, under tight limits, the type and concentration of molecules free in the CNS.

However, if an infectious organism successfully enters the CNS, there are limited defenses to fight the infection. CSF has 1/1000 the amount of antibody and complement as blood. Since the brain lacks a lymphatic system, there are few white blood cells (WBC) and limited microglia (resident CNS macrophages) to detect and combat an infection. Nevertheless, the CNS exhibits an inflammatory response, the hallmark of CNS infections. Neutrophils and mononuclear cells from blood cross areas of activated endothelial cells and open blood–brain barriers to appear in the meninges, brain parenchyma, and perivascular spaces. The mononuclear cells usually show specific immune activity against the

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Table 13.1 Keys to suspecting a CNS infection

Fever
Acute or subacute onset
Headache
Focal or diffuse symptoms and signs depend on location of infections (see Table 13.2)
Elevated white blood count and erythrocyte sedimentation rate
Increased frequency in immunosuppressed individuals

infectious agent. Unfortunately, the brain inflammatory response is ineffective against bacteria and fungi and patients usually die unless treated with appropriate antimicrobial drugs.

The signs and symptoms of a CNS infection depend on the site of the infection and not the infectious organism. The organism determines the time course and severity of the infection.

Table 13.1 gives the keys to suspecting a CNS infection. The patient's signs and symptoms suggest the likely location of the infection but not the infectious organism. The time course of the infection may help determine the type of infectious organism; viruses after entering the meninges produce CNS signs in hours to 1 day; aerobic bacteria in hours to a few days; anaerobic bacteria, tuberculosis, and fungi in days to weeks; and spirochetes such as *Treponema pallidum* (syphilis) in weeks to decades.

There are three major sites where infections occur in the CNS: diffusely in the meninges (meningitis), diffusely in the brain (encephalitis), and focally in the brain (abscess) (Fig. 13.1). Table 13.2 gives the major signs and symptoms for infections at these sites. Although there are many different infectious organisms that can

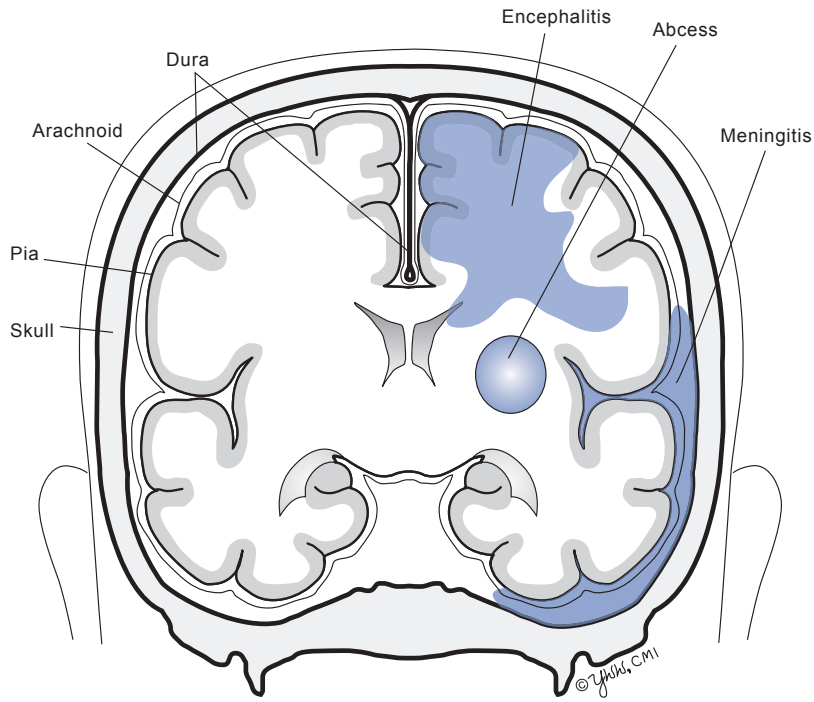

Fig. 13.1 There are three major sites where infections occur in the CNS: diffusely in the meninges (meningitis), diffusely in the brain (encephalitis), and focally in the brain (abscess)

Table 13.2 Clinical features of major CNS infections

	Meningitis	Brain abscess	Encephalitis
Common	Fever	Headache	Fever
	Headache	Mental status changes: confusion, stupor, coma	Headaches, nausea, vomiting
	Stiff neck	Seizures: generalized or focal	Mental status changes: confusion, stupor, or coma
	Confusion	6th nerve palsy	Seizures: generalized or focal
		Hemiparesis	Hyperreflexia, Babinski signs, or spasticity
		Papilledema	Mild stiff neck
Less common	Seizures	Stiff neck	Tremors, choreathetosis, papilledema
	Stupor or coma		
	Papilledema		

infect the meninges and brain, this chapter discusses the most common CNS infections. We will also consider an infection of the peripheral nervous system and a rare infection that breaks conventional rules for infectious diseases.

Meningitis

Introduction

Meningitis is due to inflammation of the meninges and is the most common CNS infection. Most infections are due to viruses or bacteria but meningitis also can be caused by fungi, parasites, chemicals, and neoplasms. Viral meningitis is the most common infection of the central nervous system and occurs worldwide with the highest incidence in children and young adults. Viral meningitis is the main cause of a broader term, aseptic meningitis, which refers to meningitis with no laboratory evidence of a bacterial or fungal infection. Viral meningitis occurs mainly in the spring and summer while bacterial meningitis occurs year around. In developed countries, bacterial meningitis occurs equally in children and adults, but is more common in individuals who are immunosuppressed.

Pathophysiology

Enteroviruses, herpes simplex virus type 2, and mumps virus (in countries that do not routinely administer mumps vaccine to children) are the most common etiologies of viral meningitis. Aerobic bacteria, both Gram positive and Gram negative, are the major causes of acute bacterial meningitis. Other bacteria such as *Borrelia burgdorferi* (Lyme meningitis), *Mycobacterium tuberculosis*, and *Treponema pallidum* (neurosyphilis) commonly cause chronic meningitis. The usual route of entry for bacteria and mumps is via the upper respiratory tract where they establish an early asymptomatic infection. Enteroviruses route of entry is oral. Herpes simplex type 2 virus invades mucosa following sexual contact. Most invasive bacterial and viral strains cross though the respiratory or GI epithelial barriers to reach capillaries, veins, and lymphatic channels and then enter the blood. In the blood stream, bacterial characteristics such as large mucopolysaccharide coats hide the bacteria from the reticuloendothelial system allowing them to persist and replicate to high titers, both risk factors for meningitis. Increasing evidence finds that bacteria that cause meningitis can attach to cerebral endothelial cells via specific receptors for each type of bacteria and travel across the barrier inside the endothelial cell to be released in the subarachnoid space. Once within the CSF, the bacteria again replicate and release endotoxin (Gram-negative bacteria) or teichoic acid (Gram-positive bacteria) from their cell walls. Viruses and these molecules stimulate resident macrophages and microglia to release cytokines (especially interleukin-1 and tumor necrosis factor) that in turn recruit neutrophils and

mononuclear cells into the CSF from the blood. In bacterial meningitis and most viral meningitis, the organism is confined in the meninges and does not invade the brain parenchyma.

As the inflammation increases in bacterial meningitis but not viral meningitis, the brain becomes irritated and damaged. Endotoxin released from the cell walls of dying bacteria and molecules released from inflammatory cells (such as tumor necrosis factor, neutrophil granule molecules) can pass through the pial lining of the brain, which lacks a blood–brain barrier to invade and kill neurons located at the surface of the cerebral cortex and cerebellum. In addition, the meningeal inflammation can cause vasospasm or thrombosis of arteries and veins passing in the meninges to reach the brain. Occlusion of these vessels leads to cerebral infarctions of the corresponding vascular territory. Thus, while bacteria do not invade the brain, severe brain damage can result from intense meningitis.

In viral meningitis, the host immune system eliminates the virus from the meninges. However, in bacterial meningitis, the immune system does not kill the bacteria, allowing continued bacterial replication until the individual dies unless appropriate antibiotics are administered.

Major Clinical Features

The clinical hallmark of any early meningitis is fever, headache, and stiff neck, and a relatively preserved mental status (Table 13.2). These symptoms have an abrupt onset over a few hours. The headache comes from inflammation of pain fibers along the base of the brain and second and third spinal nerves. The fever may be due to direct activation of the hypothalamus or CSF interleukin-1 released into the CSF by the inflammatory cells. However, all three symptoms are present in only two-thirds of meningitis patients. Patients with bacterial meningitis seldom present with focal neurologic signs but hemiparesis, aphasia, ataxia, and visual loss may develop later in the clinical course. Papilledema is rarely present at onset. Patients with bacterial meningitis can progress from early symptoms to evidence of brain damage within one to a few days.

Major Laboratory Findings

The definite diagnosis of meningitis and establishing whether the meningitis is viral or bacterial is made from the analysis of CSF. When meningitis is suspected, the lumbar puncture (LP) becomes an emergency procedure. Table 13.3 demonstrates the CSF findings in bacterial meningitis and distinguishes them from other CNS infections. Figure 13.2 illustrates the common bacteria that cause meningitis in the USA. In countries that do not give children the *Haemophilus influenzae* vaccine, *H. influenzae* meningitis is the most common type for children less than 5 years old. The administration of pneumococcal vaccine is also reducing the incidence of pneumococcal meningitis in children.

Table 13.3 CSF findings in major CNS infections[a]

	Opening pressure	White blood cells/mm3	Predominate WBC type	Protein (mg/dl)	Glucose (mg/dl)	Bacterial or fungal culture
Meningitis						
Viral	N	20−1000	Mononuclear	Sl ↑	Normal	Negative
Bacterial	N or ↑	50−5000	Neutrophils	↑	Low	Bacteria
TB or fungal	↑	50−10,000	Neutrophils and lymphs	↑	Low	Sometimes positive
CNS syphilis	N	10−1000	Lymphs	↑	Normal	Negative
Brain abscess	↑	0–20	Lymphs	Normal	Normal	Negative
Viral encephalitis	Sl ↑	10–200	Lymphs	Sl ↑	Normal	Negative

N normal, Sl slight, ↑ increase, *lymph* lymphocytes

[a] Exceptions to above rules often occur

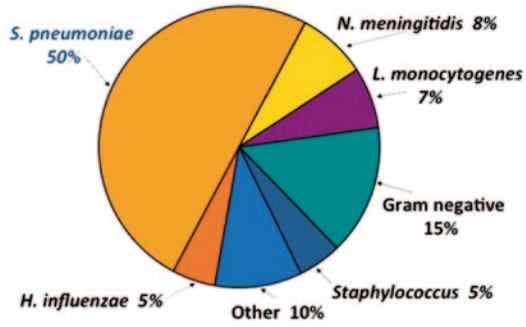

Fig. 13.2 Common bacteria that cause meningitis in the USA

For suspected viral meningitis, the etiology often can be established rapidly for enteroviruses and herpes simplex viruses by polymerase chain reaction (PCR) assay for viral nucleic acid in CSF. Viral culture of CSF obtained early in the meningitis may isolate the virus. Gram staining of CSF sediment identifies the bacterial type over 75% of the time but does not identify the strain of bacteria or its antibiotic sensitivity pattern. Aerobic bacterial culture of CSF sediment usually isolates the organism and allows subsequent studies to determine antibiotic sensitivity.

Almost all patients with bacterial and many with viral meningitis have an elevated blood WBC count. In bacterial meningitis, neutrophils are elevated and there are elevated numbers of immature cells or a "shift to the left." The blood erythrocyte sedimentation rate (ESR) and serum C-reactive protein are also elevated.

Neuroimaging usually does not diagnose meningitis. Cranial computed tomography (CT) scans might be indicated before the LP if intracranial masses or acute hydrocephalus is suspected (see section on CSF in Chap. 3 on common neurologic tests). Enhancement of the meninges, especially in the basal cistern area, is commonly seen with gadolinium-enhanced magnetic resonance imaging (MRI) in bacterial meningitis but not viral meningitis. If neurologic complications develop in the patient, neuroimaging may demonstrate communicating or obstructive hydrocephalus, brain infarctions, or focal areas of brain necrosis across the cortical surface.

Principles of Management and Prognosis

For viral meningitis, management is symptomatic with antinausea and analgesic medications. Acyclovir is a drug that prevents herpes simplex virus replication and may shorten the duration of herpes simplex meningitis. Over 95% of patients with viral meningitis make a full recovery within 1–2 weeks but patients with herpes simplex meningitis may experience relapses over the next 10 years.

For bacterial meningitis, the key to etiologic treatment is the prompt administration of appropriate antibiotics. Without antibiotics, over 95% of patients die. General principles involved in the use of antibiotics are: (1) the antibiotic should be given as early in the clinical course as possible; (2) the bacteria must be sensitive to the antibiotic administered; and (3) the antibiotic must cross the blood–CSF barrier and achieve sufficient concentration to kill the bacteria. Once the clinical diagnosis of bacterial meningitis is made, immediate treatment with broad spectrum antibiotics begins. Based on the patient's age, predisposing medical condition, immune status, CSF Gram stain or bacterial antigen tests, and knowledge of types of drug-resistant bacteria in the community, antibiotics are chosen that are likely to kill the CSF bacteria. When the bacterium is grown in the laboratory and antibacterial susceptibilities are determined, the antibiotic regiment can be appropriately modified.

The optimal initial antibiotics to be given constantly changes and one should consult the latest antibiotic recommendations. Currently, many patients with community-acquired meningitis are initially treated with third- or fourth-generation cephalosporins and vancomycin since the incidence of *Streptococcus pneumoniae* resistance to third-generation cephalosporins is now > 15% in most communities. In general, the antibiotics should be administered intravenously for 10–14 days. Early administration of corticosteroids for 2–4 days has been shown to reduce the death rate and long-term neurologic sequelae in children and adults with community-acquired bacterial meningitis.

Symptomatic treatment of seizures includes the administration of phenytoin until the patient is discharged. If severe obstructive hydrocephalus develops, a ventriculoperitoneal shunt is required.

Meningitis from *Neisseria meningitidis* and *H. influenzae* require chemoprophylaxis of immediate family members and close contacts, who have not received the meningococcal vaccine, with rifampin or ciprofloxacin (adults only) as they are at increased risk of developing meningitis.

Mortality ranges from 5 to 25% depending on the infecting bacterium, age of patient, and predisposing illnesses. In surviving children, 15% have language disorders, 10% mental retardation, 10% hearing loss, 5% weakness or spasticity, and 3% epilepsy. Adults have a similar pattern of neurologic sequelae.

Brain Abscess

Introduction

A brain abscess is a localized intracerebral infection that begins as a focal area of cerebritis and develops into a collection of pus surrounded by a capsule. If the abscess develops outside the brain and around the dura, it is called either a subdural empyema or epidural abscess. Brain abscesses most commonly occur from a bacterial infection but fungi, *Mycobacterium tuberculosis*, and protozoa can also cause a focal brain infection. Brain abscesses are uncommon with an incidence of about 1 case/100,000 persons per year and develop at all ages but are more common in males.

Pathophysiology

The brain has no normal flora of bacteria or fungi. Microorganisms that cause an abscess reach the brain primarily from adjacent infected sinuses or mastoid air cells, from blood infections, or following head trauma. Common sources of bloodstream infection include infections of lungs (bronchiectasis, empyema, and lung abscess), gastrointestinal tract, urinary system, mouth (dental abscess), heart (acute bacterial endocarditis and cyanotic congenital heart disease), and intravenous drug abuse. In about 20% of patients, no initial source for the brain abscess can be identified.

The location of the abscess depends on the source. Brain abscesses from frontal sinusitis occur in the frontal lobe adjacent to the infected sinus. Abscesses from mastoiditis develop in the temporal lobe (from upward extension) or occasionally in the cerebellum (from medial extension). The locations of abscesses from a hematogenous route are generally distributed proportional to cerebral blood flow. About three-quarters of brain abscesses are solitary.

The brain abscess begins as a small area of brain infection (cerebritis) often located at the gray–white matter junction of the cerebral cortex. Growth of the organism soon results in expansion of the cerebritis with increasing numbers of neutrophils and mononuclear cells entering the infected site. Necrosis with liquefaction of the center of the abscess then occurs. A variable amount of surrounding cerebral edema contributes to the mass of the abscess. A fibrotic and gliotic response surrounds the abscess forming a capsule but the capsule wall is inadequate to control medial expansion of the abscess. If untreated, the abscess expansion continues until the mass is large enough to cause transtentorial herniation (cerebral hemisphere abscess), foramen magnum herniation (cerebellar abscess), or rupture of the abscess contents into the ventricles (ventriculitis).

Major Clinical Features

The signs and symptoms of a brain abscess are those of a rapidly expanding brain mass that develops over 1–2 weeks (Table 13.2). Common symptoms at presentation are those of increased intracranial pressure (ICP) and focal neurologic signs. Signs and symptoms of ICP include headache (75%), lethargy and confusion (70%), focal neurologic deficits (60%), fever (50%), nausea and vomiting (30%), focal or generalized seizures (30%), and papilledema (25%).

Focal neurologic signs depend upon the abscess location but hemiparesis, aphasia, homonymous hemianopsia, and ataxia are common. Depending on the location, the focal neurologic signs may present first followed by increasing signs of ICP or vice versa. As the abscess continues to expand producing a larger mass, it causes more clinical signs including coma.

Major Laboratory Findings

The white blood cell count is elevated in 60%. The ESR and serum C-reactive protein are often elevated, indicating the presence of a systemic infection. When identified, biopsy or aspiration material from the distant site can be studied similar to the abscess pus. The most important laboratory tests involve the pus surgically removed from the abscess. The following tests should immediately be performed: (1) stain of abscess material with Gram, Giemsa, and fungal stains, (2) culture abscess material for anaerobic and aerobic bacteria and fungi, (3) culture abscess material for *Mycobacterium tuberculosis* or protozoa if clinical history warrants, (4) process tissue for histological examination if solid material is present to identify neoplasm, bacteria, fungi, protozoa, etc. Common bacteria isolated from abscess pus are anaerobic or microaerophilic and include *Streptococci* (especially *S. milleri* group and *S. viridian* group), *Bacteroides* species, *Enterobacteriaceae*, and *Staphylococcus aureus*.

The clinical diagnosis is made by neuroimaging with cranial CT with and without contrast or MRI with and without gadolinium (Fig. 13.3). Both images at the abscess stage demonstrate a hypointense center of pus surrounded by a contrast-enhancing abscess capsule and variable amounts of surrounding cerebral edema. MRI is slightly more sensitive in establishing the diagnosis since it is especially good at identifying early cerebritis, multiple abscesses, and abscesses located adjacent to bone. MRI may also help to distinguish abscess from tumor or other mass.

Principles of Management and Prognosis

Optimal management of the patient involves: (1) prompt reduction of the size of the life-threatening mass (abscess and surrounding cerebral edema); (2) collection of appropriate culture specimens; (3) definitive treatment of the brain abscesses with antibiotics and usually neurosurgical drainage or evacuation of the abscess; (4) identification and elimination of the source of the brain abscess; (5) prevention of seizures; and (6) neurorehabilitation.

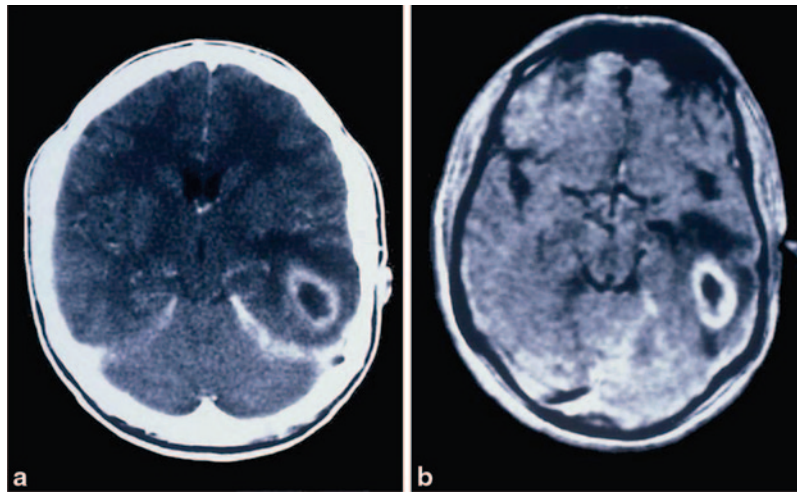

Fig. 13.3 Brain abscess shown as ring-enhancing lesion by CT scan (**a**) and MRI scan (**b**) (Courtesy of Dr. Blaine Hart)

Reduction in the mass size is best accomplished by stereotactic surgical aspiration of the abscess once it has reached the liquefaction and cavitation stage and is about 2.5 cm in diameter. Stereotactic surgery using CT or MRI guidance is minimally invasive and provides pinpoint accuracy for the aspiration of selected sites. Corticosteroids may be briefly administered to reduce the surrounding cerebral edema especially if brain herniation is possible.

The initial antibiotic treatment should be against a wide variety of anaerobic and aerobic Gram-positive and Gram-negative bacteria. Empirical antibiotics should be chosen based on suspected organism obtained from the history, likely pathogenesis, abscess location, and ability of the drug to penetrate the blood–brain barrier and abscess wall. Common initial therapy is a third- or fourth-generation cephalosporin plus metronidazole and vancomycin. The duration of antibiotic treatment ranges from 4 to 8 weeks. Administration of phenytoin is often given to prevent seizures, which dramatically further elevate the intracranial pressure. Rehabilitation after treatment helps minimize neurologic sequelae.

The mortality of a brain abscess remains 10–20 %. In survivors, 20–60 % are left with neurologic sequelae that include hemiparesis, aphasia, ataxia, visual loss, and epilepsy.

Encephalitis

Introduction

Encephalitis is a diffuse infection of the brain parenchyma. Viruses are the most common infectious agent but bacteria (e.g., general paresis from *T. pallidum*), and protozoa (e.g., toxoplasmosis) also cause diffuse brain infections. Numerous viruses cause encephalitis but herpes simplex virus and a group of arboviruses (*ar*thropod *bo*rne *viruses*) are the most common. Arboviruses are transmitted by mosquitoes or ticks. As such, human infections occur in clusters or epidemics in late spring, summer, and early fall when the vectors are present. Humans become infected when bitten by virus-infected mosquitoes.

Herpes simplex encephalitis (HSE) occurs sporadically the year around since the virus is usually latent in the host. In the USA, herpes simplex virus is the most common cause of sporadic encephalitis, and West Nile virus the most common cause of clustered or epidemic encephalitis.

The severity of the encephalitis depends mainly on the infectious organism. Thus, herpes simplex, Eastern equine encephalitis, and Japanese B viruses cause severe encephalitis while Venezuelan equine encephalitis and California viruses produce mild disease. Most viruses that cause encephalitis infect both neurons and glia. An exception to this rule is poliomyelitis where the poliovirus selectively infects only neurons involved in the motor system.

Herpes Simplex Encephalitis (HSE)

Herpes simplex virus (HSV) type 1 is most often responsible for the acquired encephalitis in children and adults. Pregnant mothers, who had acquired a genital herpes simplex infection from HSV type 2 virus, can infect infants during delivery through an infected birth canal producing neonatal encephalitis and disseminated infection.

Pathophysiology

HSV type 1 is most often acquired during early childhood as a self-limited stomatitis that is seldom diagnosed. During that infection, the virus travels up the sensory axons of the trigeminal nerve from the mouth to the trigeminal ganglia. In the corresponding ganglion neuron, the virus becomes latent in the nucleus. During latency, no viral proteins appear on the neuronal membranes so the host immune system does detect and eliminate the virus. From time to time, viral latency breaks and new virus produced in the neuron cell body travels down the axon to release virus at the skin ending where a localized infectious vesicle (fever blister) develops.

How HSV reaches the brain is poorly understood. Since HSE usually develops in healthy individuals who have been previously infected

with herpes simplex virus, activated latent virus appears reaches the brain. One hypothesis proposes that a latently infected neuron in the trigeminal ganglion innervates the base of the brain rather than the face. Should that neuron break latency, the resulting viral infection would develop in the ipsilateral temporal lobe.

Most cases of HSE start in the temporal lobe. The viral infection rapidly produces encephalitis in the medial temporal lobe then spreads to the opposite temporal lobe and throughout the brain. The pathologic hallmark of all encephalitis is widespread brain inflammation usually characterized by perivascular cuffing (lymphocytes adjacent to cerebral blood vessels) and focal areas of necrosis with secondary gliosis (glial nodules). Commonly, HSE is severe enough to produce areas of necrosis and hemorrhage. Viral-infected neurons and glia often develop an intranuclear inclusion body (Cowdry type A inclusion) that is suggestive but not diagnostic for HSE.

Major Clinical Features

Herpes simplex encephalitis develops equally in both sexes and in all ages without a prodromal illness. The acute encephalitis is characterized by the abrupt onset of fever, headache, and mental obtundation. Table 13.2 lists the most common signs and symptoms for all forms of encephalitis including HSE. Although HSE begins in the temporal lobe, there are no clinical features that allow its distinction from other viral causes of encephalitis. For example, the presence of a labial fever blister or isolation of herpes simplex virus from the blister or throat is of no diagnostic value since herpes simplex oral lesions often develop in ill patients with encephalitis from any cause.

Encephalitis differs from meningitis in that patients present with prominent mental status changes, focal neurologic signs, and minimal or absent stiff neck.

Major Laboratory Findings

The peripheral WBC count is often mildly elevated. The CSF may be under increased pressure and usually shows a mononuclear pleocytosis ranging from 10 to 300 WBC/mm^3. Occasionally, the CSF contains elevated RBC that can range over 1000 /mm^3. The CSF protein level is mildly to moderately elevated but the glucose level remains normal. Gram stain is negative. CSF viral cultures rarely grow herpes simplex virus. IgG antibodies to HSV type 1 are usually present in older children and adults, but HSE does not result in production of IgM antibody. Therefore, the presence of antibody to herpes simplex virus rarely helps make the diagnosis.

A definitive diagnosis is usually made by detection of HSV DNA in CSF by a PCR assay (see Chap. 3 on common neurologic tests). The CSF PCR assay for herpes simplex virus is positive in over 95% of HSE patients during the first few days of the encephalitis.

The EEG is abnormal in all cases of encephalitis and helps distinguish viral encephalitis from viral meningitis, which usually has a normal EEG. In some patients with HSE, the EEG demonstrates high-voltage complexes that originate from the temporal lobes in a semiperiodic nature that are suggestive but not diagnostic.

The MRI scan is very helpful in HSE. Early MR images often demonstrate T2-weighted abnormalities in the medial aspect of a temporal lobe with extension into the subfrontal and insular cortex (Fig. 13.4). When MRI changes are seen in the medial temporal lobe in a patient with encephalitis, the likelihood of HSE is increased as arbovirus encephalitis seldom begins only in the temporal lobe. CT is less helpful since abnormalities appear a few days later than the MRI. CT abnormalities include low-density lesions in one or both temporal lobes and areas of hemorrhagic necrosis.

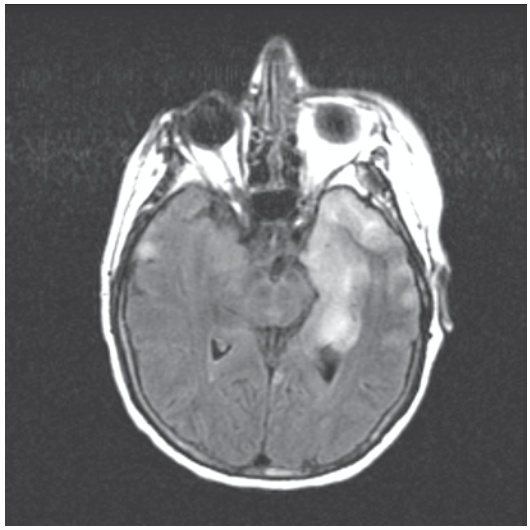

Fig. 13.4 Axial, T2-weighted MRI showing left medial temporal lobe increased signal in a 53-year-old patient with fever and encephalopathy, CSF HSV PCR positive (Courtesy of Dr. Blaine Hart)

Principles of Management and Prognosis

Treatment with the antiviral drug acyclovir in high doses for 14–21 days dramatically improves the morbidity and mortality. The sooner the acyclovir is given the better the outcome. In the presence of herpes simplex virus thymidine kinase, acyclovir is monophosphorylated within a cell. Host cell thymidine kinases then phosphorylate the drug to its active triphosphate state, which then inhibits DNA synthesis. Of note, acyclovir is relatively nontoxic to normal cells and has few side effects, but its administration requires good hydration to prevent renal failure from the drug precipitating in the kidney.

In the absence of acyclovir treatment, HSE has a mortality rate of 70% but about 70% of patients treated with acyclovir survive and 30% of survivors make a good recovery.

West Nile Virus Neuroinvasive Disease

Since the introduction of West Nile virus (WNV) into the U SA in 1999, the virus has rapidly spread and now causes encephalitis in every continental state. Human cases generally develop in late summer and fall when birds begin migrating south for winter and infected mosquitoes look for new hosts.

Pathophysiology

Following inoculation by an infected mosquito, WNV locally replicates first in the epidermis and then in local lymph nodes where the host starts a humoral and cellular immune response. After several days, a viremia develops that is asymptomatic. About 80% of individuals remain asymptomatic, 20% develop a flulike fever, and only 1% develop encephalitis. Evidence suggests that the host IgM antibody response in most patients eliminates the viremia before the virus can enter the brain. Those developing encephalitis tend to be older adults or are immunocompromised.

Major Clinical Features

Encephalitis patients develop fever, headache, confusion, and varying focal signs that include delirium, tremors, memory loss, aphasia, limb weakness, seizures, and coma, which are not distinguishable from most other types of encephalitis. However, about 10% of patients also develop a myelitis that resembles poliomyelitis with virus infecting the spinal cord anterior horn neurons producing flaccid paralysis in muscles of one or more limbs.

Major Laboratory Features

Elevated white blood counts occur in about half and hyponatremia is seen in about one-third of the patients. The CSF shows a mean of 225 WBC/mm^3 containing a lymphocyte and neutrophil mixture, mean protein of 100 mg/dL, and normal glucose level. WNV is rarely isolated from CSF but viral RNA can be identified by reverse-transcriptase PCR assay.

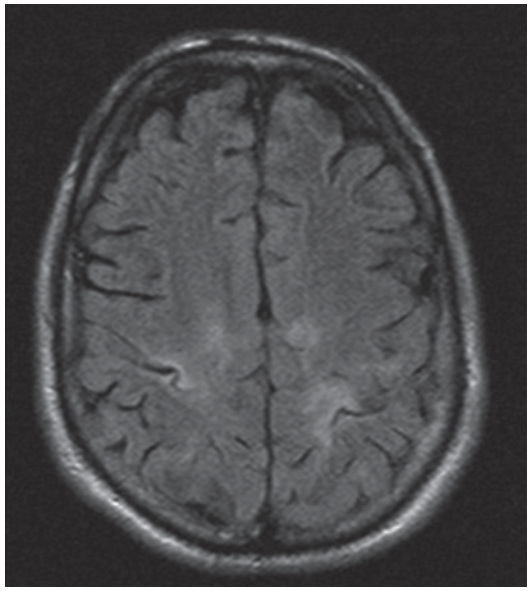

Fig. 13.5 Axial, T2-weighted MRI showing bilateral multifocal cortical areas of increased signal in a 49-year-old male with a 1-week history of headache, fever, stiff neck, and delirium. CSF studies revealed a mild lymphocytic pleocytosis and serum IgM for West Nile virus was present. (Courtesy of Dr. Blaine Hart)

The MRI may be normal or demonstrate small scattered foci of hyperintensity in T2-weighted images particularly in the gray matter, basal ganglia, and brainstem (Fig. 13.5).

The diagnosis is usually established by finding an elevated serum or CSF IgM antibody titer to West Nile virus. The test is usually positive by the first few days of the encephalitis.

Principles of Management and Prognosis

Since arboviruses are RNA viruses, there is no antiviral treatment available. Elimination of the virus occurs from the host immune response entering the brain and eliminating infected brain cells. The acute illness lasts only a few weeks but recovery slowly occurs over months. The majority of patients make a good recovery but persistent cognitive complaints, tremors, and Parkinsonism may occur. Individuals who developed a poliomyelitislike syndrome with flaccid paralysis usually make some motor recovery but often are weak. Mortality rate of those with encephalitis ranges from 5 to 15%.

Mortality from encephalitis from arboviruses varies by the viral strain and ranges as high as 50% for Eastern equine encephalitis and Japanese B to 5–15% for many other arboviruses.

Herpes Zoster or Shingles

Introduction

Shingles is the most common infection of the nervous system and develops in over 1 million individuals per year in the USA. The lifetime incidence is as high as 30% but the lifetime incidence in individuals over the age of 85 years is 50%. Age over 60 years and immunosuppression are the most important risk factors for the development of shingles.

Pathophysiology

Varicella-zoster virus (VZV) is a member of the herpesvirus family, infects exclusively humans, and shares many common properties with herpes simplex virus. The primary infection causes chickenpox mainly in children. A viremia spreads virus to the skin epithelial cells where multiple vesicles develop. Free virus in the vesicle enters a sensory nerve ending in infected skin and travels retrograde to the neuron cell body located in a dorsal root ganglia or trigeminal ganglia. The herpesvirus can also directly reach the sensory ganglion neuron via the blood stream. At that point, the viral nucleic acid enters the cell nucleus and becomes latent for decades. Evidence suggests that the latency is maintained by the host cellular immune system.

As the individual ages or becomes immunosuppressed, cellular immunity falls to a level that somehow enables one latent VSV to break latency. The virus then replicates in the neuron and spreads to other ganglion neurons for several days. During the prodomal period, patients often complain of dermatomal aches or itching without a correspond-

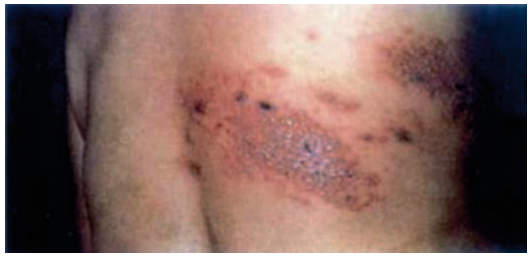

Fig. 13.6 Herpes zoster acute vesicular rash in a thoracic dermatome (Courtesy of Dr. Larry Davis)

ing rash. VZV then spreads centrifugally down the dermatomal sensory nerves causing macules that turn to clusters of vesicular eruptions on an erythematous base similar to that seen in chickenpox (Fig. 13.6). The vesicles may be patchy over parts of the dermatome or cover the entire dermatome. The clear vesicles become cloudy, pustulate, rupture, and crust over 1–2 weeks with healing occurring over the next 2–6 weeks.

Major Clinical Features

Patients complain of variable pain or itching along a distribution restricted to the dermatome. The pain intensity varies from mild (40 %) to moderate (35 %) to severe (25 %). The most common pain type is a burning or aching sensation. Some patients also develop lancinating pains lasting seconds and some develop allodynia or painful sensations developing in affected areas of the dermatome from light touching of clothing, cold or warm temperatures placed on the skin, or breezes blowing over the skin.

Major Laboratory Features

The appearance of a vesicular rash on an erythematous base corresponding to a unilateral dermatome is sufficiently distinctive that a clinical diagnosis of shingles is usually accurate. Occasionally, it is necessary to confirm the diagnosis with direct fluorescent antibody (DFA) staining of VZV-infected cells in a scraping of cells from the base of the lesion or direct viral isolation or PCR assay of vesicle fluid.

Principles of Management and Prognosis

Three antiviral drugs (acyclovir, valacyclovir, and famciclovir) have been shown in prospective randomized, double-blind clinical trials to: (1) shorten the duration of new lesions by about one day, (2) reduce the total number of vesicles by 25 %, (3) lessen the duration of viral shedding from the rash, (4) shorten the time to rash healing by a few days, (5) lessen the intensity and duration of acute pain during the rash in about one-third of patients, (6) reduce the risk of VZV dissemination in immunosuppressed patients, and (7) slightly reduce the risk of postherpetic neuralgia (PHN).

Pain management needs to be approached based on the individual patient's pain and underlying conditions with an eye toward treating aggressively and early. For mild pain, acetaminophen or NSAIDs help but weak opiates such as codeine or tramadol may be necessary. Occasional patients will require the addition of tricyclic antidepressants (nortriptyline) or anticonvulsants (gabapentin) for pain control.

In the majority of patients, the rash heals in several weeks and the pain subsides by 1–12 weeks. However, in a few patients the pain persists longer than 3 months and postherpetic neuralgia (PHN) develops. These patients develop all three types of pain with allodynia frequently being the worst. Managing the dermatomal pain in these patients is difficult and frequently requires narcotics. PHN may persist for months to years.

The new varicella-zoster vaccine has been shown to prevent the development of shingles by 50 % and development of PHN by 67 %.

Prion Diseases

Introduction

Prion diseases are rare and occur as Creutzfeldt–Jakob disease (CJD), the juvenile variant of CJD (vCJD), Gerstmann–Straussler syndrome, fatal familial insomnia, and Kuru in humans, scrapie in sheep, and bovine spongiform encephalopathy

(mad cow disease) in cattle. These prion diseases are discussed because the infectious agent (prion) breaks the conventional rules for infectious agents and may represent a new class of misfolding diseases. First, the infectious particle whose DNA resides in host chromosome 20 of humans is a single unique protein molecule (prion) of 27–30 kD. No nucleic acid has been identified that is attached to the protein. Second, the infectious particle is not killed by formalin, ethanol, or boiling but can be destroyed by autoclaving. Third, patients with the illness do not present with typical signs of an infection. They lack fever or elevated white blood cell counts and have normally appearing CSF although the CSF contains infectious prions. Fourth, the host makes no immune response to the infectious protein so the brain lacks inflammatory cells typical of encephalitis.

Pathophysiology

Prion diseases occur by three different routes: sporadic, infectious, and hereditary and all share an abnormal brain protein called a prion. The *PRNP* gene produces a normal cellular protein (PrP^c) that has a specific three-dimensional (3-D) configuration that is found in membranes of neurons and other cells. In prion diseases, the normal cellular protein somehow alters its 3-D configuration to become a family of abnormal prion proteins, commonly called PrP^{sc}, that all contain the same amino acid sequence. Each different 3-D configuration causes a human disease that has a different clinical picture (phenotype). The probability of the protein misfolding increases if genetic mutations are present at specific DNA sites. The abnormal protein not only causes neurologic disease but also is infectious.

When the abnormal prion enters a normal cell containing only normal PrP^c proteins, the prion causes PrP^c proteins to reconfigure their 3-D structure to become identical to the 3-D structure of the abnormal prion. Prions are poorly catabolized by the host neuron, accumulate, eventually kill the cell, and spread to other neurons. The abnormal prion is structurally so close to the normal cell protein that the host does not recognize prions as foreign and hence produces no immune response. As such, prion diseases appear like a degenerative disease without inflammatory cells or the production of specific antibody.

Once CJD starts from any cause, the entire nervous system becomes infectious. Infectious transmission producing CJD in the recipient has been shown to occur following transplantation of corneas, pituitary extracts, and dural grafts. There is considerable evidence that the juvenile variant of CJD seen in the UK can rarely develop from oral consumption of the meat of infected cattle. Finally, CJD and other human prion diseases can be an autosomal-dominant hereditary diseases occurring in families with specific single-site mutations in the *PRNP* gene.

The pathologic hallmarks of CJD are generalized brain atrophy, spongiform degeneration ("tiny holes" in the cortex), and widespread gliosis without inflammation. Amyloid plaques are seen in the juvenile variant of CJD and Gerstmann–Straussler syndrome.

Some proteins that are capable of folding into different 3-D configurations may actually be normal. There is now evidence that a prion-like protein is involved in altering hippocampal synapses to produce new long-term memories.

Major Clinical Features

CJD is the most common prion disease with an incidence of 1/1,000,000 adults. The majority of cases are sporadic developing in previously healthy adults with a mean age of 65 years. The onset is insidious, producing a rapidly progressive dementia. Myoclonus appears in over half the patients. Patients lack systemic symptoms of fever, headache, and myalgia. Within 4–6 months, patients are severely demented, rigid, mute, and unresponsive.

Major Laboratory Findings

Routine blood tests are normal. CSF is under normal pressure and contains no cells and normal

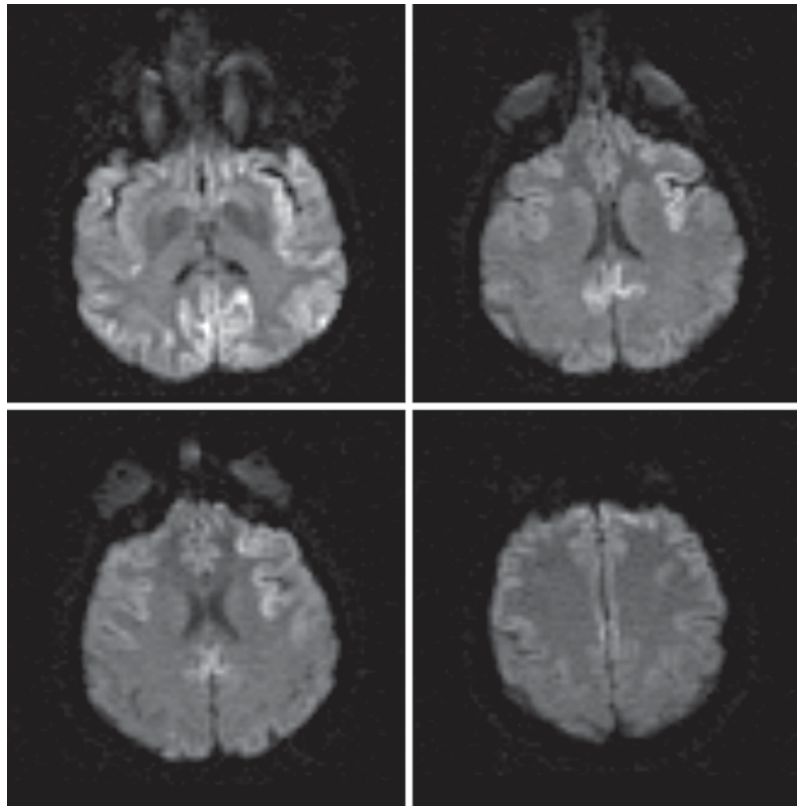

Fig. 13.7 Axial, diffusion-weighted imaging (DWI) sequence MRI of 60-year-old man with 3-month rapidly progressive dementia and myoclonus showing increased signal in cortex (e.g., cortical ribboning). EEG and laboratory studies are also consistent with a diagnosis of CJD (Courtesy of Dr. Blaine Hart)

glucose and protein. Oligoclonal bands are not seen. The CSF often contains a nonprion protein, called 14-3-3. An EEG may show characteristic abnormalities, particularly later in the illness. The MRI shows progressive brain atrophy and often demonstrates increased signal in the basal ganglia and cortex on diffusion-weighted MR images (Fig. 13.7).

Isolation of the prion infectious agent requires incubation in small laboratory animals for months. CSF, brain, pituitary, and peripheral nerves that innervate cornea and dura contain infectious prions. The infectious agent does not appear to be present in saliva, urine, sweat, or stool, so isolation of the patient is not necessary. Blood should be considered infectious but no documented human cases have occurred from blood transfusions.

Principles of Management and Prognosis

Currently, there is no available treatment to stop disease progression. Death in CJD usually occurs within 6 months of diagnosis. Since the infectious agent is present in tissues, patients suspected of a prion disease should not donate blood or autopsy organs.

Paraneoplastic Anti-NMDAR Limbic Encephalitis

Introduction

It is increasingly recognized that not all acute and subacute encephalitis syndromes are infectious. For older children and young adults with an

unclear encephalitis, the California encephalitis project has recently found anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis to be the most common proven etiology (40 % of total proven cases). Anti-NMDAR limbic encephalitis mainly develops in females from 13 to 40 years of age and is uncommon outside this age range.

Less common paraneoplastic antibodies causes of limbic encephalitis or encephalomyelitis include anti-Hu, anti-Ma, antibodies to voltage-gated potassium channel-associated proteins, and anti-AMPAR (α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid receptor).

Paraneoplastic antibodies are recognized to be directed against components of the CNS, peripheral and autonomic nervous system, neuromuscular junction, and muscle. Some paraneoplastic antibodies are associated with unique clinical syndromes (i.e., Eaton–Lambert myasthenic syndrome or opsoclonus–myoclonus syndrome of infants) while other antibodies are associated with dysfunction of several parts of the nervous system. Some antibodies are associated with both specific tumors and specific syndromes (i.e., anti-Yo antibody, cerebellar degeneration, and breast or ovarian cancer) while other antibodies are associated with several tumors. Current generalizations about paraneoplastic antibodies and their syndromes are summarized in Table 13.4. Also see myasthenia gravis in chapter on neuromuscular junction.

Pathophysiology

Compelling clinical and laboratory evidence finds that anti-NMDAR antibodies are pathogenic by direct immune-mediated mechanisms. IgG anti-NMDAR antibodies rapidly bind to the NR1 subunit of NMDA (*N*-methyl-D-aspartate)-type glutamate surface receptors located at the synapse. NMDA receptors require coactivation by two ligands, glutamate and glycine. The antibody receptor binding prevents neurotransmitters from the presynaptic side of the synapse from attaching to the receptor, which blocks the neuron from firing. In addition, the antibody binding to the receptor protein triggers capping and internalization of the receptors with their subsequent catabolism leading to a deficiency of surface receptor proteins.

The source of anti-NMDAR antibodies originates from an immune response usually against an ovarian teratoma in young women that produces antibody both against the teratoma and NMDA receptor neurons. However, in up to 40 % of patients, especially in males, young children, and older adults, no cancer is identified. Histology of the teratoma usually shows inflammatory infiltrates around the tumor cells. However, biopsies of affected brain are usually normal or show nonspecific findings with sparse inflammatory infiltrates (perivascular cuffing) and parenchymal T cell infiltrates. Because the neurons do not die, the syndrome is reversible.

Major Clinical Features

About 70 % of patients have a prodrome of headaches, fever, nausea, diarrhea, and respiratory symptoms for several days. Patients then develop psychiatric symptoms of insomnia, anxiety, delusions, mania, and paranoia. Memory problems and language deterioration often develop, which can lead to aphasia or mutism. Focal or generalized seizuresmay develop. The patient then progresses to decreased responsiveness and abnormal movements that include oral–lingual dyskinesias, choreoathetosis, dystonia, and rigidity (see video). Autonomic abnormalities may include hyperthermia, tachycardia, hypotension, and hypersalivation. Some patients progress to coma requiring intubation and ventilation. The entire progression of signs occurs over days to a few weeks.

Major Laboratory Features

The brain MRI is abnormal in 50 % and shows mild fluid-attenuated inversion recovery (FLAIR) signal hyperintensity in the hippocampi,

Table 13.4 Generalizations known about paraneoplastic antibodies

Uncommon cause of diseases against the CNS, PNS, neuromuscular junction, and muscle	
Usually directed against one part of nervous system	
Clinical onset usually subacute over few weeks	
Directed against cell surface or intracellular antigens	
Only 60% associated with cancers	
Often produce neurologic signs before cancer detected	
Prognosis depends on type of antibody	
Antibody directed against cell surface antigen such as neurotransmitter receptor or membrane channel	Most antibody directed against PNS but some CNS
	Patients dramatically improve if treated early with:Tumor removal and/or Steroids, IVIg, plasmapheresis, and continued with immunotherapy
Antibody directed against intracellular antigen	Mainly seen in CNS syndromes
	Does not improve with tumor removal or steroids, etc
	Damage may be due to T-cells and antibody is a biomarker

cerebellar or cerebral cortex, frontobasal and insular areas, basal ganglia, and brainstem. The EEG is abnormal showing nonspecific, slow, and disorganized activity and occasionally seizures. The CSF is abnormal in 80% and demonstrates mild lymphocytic pleocytosis, mildly elevated protein, normal glucose, and CSF-specific oligoclonal bands.

The diagnosis is established by finding CSF and serum anti-NMDAR antibodies.

Principles of Management and Prognosis

Management focuses on identification and surgical removal of the tumor plus immunotherapy. Most patients respond to intravenous immunoglobulins and corticosteroids. A few patients do not respond and require second-line immunotherapy that may include rituximab or cyclophosphamide. About 75% of patients recover or have mild sequelae, but a few patients die or have major neurologic sequelae. Relapses requiring retreatment develop in 20% of patients.

Recommended Reading

Ziai WC, Lewin JJ. Update in the diagnosis and management of central nervous system infections. Neurol Clin. 2008;26:427–68. *(Reviews current concepts of the major CNS infections)*.

Logan SAE, MacMahon E. Viral meningitis. Brit Med J. 2008;336:36–40. *(Good review of the many causes of viral meningitis)*.

Kim KS. Acute bacterial meningitis in infants and children. Lancet Infect Dis. 2010;10:32–42. *(Excellent review of pathogenesis, characteristics, diagnosis, and management of bacterial meningitis)*.

Whitley RJ. Herpes simplex encephalitis: adolescents and adults. Antiviral Res. 2006;71:141–8. *(Good review of diagnosis, pathology, and management of HSE)*.

Davis LE, Beckham JD, Tyler KL. North American encephalitic arboviruses. Neurol Clin. 2008;26:727–57. *(Reviews all major arbovirus encephalitis viruses that cause infections in the USA)*.

Schmader, K. Herpes zoster and postherpetic neuralgia in older adults. Clin Geriatr Med. 2007;23:615–32. *(Good review of epidemiology, clinical, diagnosis, and management of shingles and postherpetic neuralgia)*.

Brown P. Transmissible spongiform encephalopathy in the 21st century. Neuroscience for the clinical neurologist. Neurology. 2008;70:713–22. *(Excellent review of progress in understanding prions)*.

Rosenfeld MR, Dalmau J. Update on paraneoplastic neurologic disorders. The Oncologist. 2010;15:603–17. (*Excellent review of the types, clinical features, workups, and management of paraneoplastic syndromes).*

Brain Tumors

14

A 70-year-old man developed a new right-sided headache that slowly became more intense over 2 weeks. He then noted weakness in his left arm that progressed over 1 week. An MRI scan ordered by his physician demonstrated a 4 cm irregular mass in the right frontal lobe that had a heterogeneous low intensity center surrounded by an irregular ring of gadolinium enhancement and adjacent cerebral edema. A right craniotomy with moderate debulking of the mass that was a malignant glioma. He received whole head irradiation with lessening of the headache. Over the next 5 months the headache returned in spite of receiving dexamethasone and the weakness progressed to a left hemiplegia and hemisensory loss. He died 6 months after the diagnosis.

Overview

The term brain tumor refers to a collection of neoplasms of differing cell types, biology, prognosis, and treatment arising as a primary tumor or metastasis. Each year in the USA about 600,000 people die from cancer. About 25% of patients with cancer had a neoplasm that involved the brain or its coverings at some time during the cancer illness. Each year, 20,000 new primary brain tumors are diagnosed and about 100,000 individuals acquire a CNS metastasis from a systemic cancer. In adults dying from an intracranial cause, only strokes have a higher mortality rate than CNS tumors. In children, primary brain tumors constitute the most common solid tumor and account for 20% of childhood tumors.

Primary brain tumors in adults develop mainly above the tentorium (70%) with the peak incidence in the elderly. Primary tumors develop in infants and children mainly in the posterior fossa (70%) (particularly in the cerebellum), and have different histologic types than those in adults. Most CNS tumors are of glial (astrocytoma > oligodendroglioma) origin (>90%) and rarely are of neuronal origin (1%).

Brain tumors produce signs and symptoms by three mechanisms. The first is the tumor location. In adults since the hemispheres are often affected, common signs include hemiparesis, hemisensory loss, aphasia, and visual field deficits. When the cerebral gray matter is involved, seizures are common and may be either focal or secondarily generalized. As the tumor spreads, cognitive dysfunction is common. In children with a posterior fossa tumor, cerebellar dysfunction with gait and limb ataxia and brainstem signs are common.

Second, the mass of the tumor can produce signs and symptoms as it expands in a closed intracranial space. The adult cranial cavity contains 1400 mL brain, 140 mL CSF, and 150 mL blood. A tumor grows by compressing the brain, CSF,

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and blood compartments. Adding to the mass of a brain tumor is surrounding cerebral edema. Many tumors release poorly understood proteases that disrupt the blood–brain barrier in vessels surrounding the tumor allowing vasogenic edema to develop. Once a critical size is reached, the intracranial pressure (ICP) increases.

Increased intracranial pressure causes headaches, psychomotor retardation (slowing in the amount and speed of cognitive functions coupled with slowing of motor activities), nausea, vomiting, and papilledema (blurring of optic discs, retinal edema and flame hemorrhages without early loss of vision). Papilledema from increased ICP results from impairment of axonal transport in the optic nerve and blockage of venous drainage from the optic nerves. The headache is ill defined, intermittent, and may be lateralizing. The headache occurs most likely due to mass expansion and increased intracranial pressure that stretches the surrounding sensory neurons in meningeal blood vessels since brain parenchyma lacks pain receptors itself. As the tumor expands, the headache becomes more intense, constant, and increases with coughing or straining at stool (i.e., valsalva maneuver).

Third, as the mass expands, the resulting increased intracranial pressure may shift intracranial structures enough downward to produce brain herniation.

Brain Herniation Syndromes

Brain herniation may be from downward herniation of brain through the tentorium (central and uncal herniation), cingulate gyrus herniation under the falx (subfalcine herniation), or the cerebellar tonsillar herniation into the foramen magnum and against the medulla (tonsillar herniation) (Fig. 14.1). Death from central brain herniation is from progressive bilateral parenchymal impairment of the diencephalons leading to ischemia and necrosis of the midbrain and pons (Duret hemorrhages). Signs and symptoms of progressive central brain herniation include: (1) impairment of alertness that progresses to stupor and coma, (2) sighs and yawns that progress to Cheyne-Stokes breathing then to fixed hyperventilation and finally to apnea, (3) small pupils (1–3 mm) that barely or do not react to light and progress to midposition (3–5 mm) pupils, and (4) vestibulo-ocular reflex (Dolls eyes reflex) and ice water caloric test (ice water placed in the external auditory canal) that progress from normal to being nonresponsive (see Chap. 16 on Coma and Cerebral Death).

Uncal herniation occurs when a lateral hemisphere mass displaces the medial edge of the uncus and hippocampal gyrus through the tentorium. Initially there is dilation of the ipsilateral pupil due to compression of the third nerve followed by ipsilateral hemiparesis from compression of the cerebral peduncle against the tentorial edge. Compression of the posterior cerebral artery may occur with ischemia/infarction of the ipsilateral occipital lobe producing a contralateral homonymous hemianopia. The late events are similar to that of central herniation.

Tonsillar herniation is due to compression of the cerebellar tonsils against the medulla producing early nuchal rigidity and head tilt followed by coma and respiratory arrest.

Depending on the tumor's rate of growth, death can occur as early as the tumor reaches the size of about 100 g ($\sim 1 \times 10^{11}$ cells) or about the size of a golf ball. This is compared to systemic tumors where death occurs typically when the tumor reaches about 1000 g. Slow growing CNS tumors can grow considerably larger before herniation develops.

Cerebral Edema

Cerebral edema, excess fluid either locally or diffusely in the brain, develops as a result of many pathological processes including brain tumors, head trauma, brain abscess and meningitis, anoxia, and some metabolic disorders. Cerebral edema has been divided into three types: vasogenic, cytotoxic, and interstitial. Interstitial edema is uncommon and results in obstructive

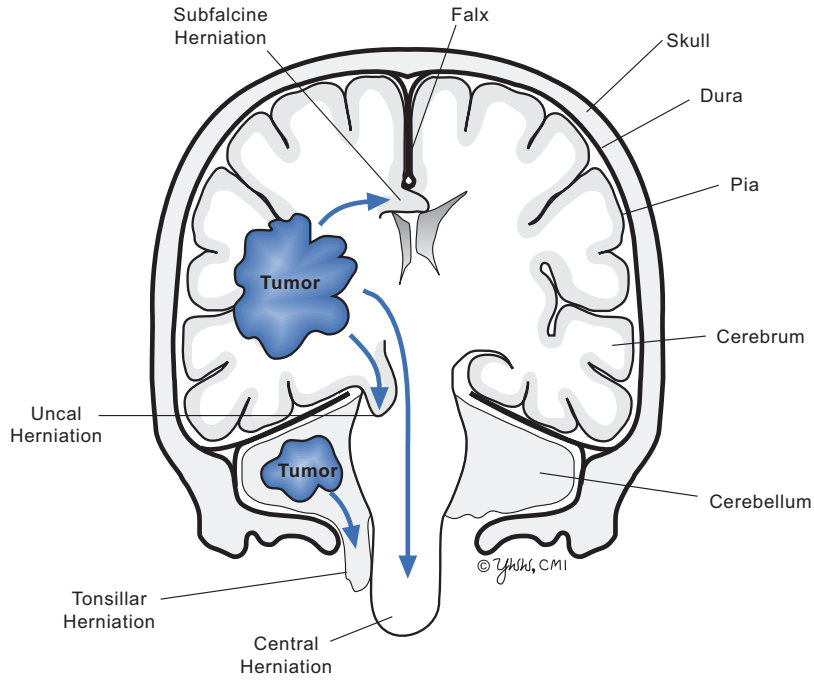

Fig. 14.1 Herniation syndromes

hydrocephalus with CSF backing into the white matter around ventricles.

Vasogenic edema is the most common form of cerebral edema and frequently surrounds brain tumors. The edema results from the tumor secreting proteases causing localized dysfunction of the blood–brain barrier with increased permeability of capillary endothelial cells. Vasogenic edema develops mainly in cerebral white matter and uncommonly in gray matter. Vasogenic edema from a brain tumor is reduced following administration of corticosteroids presumably because steroids restore the blood brain barrier. Unfortunately, steroids seldom improve cerebral edema following cerebral infarction or head trauma. Interestingly, hypoalbuminemia and increased systemic venous pressure cause peripheral edema but not edema in the brain.

Cytotoxic edema develops from a fluid swelling of neurons, glia, and endothelial cells usually following hypoxia. Hypoxia causes failure of the ATP-dependent sodium pump within cells with subsequent accumulation of intracellular sodium and water. Cytotoxic edema causes a reduction in the extracellular fluid space so there is little increase in the mass effect. Brain tumors cause mainly vasogenic edema while infarctions cause both cytotoxic and vasogenic edema. Cytotoxic edema is difficult to reduce and does not respond to corticosteroids. Characteristics of vasogenic and cytotoxic edema are listed in Table 14.1.

Malignant Gliomas

Introduction

Malignant gliomas account for 70 % of new cases malignant primary brain tumors in adults each year. The tumor tends to occur in older adults (mean age 55 years). No underlying cause has been identified for the majority of malignant gliomas with the only established risk factor being exposure to ionizing radiation. The prognosis for malignant gliomas is poor with no adequate treatment currently available.

Table 14.1 Features of vasogenic and cytotoxic brain edema

Feature	Vasogenic	Cytotoxic
Pathogenesis	Opening of blood–brain barrier with increased capillary permeability	Cellular swelling of glia, neurons, and endothelial cells from hypoxia
Edema location	Chiefly white matter	Gray and white matter
Edema fluid composition	Plasma filtrate	Increased intracellular water and sodium
Common causes	Brain tumor, abscess, infarction, trauma, lead encephalopathy, hemorrhages, and bacterial meningitis	Brain hypoxia/ischemia
Corticosteroid effect	Reduces edema	No edema reduction
Osmotic agents	Acutely reduces water in normal brain	Acutely reduces water in edematous brain

Pathophysiology

Grade 1 astrocytomas are slow growing, have a normal cellular morphology, and do not induce abnormal vascularity. The most benign astrocytomas typically arise in the optic nerve or brainstem and patients often survive decades after diagnosis.

Malignant glioma or glioblastoma multiforme usually arises in the cerebral hemispheres and appears grossly as a soft relatively circumscribed mass that may contain cysts or necrosis (Fig. 14.2). The tumor extends many centimeters beyond the apparent gross or neuroimaging margin. Microscopically, the tumor is highly cellular containing heterogeneous, extremely pleomorphic cell types. Multinucleated giant cells are frequently seen. There is extensive neovascularization with marked proliferation of endothelium of small capillaries feeding the tumor. Gliomas rarely metastasize outside the brain.

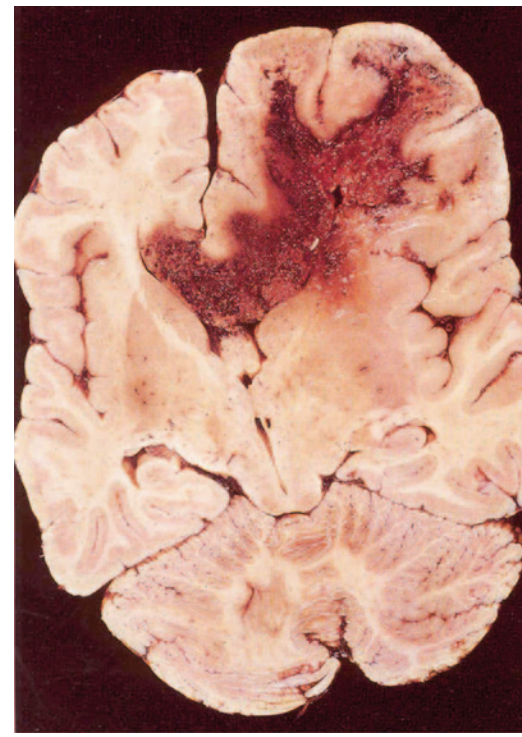

Fig. 14.2 Pathology, glioblastoma multiforme with cysts and necrosis and extension into the corpus collosum. (Courtesy of Dr. Mark Becher)

Malignant gliomas are characterized by self-initiation, uncontrolled proliferation, evasion of apoptosis, avoidance of immune surveillance, increased angiogenesis, necrosis, and diffuse tumor cell invasion into adjacent normal brain. Common genetic alterations common in malignant gliomas include amplification and/or over expression of receptor tyrosine kinases and angiogenesis factors. Epidermal growth factor receptor (EGFR) gene amplification is the most prominent mutated receptor tyrosine kinase receptor. Platelet-derived growth factor (PDGF) and its receptors are important in angiogenesis and tumor growth in gliomas. The tumor-suppressor phosphatase and tensin homolog (PTEN), which normally is important for suppressing tumors, can be removed when chromosome 10 is deleted in some malignant gliomas. The exact cell origin of gliomas is not known but there is increasing interest in glioma stem cells as the potential genesis. The hypothesis is that the normal stem cell becomes

malignant and replicates producing tumor cells even though the pool of stem cells in the tumor remains small. The abnormal stem cells maintain their stem cell properties and are relatively resistant to chemotherapy and radiotherapy and induce angiogenesis.

Major Clinical Features

Early signs and symptoms include headaches in 50%, altered mental status with confusion or memory loss in 50%, hemiparesis in 40%, aphasia in 15%, visual field loss in 5%, and seizures in 20%. The seizures may be either focal seizures (usually motor) or secondarily generalized tonic-clonic seizures. The classic headache is a morning severe headache that can awaken the patient but often the headache is similar in character to a tension headache. Papilledema may be seen on fundoscopy. In the absence of treatment, symptoms of glioblastoma progress relatively rapidly over weeks.

Major Laboratory Findings

MRI with gadolinium is the test of choice. On MRI, the tumor characteristically has low signal intensity on T1-weighted and high signal intensity on T2-weighted images (Fig. 14.3). The appearance of contrast-enhanced T1-weighted images is that of a heterogeneous central low signal surrounded by a ring of high intensity enhancement. Areas of central necrosis are common. Surrounding the high intensity ring are hypointense signals representing cerebral edema and tumor infiltration. The extent of cerebral edema varies from tumor to tumor. The CT scan shows variably hypodense or isodense lesions surrounded by hypodense cerebral edema.

The EEG shows focal or extensive slowing (delta waves) in the region of the tumor with varying degrees of spikes at the tumor edge and surrounding edematous brain.

Principles of Management and Prognosis

Glioblastoma multiforme (WHO grade IV) is always fatal. Thus, palliative management aims at slightly prolonging survival and controlling symptoms. Corticosteroids reduce the surrounding edema and temporarily improve symptoms, prolonging survival for 1–3 months. Following steroids, the headache lessens, the mental status perks up, and focal neurologic signs (such as hemiparesis) improve. Since steroids do not affect tumor growth, the signs and symptoms eventually return. Neurologic side effects of high dose

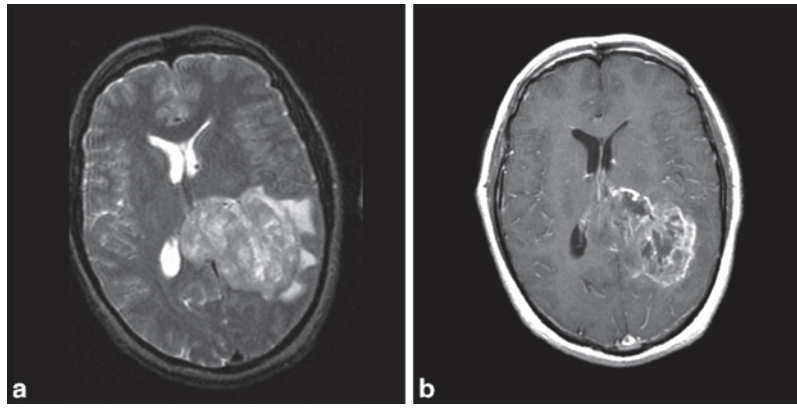

Fig. 14.3 **a** Axial, T2-weighted MRI showing left parietal glioblastoma multiforme extending into corpus collosum with surrounding vasogenic edema and causing midline shift. **b** Axial, T1-weighted MRI with gadolinium showing enhancement of glioblastoma multiforme. (Courtesy of Dr. Blaine Hart)

corticosteroids include psychosis, hyperactivity, irritability, insomnia, and myopathy.

Surgical removal of the main tumor mass (debulking) only slightly improves the length of survival but often temporarily improves neurologic signs by reducing intracranial pressure. Since fingers of the tumor have already spread far beyond the main tumor margins, debulking is never curative. However, it does allow for a histologic diagnosis and molecular studies. Brain biopsy and minor tumor removal have no effect on survival.

Radiotherapy after surgery only slightly improves survival compared to surgery alone because malignant gliomas are highly resistant to radiotherapy. Side effects of the radiotherapy commonly include anorexia, nausea, hair loss, and fatigue and may include late radiation necrosis of normal brain.

The value of many chemotherapeutic agents for gliomas is controversial. The choice of an agent is difficult as many antineoplastic agents do not cross the blood–brain barrier and thus poorly penetrate the tumor. However, temozolomide along with radiotherapy in patients whose tumor has epigenetic silencing of the O^6-methylguanine-DNA methyltransferase (MGMT) gene do benefit and show a median survival of 22 months. MGMT promoter methylation (present in 40 % of malignant gliomas) silences the gene and decreases DNA repair activity which heightens tumor cells susceptibility to temozolomide. Unfortunately, the mean time to tumor recurrence is only 7 months.

In summary, if the malignant glioma (WHO grade IV) is untreated, the mean survival from diagnosis is less than 6 months and few adult patients survive longer than 18 months. For previously healthy adult patients receiving corticosteroids, surgical tumor debulking and radiotherapy, 40 % survive one year, 10 % survive 2 years, and < 1 % survive 5 years. The prognosis for anaplastic astrocytoma (WHO grade III) is 2–3 years and for low grade astrocytoma (WHO grade II) is 5–10 years. Poor prognostic factors include old age and the presence of many clinical signs.

Palliative care minimizes the patient's discomfort and disability. Headaches can be controlled with surgical debulking, corticosteroids, and analgesics. Anticonvulsants should be given to patients who experience seizures. Cognitive dysfunction can arise from tumor progression, effects of radiotherapy and chemotherapy, corticosteroids, metabolic disturbances, and depression. Treatment efforts should be aimed at the appropriate causes.

Meningioma

Introduction

Meningiomas are the most common adult brain tumor accounting for 30 % of all primary brain tumors. They belong to a group of brain tumors that are often called "benign" since they are slow growing, do not invade surrounding structures, and are not histologically malignant. Other common benign tumors include pituitary adenomas, acoustic neuromas, and epidermoid cysts. Meningiomas are usually solitary and only rarely metastasis inside or outside the skull. Meningiomas have a prevalence of 97 per 100,000 population with 175,000 adults currently diagnosed with the tumor. The peak incidence is in older adults. Meningiomas are located outside the brain, occur twice as often in women as men, and 3 % are incidental findings at autopsy. Table 14.2 lists their most common locations.

Table 14.2 Location of meningiomas

Location	Percent (%)
Falx/parasagittal	25
Cerebral convexity	20
Sphenoid wing	20
Olfactory groove	10
Suprasellar	10
Posterior fossa	10
Other	5

Pathophysiology

The cause of meningiomas is unknown but deletion and inactivation of the neurofibromatosis 2 (NF2) gene on chromosome 22 is a common feature of sporadic meningiomas, and accounts for the increase of meningiomas in patients with neurofibromatosis type 2. Many meningiomas contain high-affinity, robustly expressed progesterone receptors that may account for the tumor's higher predilection in women.

Meningiomas are felt to arise from neoplastic meningeal (arachnoid cap) cells and thus may develop at any dural site and receive their blood supply from the external carotid artery. Grossly, the tumor is firm, round and flat, and has a smooth edge. Histologically, the classical tumor is characterized either by a sheet-like syncytial pattern in which the nuclei appear to be lying in an undivided expanse and/or a fibroblastic pattern with fascicles of spindle cells bundled in sweeping, parallel, gentle curves and whorls throughout the tumor. The whorls may form a nidus for calcifications. Few mitotic figures are seen.

Major Clinical Features

Meningiomas are very slow growing tumors and may be present for more than a decade before they cause symptoms. Symptomatic meningiomas most commonly present with seizures which may be generalized (60%), partial (37%), complex partial (8%), or a combination of these. Headaches may develop as the tumor enlarges. Large frontal lobe meningiomas may cause psychomotor or behavioral symptoms. If the tumor arises from the base of the skull, cranial neuropathies may occur that include visuomotor disturbances. Meningiomas in the falx cerebri often present with paraparesis due to bilateral compression of the leg areas of the motor cortex. However, many tumors are asymptomatic, incidental findings identified from CT or MRI done for other indications.

Major Laboratory Findings

The CT demonstrates the typical meningioma to be a smooth, lobulated, isodense tumor that is adjacent to dura and enhances uniformly with contrast. Multiple small calcifications are sometimes seen in some tumors. On MRI T1-weighted images, the tumor is isointense or hypointense and on T2-weighted images it is isointense or hyperintense. With gadolinium, T1-weighted images show intense and homogenous enhancement (Fig. 14.4). Some meningiomas show edema in the adjacent brain but rarely do they appear to invade brain.

Principles of Management and Prognosis

Since meningiomas are slow growing, many small asymptomatic tumors can be followed safely with periodic neuroimaging. However, when the tumor becomes symptomatic, surgical removal is indicated. Depending on the location, the tumor can be totally excised or partially removed. Total surgical removal is usually cura-

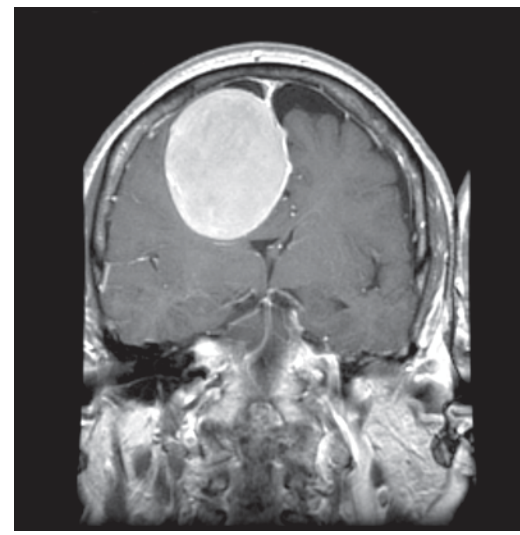

Fig. 14.4 Coronal, T1-weighted MRI with gadolinium showing a very large parafalcine meningioma uniformly enhancing with no apparent surrounding edema. (Courtesy of Dr. Blaine Hart)

tive. If the meningioma is subtotally removed, recurs, or is located in a difficult surgical location, radiation, especially with stereotactic radiosurgery, is often successful. Anticonvulsants are required if seizures are present.

Pituitary Adenoma

Introduction

The pituitary lies in the sella turcica surrounded by the sphenoid bone and covered by the sellar diaphragm. The hypothalamus and optic chiasm lie above and the cavernous sinus lies laterally. The pituitary is the shape of a bean, weighs about 0.6 gm and physiologically enlarges during pregnancy and lactation. It divides into the adenohypophysis (80%) and neurohypophysis (20%). Blood supply mainly comes from the portal circulation and lacks a blood–brain barrier. Pituitary adenomas are age-linked and become more numerous each decade. Over 70 years of age, small adenomas can be detected in 20% of asymptomatic individuals by neuroimaging or at autopsy.

Pituitary adenomas account for 10% of all intracranial tumors in adults and can be divided into microadenomas (<10 mm diameter) and macroadenomas (>10 mm diameter) or divided into the cell types that secrete different hormones. Macroadenomas first compress the pituitary gland and then expand above the sella turcica often compressing the optic chiasm or may enlarge laterally into the cavernous sinus to entrap cranial nerves. The most common macroadenomas are prolactinomas in men because they are not symptomatic as early as in women allowing more extensive growth and nonfunctioning adenomas because they do not produce hormonal effects early. Microadenomas are usually suspected based on hormonal changes in the patient or incidentally identified on MRI scans performed for other reasons.

Prolactinomas are the most common pituitary tumors. Prior to 50 years of age, there is a marked female predominance but after 50 years of age, the incidence is equal. Table 14.3 lists the frequency of the three main hormonal adenomas.

Pathophysiology

The cause of the tumor formation is unknown. The adenomas are mainly sporadic and recognized to be a monoclonal neoplasm. There is thought that normal feedback inhibition somehow is impaired or mutated or there are epigenically silenced tumor suppressor factors involved in the neoplasm genesis. Overall, adenomas rarely appear malignant, seldom metastasize, grow slowly, and may remain stable in size for years. Some tumors, such as prolactin secreting adenomas, are responsive to hormones or drugs and expand or shrink in size in response to these compounds. However, the blood hormone level may not correlate with the patient's symptoms. About 30% of pituitary tumors are nonfunctioning adenomas and do not secrete any hormones or respond to hormone secretion inhibitors. Table 14.3 lists the most common types of hormone secreting pituitary adenomas and their hormonal features, diagnostic tests, and treatments.

Major Clinical Features

Macroadenomas with upward growth put pressure on the optic nerves and chiasm causing visual loss in 50% of untreated patients. The most characteristic visual sign from damage to the optic chiasm is bitemporal hemianopsia (loss of temporal vision in each eye, which may not be apparent to the patient with both eyes open). There may be optic disk atrophy seen on fundoscopy if the optic chiasm pressure has been chronic but papilledema is rare. Headaches are common (75%) and are likely due to traction on the diphragma sellae or surrounding dural structures. The character and location of the headache is nondiagnostic. If the adenoma expands laterally into the cavernous sinus, the tumor may entrap cranial nerves 3, 4, 6 and the first and second divisions of 5 producing diplopia and unilateral upper and mid-facial numbness or pain. Rarely, an adenoma may hemorrhage or infarct. Pituitary apoplexy then presents with acute onset headache, ophthalmoplegia, bilateral visual loss, and drowsiness leading to coma. The acute Addiso-

Table 14.3 Common hormone-secreting pituitary adenomas

	Prolactinoma	Acromegaly	Cushing's disease
Hormone secreted	Prolactin	Growth hormone	ACTH
Cell type	Lactotroph, mammotroph	Somatotroph	Corticotroph
Percentage of cell type in normal pituitary	20%	50%	20%
Tumor percentage of all adenomas	20–75%	10–20%	5–10%
Major signs due to hormone secretion in adults	Women	Recent extremity growth	Weight gain
	Glactorrhea	Arthalgias	Centripetal obesity
	Abnormal menstruation	Excessive sweating	Moon facies
	Infertility	Myopathy	Skin striae
	Men	Jaw malocclusion	Myopathy
	Hypogonadism with decreased libido and impotence	Carpal tunnel syndrome	Depression and occasional psychosis
	Gynecomastia	Hypertension	
Common tumor type	Microadenoma in women and macro-adenoma in men	Microadenoma	Microadenoma
Hormone tests	Elevated serum prolactin level	Elevated serum growth hormone	Elevated 24 h-urine-free cortisol level
		Failure of growth hormone to rise after glucose administration	Dexamethasone suppression test fails to suppress urinary glucocorticoids
		Elevated serum insulin-like growth factor	Abnormal midnight salivary cortisol
Main therapy	Cabergoline	Transphenoidal excision	Transphenoidal excision
Other causes	Pregnancy, breast feeding, medications		Exogenous corticosteroids, adrenal hyperplasia, ACTH secreting tumors elsewhere

nian state requires emergency hydrocortisone replacement.

Major Laboratory Findings

Pituitary tumors (both macro and microadenoma) have characteristic abnormalities on high resolution imaging of the sella turcica with MRI and gadolinium or CT with contrast. Common findings include upward convexity of the gland, increased size of gland, stalk deviation, floor erosion, gland asymmetry and focal hypodensity, or hypointensity in the gland (Fig. 14.5). The normal pituitary gland rapidly enhances with gadolinium but the adenoma does not, thus enabling its identification by pituitary foci lacking enhancement. Neuroimaging may demonstrate macroadenomas expanding upward to compress the optic nerve chiasm and invading the hypothalamus or expanding laterally into the cavernous sinus (Fig. 14.5).

Table 14.3 lists common blood tests to help make the diagnosis. Serum prolactin levels are elevated in prolactinomas but prolactin levels also may be elevated by pregnancy, breast-feeding, marked renal failure, cirrhosis, and medications including antidepressants and antipsychotics, such as risperidone, and opiates. Thus, a patient with a prolactinoma should have both an elevated serum prolactin level and an adenoma found on neuroimaging.

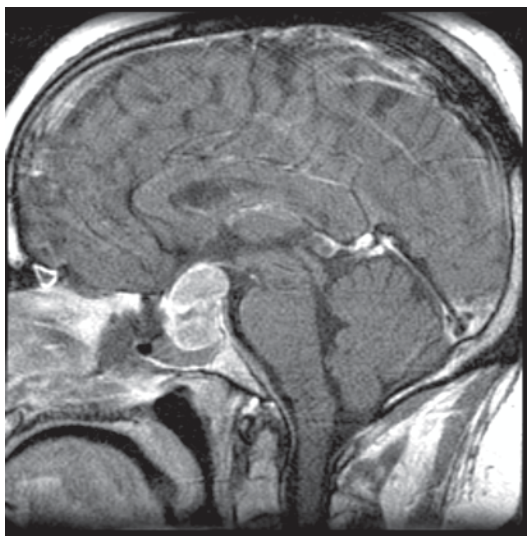

Fig. 14.5 Sagittal, T1-weighted MRI with gadolinium showing a pituitary macroadenoma extending upward and displacing optic chiasm. (Courtesy of Dr. Blaine Hart)

Principles of Management and Prognosis

Goals for treatment are to reduce hormone hypersecretion to normal, shrink tumor size, correct any visual or cranial nerve abnormalities, and restore any abnormal pituitary function. For macroadenomas, except prolactinomas, surgical removal of the adenoma is commonly required to preserve vision. About 60–75% of patients with transsphenoidal surgery are cured (total tumor removal by MRI and return of involved pituitary hormones to normal blood levels). Surgery is also indicated when there is failure of medications to stop tumor growth.

Prolactinomas dramatically respond to dopamine agonists (cabergoline or bromocriptine) with a prompt reduction in serum prolactin levels, shrinkage of the tumor, and disappearance of the signs and symptoms. The benefit of continued cabergoline administration persists for years to decades. Thus, administration of cabergoline usually precludes the need for surgery even when the tumor is a macroadenoma affecting the visual system. However, if the drug is stopped, prolactin levels again elevate and the tumor again grows.

Radiotherapy may reduce growth of the macroadenoma but usually does not stop hormone secretion. Chemotherapy has not been beneficial.

Cerebral Metastases

Introduction

Brain metastases are neoplasms that originate in tissues outside the brain and spread secondarily to involve the brain. Up to 25% of cancer patients develop brain metastases before death and two-thirds are symptomatic. As such, cerebral metastases are the most common type of brain

tumor in adults. Reports show that recently the incidence of metastatic brain tumors is increasing and is now 14 per 100,000 population. Reasons for the increased incidence include more elderly, longer survival of patients with cancer allowing more cerebral metastases to develop, and improved neuroimaging to detect cerebral metastases.

There are more than 100,000 brain metastases annually in the USA. In adults, 80% of metastases are supratentorial, 15% are cerebellar, and 5% locate in the brainstem or spinal cord. Of patients with symptomatic metastases, 25% of metastases are discovered before or at the time of diagnosis of primary systemic tumor, 60% develop in the next 6 months, 10% develop from 7 to 12 months, and 5% more develop during the second year.

The most common sources of intracranial metastases are lung (55%), breast (20%), gastrointestinal and genitourinary (5%), skin (melanoma) (10%), and leukemia (5%). For unknown reasons, a few cancers, such as prostate, uterine, and ovarian, seldom metastasize to the brain. One-third of metastases are single at the time of diagnosis and two-third are multiple. Ninety-nine percent of those with cerebral metastases have metastases elsewhere in the body. In addition, it is common for a patient with an initial single metastasis to subsequently develop other cerebral metastases.

Pathophysiology

Metastases dislodge from the primary systemic tumor as small foci of tumor cell clones that have reduced intercellular adhesion and disordered cytoarchitecture. The tumor focus travels via blood and lodges as an embolus commonly at the gray–white matter junction. A few metastases reach the spinal cord by retrograde flow via the veins in Batten's plexus or by extension into brain from dural or skull metastases. The tumor embolus begins to grow and produces angiogenesis factors that stimulate new vessel formation to supply blood to the tumor bed. These new blood vessels lack a blood–brain barrier. Brain metastases release poorly characterized proteases altering adjacent blood vessel permeability producing vasogenic edema surrounding the tumor that may exceed the size of the tumor. Thus, the mass effect of even small metastases may be considerable.

Metastases produce clinical symptoms through several mechanisms. The most common is the displacement of brain tissue by the mass effect of the rapidly growing tumor and adjacent cerebral edema. The displacement causes vessel compression, secondary ischemia, alterations in normal anatomy, and compression of extracellular fluid spaces. If the tumor is located in eloquent cortex, the tumor itself may destroy critical neurons or their axons producing clinical symptoms. A metastasis may suddenly become necrotic, hemorrhage, and rapidly expand in size producing abrupt increase of symptoms. The tumor may "irritate" adjacent cerebral cortex neurons triggering focal or generalized seizures. Finally, the mass effect of the tumor and cerebral edema may trigger brain herniation (see overview section).

Cerebral metastases must be distinguished from other brain lesions such as a primary brain tumor, cerebral hemorrhage, cerebral infarction, and brain abscess. In autopsy series, 5–10% of lesions thought to be a solitary metastasis had another etiology.

Major Clinical Features

Cerebral metastases are usually symptomatic but a few are discovered at autopsy. Over two-third of patients have neurologic signs and symptoms that are similar to other mass lesions (Table 14.4). Seizures are usually focal motor seizures, some of which become secondarily generalized. As

Table 14.4 Clinical signs of brain metastases

Sign	Percent (%)
Impaired cognition	60
Hemiparesis	60
Headache	50
Aphasia	20
Hemisensory loss	20
Seizures	25
Papilledema	15
Visual field cut	10
Stupor/coma	5

metastases expand and produce increased intracranial pressure, deterioration of mental status develops and brain herniation may occur.

Major Laboratory Findings

MRI with gadolinium enhancement is the best diagnostic test. A negative test essentially rules out cerebral metastases. T1-weighted images with gadolinium show a heterogeneous or ring enhancing lesion usually with surrounding edema. T2-weighted images show areas of increased intensity that encompass both the tumor and surrounding edema. Shifting of brain structures from the tumor mass effect are commonly seen on all images. A careful search for other metastases should be made, as all lesions are not the same size. Positron emission tomography (PET) scans are useful in delineating all the locations of all the patient's metastases and often separate the actual size and shape of the cerebral metastasis from the surrounding cerebral edema.

Principles of Management and Prognosis

Surgical removal of the metastasis only occasionally markedly prolongs life. Surgery should be considered when the diagnosis is in doubt, the metastasis is solitary or two, small in size, when the patient is in good overall health, the primary systemic tumor is small and responding to treatment, and there are no other critical systemic metastases. Surgical tumor removal will then improve the duration and quality of survival.

Dexamethasone reduces the cerebral edema and often dramatically improves the patient's symptoms for 1–2 months. Localized radiotherapy is effective for single metastases less than 3 cm diameter but does not irradiate tumors not seen initially. Whole brain irradiation is more effective for multiple metastases. The addition of radiotherapy adds a few more months of survival but the patient must undergo the complications of radiation. Chemotherapy appears to add little to survival but the patient often receives systemic chemotherapy for the primary tumor.

Palliative supportive care thus becomes important. Seizures should be controlled with anticonvulsants (often levetiracetam since it does not interfere with chemotherapeutic agents used in systemic chemotherapy); venous thromboembolism should be prevented; nausea should be minimized with antinausea drugs and proton pump inhibitors; pain treated with opioids; and depression treated with compassion and antidepressants.

In summary, the median survival without any treatment is 1–2 months from the discovery of the brain metastasis. With corticosteroids, the survival extends to 2–4 months. The median survival of steroids along with radiotherapy is between 3–6 months with 10% surviving 1 year. Unfortunately even in patients with the best prognosis (good performance status, controlled systemic disease, age less than 65 years, and optimal tumor management, the median survival is only 7 months.

Leptomeningeal Metastases or Carcinomatous Meningitis

Widespread dissemination of metastatic tumor cells in the meninges develops in 8% of cancer patients. Leukemia, lymphoma, breast cancer, lung cancer, gastrointestinal tumors, and melanoma are the most common systemic tumors. Clinical symptoms of multiple cranial nerve palsies develop from localized deposits of tumor cells along the base of the brain trapping cranial nerves. Sciatica, backache, and radiculopathy develop from deposits of tumor cells falling to the lumbar space and cauda equina trapping lower lumbar and cauda equina nerve roots. Clinical symptoms of headache, meningismus, nausea, and vomiting develop from increased intracranial pressure due to tumor blockage of CSF pathways producing hydrocephalus.

The presence of malignant cells in CSF is diagnostic. The CSF commonly has up to 100 cells/mm^3 containing lymphocytes and some tumor cells, elevated protein, and depressed glucose. Opening pressure may be normal or elevated if

hydrocephalus is present. Treatment may be with local radiotherapy to the brainstem or cauda equina or intrathecal chemotherapy with anticancer drugs like methotrexate. If hydrocephalus develops, CSF shunting is necessary. Unfortunately, the median survival is only 6 months from the diagnosis.

Recommended Reading

Wen PY, Kesari S. Malignant gliomas in adults. N Engl J Med. 2008;359:492–507. *(Excellent overall review)*.

Fishman RA. Brain edema. N Engl J Med. 1975;293:706–11. *(Classic review of types of cerebral edema and their treatments)*.

White IR, Smith C, Navoo P, Collie D. Meningiomas. Lancet. 2004;363:1535–43. *(Reviews of clinical, neuroimaging, and treatment of meningiomas)*.

Lleva RR, Inzucchi SE. Diagnosis and management of pituitary adenomas. Curr Opin Oncol. 2010;23:53–60. *(Covers epidemiology, pathogenesis, presentation, neuroimaging, and. management of the common pituitary tumors)*.

Khasraw M, Posner JB. Neurologic complications of systemic cancer. Lancet Neurol. 2010;9:1214–27. *(Good brief review of brain metastases and the treatment options)*.

DeAngeles LM, Posner JB. Neurologic complications of cancer. 2nd Ed. New York: Oxford University Press; 2009. *(Excellent comprehensive review of all types of CNS cancer complications including metastases to brain and leptomeninges, CNS infections, paraneoplastic syndromes and side effects of chemotherapy and radiation)*.

Seizures and Status Epilepticus

15

A 20-year-old woman was brought by an ambulance to the emergency room for a new onset seizure. Previously healthy, she was in the library studying for an exam when she suddenly had a seizure. The seizure was described by witnesses as two minutes of generalized tonic-clonic activity with urinary incontinence. She was lethargic afterward and confused. By the time she reaches the ER, she is awake and alert. She does not recall the event, but feels sore all over. Her neurologic exam, head CT, and laboratory work were all normal. She is cautioned not to drive for 6 months according to her state's driving laws. She is scheduled for an outpatient EEG and MRI to evaluate for any focal reason for a seizure and follow-up with the neurologist.

Overview

Approximately 10% of the population will experience a seizure in their lifetime. Although a single seizure occurring is relatively common, a single seizure resulting in recurrent unprovoked seizures (epilepsy) is less common. Still epilepsy is the third most common neurologic problem seen in clinics across the world—only surpassed by headache and back pain. The prevalence of epilepsy is approximately 6 per 1,000 persons with the incidence ranging from 35 to 52 per 100,000.

Risk factors for developing epilepsy differ for children and adults. In children, febrile seizures, head trauma, CNS infections, cerebral palsy, and mental retardation all increase the risk for development of an epilepsy syndrome. In adults, similar to children, head trauma and infection are risk factors—but unlike children, stroke and Alzheimer's disease are major risk factors for adult onset epilepsy. An epileptic seizure is the behavioral manifestation of abnormal brain neuronal activity. Epilepsy is characterized by abrupt, recurrent, and usually transient episodes of disturbed brain function with some combination of loss of consciousness, altered cognitive function, and/or convulsive movements.

Pathophysiology of Seizures

Seizures can begin focally in the brain or as part of generalized brain dysfunction—and the pathophysiology differs between the two mechanisms. When a focal group of cortical (or subcortical) neurons propagate action potentials in high-frequency bursts, this group activity results in a typical EEG spike discharge that can be detected by surface EEG. Normally, synchronous

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group activity like this does not spread due to intrinsic inhibitory mechanisms (e.g., surround inhibition); but if the number of neurons involved in this process is large enough, excitation can increase—overwhelming inhibition and resulting in spreading of the group activity. Generalized seizure genesis remains poorly understood—but involvement of thalamocortical circuits is important—given that the EEG patterns seen in generalized seizures (such as absence seizures) are based on oscillatory rhythms seen in the circuitry that connects thalamus and cortex.

Etiologies of Seizures

It is important to remember that **a seizure is a symptom and not a disease**. Any individual can experience a seizure under certain conditions, such as metabolic derangements (severe hypoglycemia), infection (very high fever), drug-induced (amphetamines) or drug-withdrawal (alcohol). It is likely that unknown genes determine some people's susceptibility to developing a seizure—although only 15% of individuals with epilepsy have at least one first-degree relative with seizures. In addition, numerous other disorders that affect the brain can cause seizures. The most common causes of seizures vary by age (Table 15.1) and include brain tumors, strokes, metabolic diseases, drug reactions, drug withdrawal, and infections. When referring to *epilepsy (recurrent seizures),* the etiology is generally assigned to one of the three categories: (1) Genetic; (2) structural/metabolic; and (3) unknown.

Table 15.1 Common causes of seizures by age

Age range	Major causes
Infant	Birth injury, hypoxia/ischemia, congenital malformations, congenital infection
Childhood	Febrile seizures, CNS infection, head trauma, birth injury, idiopathic
Young adult	Head trauma, drugs, withdrawal from alcohol or sedatives, idiopathic
Elderly	Stroke, brain tumor, cardiac arrest with hypoxia, metabolic

Electroencephalogram

An EEG commonly helps to classify the individual's type of epilepsy (see Chap. 3 on common neurologic tests). Patients rarely experience a seizure during a routine EEG. However, it can provide confirmation of the presence of abnormal electrical activity, information about the type of seizure disorder, and the location of the seizure focus. On a single routine wake and sleep EEG, only 40% of epilepsy patients will have an abnormal tracing. The spike is the EEG sign of hypersynchronous activation of a population of neurons that could develop into a seizure. Unfortunately, at least 10% of epilepsy patients never have an abnormal EEG and 2% of normal individuals who never experience a seizure will have epileptiform abnormalities on their EEG—limiting both the specificity and sensitivity of this test on its own. Therefore, the routine EEG cannot rule in or rule out epilepsy; thus, the diagnosis of epilepsy remains a clinical one.

Seizure Classification

There are several classifications for types of epilepsy that are based on clinical seizure types and/or EEG findings. Seizures are classified as focal or generalized. Generalized seizures *arise within and rapidly engage bilaterally distributed networks*. The most common types of generalized seizures are tonic-clonic (*grand mal*) seizures and absence (*petit mal*) seizures. Focal seizures *originate within networks limited to one hemisphere*. Focal seizures can be characterized by common features such as aura, motor involvement, autonomic features, and/or changes in awareness or responsiveness. Focal seizures beginning in one hemisphere can spread to involve the other hemisphere—resulting in a bilateral convulsive seizure. Table 15.2 outlines the clinical features of these seizure types. Properly classifying the type of epilepsy and determining the cause of the seizures allows a better prognosis and enables selection of the best anticonvulsant medication to control the seizures.

Table 15.2 Principal seizure types and their clinical features

Type of seizure	Clinical features
Generalized seizure	
Tonic-clonic	Loss of consciousness occurs without warning, a marked increase in all muscle tone (tonic) for about 20–30 s followed by rhythmic (clonic) jerks with a gradual slowing of the rate and abrupt cessation after 20–60 s. The patient is unconscious during and immediately after seizure and slowly recovers over minutes to an hour. Tongue biting and urinary incontinence are common. The patient has no recall of the actual seizure event
Absence	Rapid onset of unresponsiveness that lasts an average of 10 s. There can be staring or other automatisms (eye blinking or lip movements), an increase or decrease in muscle tone and mild jerks. Recovery is immediate but there is no recall of event. Hyperventilation often precipitates seizure. Childhood onset
Focal seizure (symptoms will depend on brain area involved in seizure)	
Aura	Sensory, autonomic, or psychic symptoms that occur at beginning of an observable seizure. Common symptoms include GI upset or a strange smell or taste
Dyscognitive	Seizure propogates to involve limbic or bilateral structures that alters awareness or consciousness

Focal Seizure

Introduction

Focal seizures originate in one hemisphere in a group of neurons or in a distributed network of neurons. The clinical manifestations of a focal seizure will be based on the particular area of the hemisphere involved.

Major Clinical Features

An *aura* is a focal seizure (previously known as a simple partial seizure) consisting of psychic, sensory, or autonomic phenomena that are experienced by the patient. It can signal the start of an observable seizure or be a seizure in and of itself. It is typically not observed, but can be elicited by a careful history. An aura can have many forms depending on the localization of the epileptic activity but common aura descriptions include: A rising or falling sensation in their abdomen, a disgusting smell, or metallic taste.

Other focal seizures can manifest as observable motor phenomena if they involve focal motor pathways. In focal seizures arising from the *rolandic* area, the patient experiences hand tingling which then progresses to hand movements, arm movements, and then leg movements (known as a *jacksonian* march). When awareness is altered during a focal seizure, it is called a dyscognitive seizure (previously known as a complex partial seizure)—implying limbic involvement and possibly bilateral involvement as well.

The most common cause of focal dyscognitive seizures in adults is seen in *mesial temporal lobe epilepsy with hippocampal sclerosis*. A typical seizure would begin with cessation of verbal activity associated with a motionless stare and without normal response to verbal or visual stimuli. Automatisms may occur that are gestural (picking at objects, repetitive hand washing movements) or oral (lip smacking) and the patient may wander aimlessly. These movements tend to be stereotyped for each patient and occur with most seizures. Purposeful movements or violence is unusual. The ictal event (seizure) lasts for 1–3 min followed by a period of postictal confusion that usually lasts for 5 to 20 min. The patient does not recall events during the dyscognitive seizure. The majority of patients with this epilepsy syndrome (70 %) will have a risk factor that predisposes to epilepsy (e.g., complicated febrile seizures before 4 years of age, encephalitis or trauma).

Focal seizures that occur in succession without return to normal behavior in between events results in focal status epilepticus. This can present as prolonged confused behavior and requires an EEG study for diagnosis.

Major Laboratory Findings

The EEG is often helpful in establishing the diagnosis, particularly when interictal spikes are identified coming from the focal region. Because the temporal lobe and underside of the frontal lobe are distant from EEG electrodes, it is difficult to find spikes in some patients. The use of sleep deprivation and special nasopharyngeal and sphenoidal electrodes may improve diagnostic yield. Magnetoencephalography can also be used to identify interictal discharges.

The MRI scan is often performed with special views of the hippocampus to demonstrate mesial temporal sclerosis and also to look for focal pathology elsewhere in the brain (Fig. 15.1). Mesial temporal sclerosis is a scarring of the inner temporal lobe, specifically the hippocampus. It can be the result of head trauma, hypoxia, or infection. In many cases, the scarring is seen on imaging but no clear cause is identified. This scarring is associated with mesial temporal lobe epilepsy as described above.

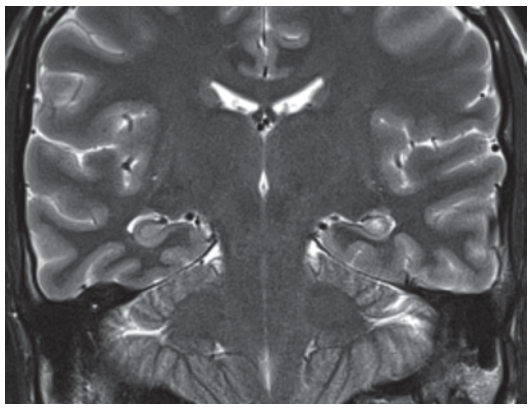

Fig. 15.1 MRI T2-weighted coronal image of a 25-year-old patient with seizures showing small left hippocampus with bright signal intensity and loss of internal architecture consistent with mesial temporal sclerosis. (Courtesy of Dr. Blaine Hart)

Principles of Management and Prognosis

Management is aimed at controlling the focal seizures and identifying any focal structural lesions that are epileptogenic. (See Table 15.3 for a list of anticonvulsants and their indications). The exact choice of medication will depend on the patient characteristics such as medication interactions. The goal is complete seizure suppression and no medication side effects.

Patients with focal seizures that are refractory to treatment are possible candidates for surgical intervention. These patients can be evaluated in specialized epilepsy centers by multidisciplinary teams. The goal of the evaluation is to identify the localization of the seizure focus by clinical manifestations, focal structural pathology (MRI), and focal brain dysfunction (EEG). Temporal lobe resection has shown the most dramatic improvement versus medical management in the appropriate patient population, 58 % seizure free vs. 8 %, respectively.

Generalized Convulsive Seizure

Introduction

Involvement of both hemispheres in synchronous activity quickly after the start of the seizure results in a generalized seizure. When a seizure is characterized by widespread abnormal muscle contractions—typically in a tonic and clonic fashion—it is known as a *convulsive* seizure. These have been known in the past as a *grand mal* seizure or a generalized tonic-clonic seizure. Other generalized seizures are myoclonic *(brief episodes of sudden muscle contraction),* absence *(discussed further below),* atonic *(sudden decrease in muscle tone),* and tonic *(sudden increase in muscle tone)* seizures but all resulting from generalized dysfunction of both hemispheres.

Major Clinical Features

When the convulsive seizure begins, consciousness is always lost and there is no memory of the seizure event. In the tonic phase, the body and limbs stiffen for 20–30 s. If the patient is standing, she/he will fall like a log, often resulting in traumatic injuries. If air forces out the closed glottis, a grunting sound or cry may occur. Patients may also bite their tongue, lip, or cheek and become incontinent of urine. Occasionally in the elderly, the tonic phase may be severe enough to cause a compression fracture usually involving a thoracic vertebra. Since breathing does not occur during the tonic phase of the seizure, blood may become sufficiently oxygen desaturated to make the patient temporarily cyanotic (blue).

In the clonic phase, rhythmic jerking of the limbs begins in rapid synchrony that slows in intensity and frequency over 20–40 s. Usually, the jerking then abruptly ceases and the seizure ends.

The postictal period lasts for minutes to over an hour but may be longer following a prolonged seizure or multiple closely spaced seizures. The patient is unconscious initially and then is difficult to arouse and confused for sometime. The patient often sleeps following the seizure which can cause witnesses to describe the seizure as lasting for an hour or more.

Disorders that must be distinguished from a convulsive seizure include syncope, migraine, transient ischemic attack, nonepileptic seizure (psychogenic nonepileptic seizure), rage attacks, Meniere's disease attack and movement disorders. In children, breath-holding spells, night terrors, and pallid infantile syncope must also be considered.

Syncope is suggested by the onset always occurring when the patient is erect (seizures occur in any position). Before fainting, the patient usually has a feeling of being "light-headed" or of impending faint that may be accompanied by loss or darkening of vision. Syncope is brief (10–20 s) and results in loss of muscle tone so the patient collapses with less chance of hurting themselves. Syncope seldom causes muscle twitching, which, if present, should always be very brief (few seconds). Syncope does not cause postictal confusion.

Nonepileptic seizures should be considered when the patient has: (1) Complex, prolonged, and variable warnings, (2) nonsymmetrical limb movements, (3) nonrhythmic or semi-purposeful limb movements, (4) prolonged limb movements that subside and then amplify, and (5) no postictal confusion and (6) memory of the event.

Following a first seizure, the physical examination should search for other findings suggestive of the cause. There should be a search for signs of head trauma, infections of ear, sinuses, brain, or meninges, congenital abnormalities (like tuberous sclerosis), focal or diffuse neurologic abnormalities, and alcohol or drug abuse and cancer.

Major Laboratory Findings

In general, the following tests are usually performed on a new seizure patient with a normal neurologic examination: Serum electrolyte and liver function tests, complete blood count, neuroimaging, and an EEG done at least 48 h after the seizure. The MRI is preferred over CT because it can detect small masses and mesial temporal sclerosis. Seldom are major abnormalities of blood or CSF found. Elderly patients are more likely to have abnormalities on neuroimaging to account for the seizure etiology.

Principles of Management and Prognosis

Management of epilepsy should be directed toward preventing future seizures and eliminating or controlling the cause. If this is the first unprovoked seizure, a decision whether to administer anticonvulsants must be made based on the neurologic exam, EEG, and other ancillary studies completed. The risk of developing recurrent seizures ranges from, approximately, 20–70 %—and the risk is greatest in the first 6 months and then decreases after that. The

best predictors for seizure recurrence include evidence of a neurologic reason for seizures (by exam or MRI) and abnormalities on EEG. A thorough discussion with the patient regarding the risks of further seizures balanced with the risks of daily anticonvulsant use must be undertaken. If a woman is of childbearing age, a discussion of possible teratogenic effects on the fetus should be discussed. In addition, all states require individuals with a driver's license to notify the motor vehicle department following a seizure and most prohibit driving for 6–12 months after their last seizure.

Anticonvulsants all inhibit excessive neuronal activity by: (1) blockade of voltage-gated sodium channels, (2) indirect or direct enhancement of inhibitory GABA neurotransmission, and (3) inhibition of excitatory glutamatergic neurotransmission. In Table 15.3, the major anticonvulsants, first-line seizure indications (most effective drugs with least toxicity), mechanisms of action, and common toxicities are listed. For generalized seizures, the first line anticonvulsants are valproate, phenytoin, levetiracetam, and lamotrigine. About two thirds of the patients can be well controlled with anticonvulsants. If seizure control is not achieved with the first drug, a second drug should be substituted. If the patient is compliant in taking their medication, success with anticonvulsants is seldom achieved if the third drug trial fails. Some of these patients benefit from two drug regiments or from alternate methods such as vagal nerve stimulators or surgical removal of a seizure focus.

The decision when to stop anticonvulsants is complex and most patients should continue their anticonvulsant for at least 2 years after their last seizure. Reasons to discontinue anticonvulsants are to prevent drug interactions, side effects, risk of teratogenicity if pregnancy is desired, and cost of medication. Factors to consider anticonvulsant continuation include the social stigma of a seizure and the risk of another seizure which would result in loss of driving privileges for 6–12 months.

Absence Seizure

Introduction

After convulsive seizures, absence seizures are the second most common type of generalized seizure. The onset is in childhood—generally between the ages of 3 and 12 years. Although the seizures can occur very frequently—from dozens to hundreds of times per day in some cases, they are not associated with progressive neurologic disease and may remit in adulthood.

Pathophysiology

The etiology of absence seizures is unknown. Since the EEG shows the onset to be simultaneous and synchronous 3 Hz spike and wave discharges diffusely in both hemispheres, the origin is thought to be in deep diencephalic structures with early spread of the seizure throughout both hemispheres.

Major Clinical Features

The typical seizure begins with arrest of speech and the abrupt onset of loss of awareness but does not cause loss of muscle tone and falling. A brief period (~10 s) of staring without being able to communicate is the most common presentation—but with longer duration seizures (up to 30 s) eye blinking or minor body jerks *(myoclonus)* can also occur. The individual then becomes alert but does not recall the episode. Since the seizure begins in a generalized manner, there is no aura and due to the brief nature of the spells, no postictal period. The seizures may occur in clusters and are often precipitated by hyperventilation. In school, teachers may think that the child is daydreaming or deliberately not paying attention.

Table 15.3 Major anticonvulsants

Anticonvulsant	Main seizure indications	Likely mechanisms of action	Major side effects[a]
Carbamazepine and Oxcarbazepine	Focal seizures Generalized convulsive seizures	Inhibits voltage-dependent sodium channels in a voltage- and use-dependent manner	Ataxia Dizziness Diplopia Blood dyscrasia
Ethosuximide	Absence seizures	Blocks voltage-dependent calcium channels which affect T currents	Headache GI distress Ataxia Blood dyscrasia
Gabapentin	Focal seizures	Increases synaptic concentrations of GABA	Dizziness Sedation
Lamotrigine	Generalized seizures Focal seizures	Inhibits voltage-dependent sodium channels in a voltage- and use-dependent manner	Abnormal thinking Ataxia Dizziness Nausea
Levetiracetam	Focal seizures Generalized seizures	Inhibits presynaptic calcium channels	Irritability Drowsiness Dizziness
Phenytoin	Generalized seizures Status epilepticus	Inhibits voltage-dependent sodium channels in voltage- and use-dependent manner	Nystagmus Ataxia Gingival hyperplasia Hirsutism
Topiramate	Focal seizures Generalized seizures (absence)	Blocks voltage-dependent sodium channels Also a carbonic anhydrase inhibitor	Weight loss Paresthesias Kidney stones
Valproate	Generalized seizures Focal seizures Myoclonic seizures	Inhibits voltage-dependent sodium channels in voltage- and use-dependent manner plus other mechanisms	GI distress Ataxia Weight gain Hepatic dysfunction
Zonisamide	Generalized seizures Focal seizures Myoclonic seizures	Blocks sodium and calcium channels Carbonic anhydrase inhibitor	Anorexia Kidney stones Paresthesias

[a] Most anticonvulsants are metabolized by the liver, cause sedation to a varying extent, cause idiosyncratic rashes, and are teratogenic

Major Laboratory Findings

The EEG is diagnostic and usually shows a 3 Hz spike and wave discharges that can be induced with hyperventilation. Atypical absence seizures can occur with EEG discharges slightly faster or slower than 3 Hz and these may coexist with other seizure types. Neuroimaging is normal.

Principles of Management and Prognosis

First-line treatment choices are valproate and ethosuximide for typical absence seizures and valproate for atypical absence seizures. In young adulthood, absence seizures stop in about two thirds of patients. In the remaining patients, absence seizures may progress to primarily generalized seizures or atypical absence seizures.

West's Syndrome

Introduction

In infancy, a triad of epileptic spasms, hypsarrhythmia on EEG, and mental retardation characterizes West's syndrome. Epileptic spasms (previously known as *infantile spasms*) affect 1 in 3,000 live births. The seizures begin in the first year of life with a peak onset between 2 and 8 months.

Pathophysiology

The pathophysiology of epileptic spasms and hypsarrhythmia is unknown but most cases are associated with nonprogressive single or multiple prenatal and postnatal cortical lesions that include cerebral malformations, congenital infections, vascular malformations, metabolic disorders, asphyxia, leukomalacia (abnormal softening of white matter), kernicterus (deposition of the bile pigment in deep brain nuclei with degeneration from neonatal jaundice), head trauma, and intracranial hemorrhage.

Major Clinical Features

Epileptic spasms are characterized by brief, symmetric contractions of neck, trunk, and limb muscles. The spasm may involve groups of muscles (usually both extensor and flexor muscles) or an isolated muscle. Eye deviation, nystagmus, and interrupted respiration are common during the spasm. The spasm is usually followed by a brief tonic phase. The spasms occur in clusters of up to 100 and are most common during sleep or upon arousal. Cognitive disorders may include mental retardation, speech delay, visuomotor apraxia, and autism.

Major Laboratory Findings

The EEG classically shows hypsarrhythmia—random, high-voltage slow waves, and spikes that vary from moment to moment in location and duration. During sleep, the EEG may show a burst-suppression pattern. The more severe the EEG pattern, the more frequent and severe are the infantile spasms.

Principles of Management and Prognosis

Empirically, adrenocorticotropic hormone (ACTH) and vigabatrin have been found to reduce the frequency of infantile spasms. Both drugs are most effective when given as soon as the infantile spasms begin but neither drug has been proven to improve the long-term outcome of affected children.

Infantile spasms disappear at 1–5 years whether or not the child received treatment. However, the outcome for most children with West's syndrome is poor. About one third die before the age of 3 years and three fourths have moderate to severe mental retardation. Half the children progress to experiencing tonic-clonic, atonic, and simple partial seizures and many of these children have EEG patterns suggestive of the Lennox–Gastaut syndrome—a difficult to treat form of childhood epilepsy. Good prognostic factors

include normal development until seizure onset, cryptogenic cause, and mild hypsarrhythmia.

Status Epilepticus

Introduction

A widely accepted definition of status epilepticus is more than 5 min of continuous clinical (and/or electographic) seizure activity or recurrent seizures without full recovery to baseline between seizures. The previous timeline of 30 min of continuous seizure activity as status epilepticus has been shortened due to experimental data suggesting that permanent neuronal injury can occur before 30 min of continuous seizure as well as the fact that seizures longer than 5 min typically do not stop spontaneously. The exact incidence of status epilepticus is not known, but is estimated at 50 cases per 100,000 people per year. Status epilepticus has the highest incidence in the first year of life and in the elderly but the elderly that have the highest mortality. Over 10% of adults with their first seizures present status epilepticus. Table 15.4 lists the etiologies for status epilepticus.

Pathophysiology

Presumably, the seizures begin by the same mechanism as all seizures. However, status epilepticus involves a failure to terminate the seizure. Experimental studies find that this failure can arise from abnormally persistent, excessive excitation, or ineffective recruitment of inhibition. Standard drugs used for status epilepticus are more effective if given in the first hour of status.

Table 15.4 Etiologies of status epilepticus

Etiology	Frequency (%)
Low anticonvulsant level	34
Cerebrovascular accident	22
Hypoxia/anoxia	18
Metabolic cause	15
Drug overdose	13
Alcohol related	13
CNS infection	10
Brain tumor	7
Other	5

Status epilepticus can cause cerebral injury, especially in limbic structures, such as the hippocampus. During early status epilepticus, the brain is able to maintain homeostasis through increases in blood flow, blood glucose, and oxygen utilization. However as status epilepticus continues, homeostatic failure begins and may contribute to brain damage. Hyperthermia, rhabdomyolysis, hyperkalemia, and lactic acidosis develop from constant widespread muscle firing. Other signs of decompensation may develop including hypoxia, hypoglycemia, hypotension, leukocytosis, and poor cardiac output. However, seizure activity itself appears sufficient to cause brain damage. One mechanism of damage is glutamate-mediated excitotoxicity, particularly in the hippocampus. The normal concentration of calcium outside of neurons is at least 1,000 times greater than inside neurons. During seizures, the receptor-gated calcium channel is opened following stimulation of the NMDA receptor by glutamine. This enables the intracellular calcium levels to rise potentially to cytotoxic levels.

Major Clinical Features

In *convulsive status epilepticus*, patients have mental status impairment (from confusion to coma) and have clinically obvious seizures with generalized tonic-clonic limb movements. Patients can proceed from convulsive status epilepticus to *nonconvulsive status epilepticus (NCSE)* which is defined as seizure activity on EEG without clinical findings of convulsions. In this setting, the only clinical signs of status epilepticus are the severely impaired mental status that can be accompanied by subtle motor movements (e.g., rhythmic muscle twitches or tonic eye deviation). Upon neurologic examination, the patient will not respond to verbal commands. She/he will have increased or decreased muscle tone, no purposeful limb movements, and frequently demonstrate Babinski signs. In general, the neurologic signs will be symmetrical.

There are occasional patients who present with constant confusion, impaired awareness, able to move limbs and walk ("the wandering confused") and have a type of NCSE which has a relatively good prognosis.

After initial treatment with benzodiazepine and another antiepileptic drug, patients who continue to exhibit status epilepticus are considered to have *refractory status epilepticus*.

Major Laboratory Findings

A marked leukocytosis (WBC > 20,000/mm^3) without an increase in bands occurs due to loss of margination of white blood cells rather than production from bone marrow as seen in an infection. As a consequence of prolonged seizures, the patient develops elevated serum potassium, metabolic acidosis (pH < 7.0), and varying degrees of hypoxia. A screen of toxins and anticonvulsant levels that are low or absent also may establish the cause.

The EEG is always severely abnormal showing continuous or nearly continuous spike and wave complexes. The findings on neuroimaging depend on the etiology of the status epilepticus as status epilepticus of unknown cause may have initially normal neuroimaging.

Principles of Management and Prognosis

The goal is to stop the seizures from status epilepticus, identify and treat the cause, and prevent complications. Initial priority is to establish an airway and maintain circulation. This is accomplished by administering oxygen by mask or cannula, monitoring heart rate, temperature, and blood pressure, following oxygen saturation by pulse oximetry, and establishing intravenous access. Fingerstick blood glucose is obtained simultaneously to diagnose hypoglycemia.

Once IV access is obtained, emergent abortive seizure therapy is given—typically lorazepam. This is followed by fluid and nutrient (thiamine and then glucose if needed) resuscitation. This is soon followed by a full intravenous loading dose of fosphenytoin or phenytoin to maintain cessation of the seizures. Fosphenytoin is a water-soluble analogue of phenytoin that is converted to phenytoin in the body. Fosphenytoin can be given at a faster rate and is somewhat safer than phenytoin but is more expensive.

If fosphenytoin and lorazepam fail to control the seizures, the patient should be intubated and placed on a ventilator. Additional IV boluses of antiepileptic medications are administered. If there is not resolution of seizure activity, continuous infusions of midazolam, propofol, or pentobarbital may be used. Once control of electrographic seizures is obtained, patients are typically kept on infusion for 24–48 h before attempts are made to wean the agents slowly.

Patients, especially children, with epilepsy who experience repeated bouts of status epilepticus can begin early treatment at home by rectal administration of a special gel formulation of diazepam. In children, this rectal delivery often stops seizures within 15 min.

Recommended Reading

Berg A, Berkovic S, Brodie M et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2010;51(4):676−85. (Up-to-date classification of seizures and epilepsy)

Brophy G, Bell R, Claassen J et al. Guidelines for the evaluation and management of status epilepticus. Neurocritical Care 2012;17(1):3–23. (Current guidelines for the treatment of status epilepticus)

Wiebe S. The epilepsies. In Goldman's Cecil Medicine, 24th edn. In: Goldman L, Schafer A, editors. 2012:2283–2294. Elsevier Saunders. (A concise overview of seizures and epilepsy)

Cardiac Arrest, Coma, and Cerebral Death

16

A 60 year-old woman with moderate congestive heart failure collapsed at church. She was unconscious without a detectable pulse. Two parishioners began cardiopulmonary resuscitation and called 911. Within ten minutes, medics arrived and determined that she was in cardiac arrest by portable EKG. Electroshocks brought her into atrial fibrillation and a pulse returned. Upon hospital admission, she had pupillary light reflexes and required intubation and ventilation. She was placed in therapeutic hypothermia for 24 h. She remained comatose for two days with a Glasgow coma score of 4. She became conscious on day 3 and was discharged on day 10 with moderate cognitive impairment but could talk, walk, and feed herself.

Overview

Consciousness has three attributes: arousal, wakefulness, and awareness of self and environment. Arousal is the ability to awaken from sleep. This normal state is characterized by specific stages, characteristic EEG patterns, and the ability of verbal or physical stimuli to terminate sleep to wakefulness. Wakefulness and awareness are states of alertness (usually with eyes open) and characterized by appropriately responding to sensation, emotion, volition, and thought. Wakefulness and awareness require the interaction of a relatively intact cerebral cortex and a normally functioning reticular activating system in the upper brainstem extending from the midbrain to the hypothalamus and thalamus.

Loss of consciousness has several stages. *Confusion* denotes lack of clarity and coherence with speech at a slower speed than usual. Patients typically have inconsistent thinking and attention and are easily distractible. The confusion is often worst in the early evening (sundown syndrome). *Delirium* is usually characterized by confusion with agitation and restlessness, sudden movements as well as rapid, fragmented, and slurred speech. These states typically result from a global process such as a toxin or metabolic disturbance. *Obtundation* is a disorder of alertness associated with slow reaction times (psychomotor retardation). Individuals can be aroused by verbal stimuli but respond poorly to questions with a prolonged delay in their verbal or motor responses. In *stupor* or *semicoma*, individuals require constant strong verbal or physical stimuli to remain aroused. Their responses are simple and often inaccurate. When the stimulus stops, they return to unconsciousness.

Coma is the pathologic state of the inability to arouse from any stimuli to produce appropriate responses. The majority of patients have impairment of reticular activating system function. Occasionally, coma results from extensive damage to both cerebral hemispheres but hemispheric lesions usually produce coma via transtentorial compression of the reticular formation.

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Pathophysiology

Etiologies causing coma can be divided into 3 major categories: supratentorial mass lesions, infratentorial destructive lesions, and metabolic causes. Specific causes of coma in each category are listed in Table 16.1. In the emergency room setting, over half the etiologies are due to drug overdoses and other metabolic causes with the remaining being divided between supratentorial or infratentorial mass lesions.

Supratentorial structurally caused coma usually begins as a unilateral hemispheric mass that progressively expands to produce brain herniation (see Chap. 14 on brain tumors). As the herniation progresses across the tentorium, the upper brainstem pushes downward often rupturing and penetrating brainstem veins (Duret hemorrhages), producing fatal brainstem hemorrhages, and ischemia. Coma from infratentorial destruction can be from ischemic brainstem stroke or mass (hemorrhage or tumor) involving the brainstem or cerebellum, which directly damages or compresses the reticular formation.

Metabolic-caused coma primarily affects reticular formation neurons in the upper brainstem and thalamus but usually the entire brain is also affected. The mechanisms causing neuronal dysfunction vary widely from hypoxia, hypoglycemia, hypothermia, exogenous drugs or toxins, endogenous toxic molecules, acidosis, etc.

Major Clinical and Laboratory Features

There are three critical questions to be answered about a comatose patient. Where is the lesion? What is the cause? Is the coma stable, improving, or worsening? Generally, the physician first determines whether the etiologic category is supratentorial, infratentorial, or metabolic. The next step is to determine the cause within the etiologic category. Obtaining a history, including drug use, from a friend or relative is extremely helpful in placing the patient into an accurate category.

Table 16.2 gives the major clinical features found in each coma category. An elevated temperature and blood white count usually implies an infection (sepsis, pneumonia, or CNS) and a low temperature usually implies patient has been comatose in a cold environment for some period of time. Rapid regular breathing often denotes a metabolic acidosis from a metabolic cause. During the physical examination, attention should be paid to find signs of trauma (especially head or neck trauma), bleeding (external or internal), organ dysfunction (especially lungs, heart, kidney, thyroid), and sepsis. Since mentation, fine sensation, and coordination cannot be tested in a comatose patient, the neurologic exam focuses on spontaneous or pain-induced limb movements, breathing patterns, ocular findings, and cranial nerve function (Tables 16.2 and 16.3).

Important clues to a supratentorial location for the coma include early history of progressive unilateral hemispheric signs, or a unilateral fixed dilated pupil. The late stages of a supratentorial coma are due to brainstem dysfunction and often appear similar to infratentorial-caused coma. Infratentorial structural coma usually has a rapid onset, involves multiple cranial nerves, and produces brainstem findings before or accompanying coma. Table 16.3 lists the brainstem reflexes that can be evaluated in a comatose patient and the clues they give regarding brainstem localization. Weakness may be unilateral if the brainstem lesion is unilateral (brainstem stroke) or bilateral if the lesion involves both halves of the brainstem (brainstem hemorrhage or tumor). Metabolic coma may have a rapid or subacute onset, usually produces mental changes before motor signs, has preserved pupillary reactions, rarely produces asymmetric motor, sensory, or reflex findings, and is often associated with systemic disease or drug intoxication (abnormal blood findings and signs of other organ failure). Occasional patients have psychogenic coma characterized by normal muscle tone and reflexes, unpredictable vestibulo-ocular reflexes with the fast phase preserved on ice water caloric testing, atypical irregular breathing patterns, and non-physiologic responses to cranial nerve testing.

Table 16.1 Major causes of coma

Supratentorial structural (20% of total)	Infratentorial structural (15% of total)	Metabolic and diffuse brain dysfunction (65% of total)
Head trauma **Contusion with brain swelling** **Subdural/epidural hematoma**	*Cerebrovascular disease* **Brainstem ischemic stroke** **Brainstem hemorrhage** Cerebellar ischemic stroke Cerebellar hemorrhage	*Drugs* **Sedatives** **Opioids** **Tranquilizers and antidepressants** Anticonvulsants Anesthetics
Cortical brain tumor Primary or metastatic	*Tumor* Brainstem Cerebellar	*Hypoxia* **Cardiac or respiratory arrest** Severe anemia Toxins (carbon monoxide)
Ischemic strokes Massive stroke with brain herniation	*Infectious* Brainstem abscess Cerebellar abscess	*Blood glucose abnormalities* **Hypoglycemic coma from excess insulin** Hyperglycemic coma from diabetes mellitus
Brain hemorrhages **Intracerebral hypertensive hemorrhage** Arteriovenous malformation hemorrhage	*Paraneoplastic syndrome* Brainstem encephalitis	*Abnormal ionic CNS environment* Hypo/hyper blood sodium, potassium, calcium, magnesium, acidosis
Infectious or paraneoplastic syndrome **Encephalitis** Brain or epidural abscess **Limbic encephalitis**		*Organ diseases* **Liver (hepatic coma)** Kidney (uremic coma) Lungs (CO_2 narcosis, respiratory failure) Thyroid (myxedema coma) Hypothermia (<30 °C)
		Diffuse intrinsic brain disorders Subarachnoid hemorrhage Status epilepticus or non-convulsive status
		Brain co-factor deficiency Thiamine (B_1) Cyanocobalamine (B_{12}) Pyridoxine (B_6)

Table 16.1 (continued)

Supratentorial structural (20% of total)	Infratentorial structural (15% of total)	Metabolic and diffuse brain dysfunction (65% of total)
		Poor cerebral perfusion Hypertensive encephalopathy Obstructive hydrocephalus Bleeding with low blood volume Decreased cardiac output (myocardial infarction, cardiac arrhythmia)
		Toxins **Ethanol** Methanol Ethylene glycol Cyanide, etc.

Bold refers to most common causes within that category

Table 16.2 Coma characteristics excluding that caused by head trauma

Characteristic	Supratentorial structural	Infratentorial structural	Metabolic
Early history	Signs suggesting dysfunction of the hemisphere (hemiparesis, hemisensory defect, aphasia, visual defect). Headaches common	Signs of cranial nerve dysfunction. Headaches and stiff neck may be present	Rapid onset (anoxia) or subacute progression (drugs, uremia, etc.). Patient looks asleep. Headaches uncommon. Fever may be present if sepsis or pneumonia present
Breathing	Normal or Cheyne–Stokes (periodic cycles of rapid breathing followed by period of apnea)	Apneustic (deep inspiration, long pause, and prolonged exhalation at a rate about 5/sec) or ataxic (irregular, ineffective breathing that is often shallow)	Normal or rapid due to metabolic acidosis
Early eye findings (See Fig. 16.1)	Pupillary light reflexes are present but pupil size may be small or unilaterally dilated. Papilledema may be seen. Vestibulo-ocular reflexes may be present or impaired	Pupil size often unequal and may be unresponsive to light (fixed). Eyes may not be parallel and vestibulo-ocular reflex is sluggish or absent. Papilledema is absent	Normal size and reaction to light, normal vestibulo-ocular reflexes, and no papilledema
Motor (See Fig. 16.2)	Asymmetric spontaneous or pain-induced limb movements. Decorticate posturing (flexion of the arm and extension of the leg on the involved side) to pain may occur	Bilateral limb weakness or quadraparesis may be present. Decerebrate posturing (unilateral or bilateral extension of arms and legs) to pain seen in midbrain lesions	Symmetric spontaneous or pain-induced limb movements
Reflexes	Often hyperactive with Babinski sign on contralateral side	Often normal or hyperactive. Babinski signs may appear	Normal or depressed. No Babinski signs
Neuroimaging	Hemispheric mass (tumor, hemorrhage, abscess, stroke), shift of midline structures, brain herniation. Occasional obstructive hydrocephalus	Mass (tumor, hemorrhage, infarction) in brainstem or cerebellum, occasional cerebellar tonsillar herniation through foramen magnum	Normal

Table 16.3 Bedside examination of cranial nerves in a comatose patient

Test	Cranial nerves tested	Testing method	Brainstem location tested
Papillary light reflex	2, 3	*Normal*: Bright light shined into one eye causes both pupils promptly to reduce in size. Large pupil that is fixed to ipsilateral and bilateral light implies damage to CN 3	Midbrain
Corneal reflex	5, 7	*Normal*: Touching cornea with cotton causes both eyelids to promptly close or blink. Failure of both eyelids to blink when stimulating one cornea implies dysfunction of ipsilateral CN 5. Failure of one eyelid to blink with direct and consensual corneal stimulation implies dysfunction of ipsilateral CN 7	Pons
Symmetrical face movement to pain	7	*Normal*: In light coma, ipsilateral or contralateral pain to face or body causes grimace of lower face. Unilateral grimace to stimuli implies dysfunction of CN 7	Pons
Vestibulo-ocular reflex or "Doll's eyes" maneuver	3, 6, 8	*Normal*: When rotating head laterally, the eyes remain fixed at original target. Abnormal test is when eyes move with head on lateral rotation	Lower pons to midbrain
Ice water caloric test	3, 6, 8	*Normal*: Irrigation with 25–50 mL of cold or ice water in one ear causes both eyes to move to side with ice water. In coma, eyes remain deviated to that side. If awake, nystagmus occurs with slow phase towards ear with cold water. If water in one ear shows no eye movements but water in opposite ear shows normal eye deviation, this implies damage to ipsilateral CN 8. In brain death, there is no eye movements with water in either ear and implies brainstem lesion in pathways of vestibular nuclei to CN 3 and 6	Lower pons to midbrain
Gag reflex	9, 10	*Normal*: Suctioning of mouth or stimulation of posterior pharynx triggers gag reflex. Absent gag implies dysfunction to medullary gag center	Medulla
Cough reflex	9, 10	*Normal*: Spontaneous cough or cough upon stimulating trachea. Absent cough implies dysfunction to cough center	Medulla
Yawn or sneeze reflexes	5, 9, 10	Presence of these long-loop reflexes implies brainstem function reasonably intact	Medulla to upper brain
Deep tendon reflexes	Spinal cord	Normal: limb movement in response to percussion of joint tendon Presence implies lack of spinal shock and intact spinal cord level but does not imply brainstem or cortical function	Spinal cord level

Principles of Management and Prognosis

In the emergency management of a comatose patient, the first step is control of the ABCs (airway, breathing, and circulation) (Fig. 16.3). Steps include ensuring airway, delivering oxygen either nasally or via intubation if needed, and establishing intravenous access. Commonly ordered tests include toxicology screen, complete blood count, electrolytes, liver function studies, creatinine, glucose, calcium, and a "save serum" specimen for possible future tests. Depending on the history and initial evaluation of the patient, the following drugs may be intravenously administered: thiamine, an opioid antagonist and a bolus of 50% glucose solution—if finger stick rapid glucose measurement shows hypoglycemia.

If a supratentorial cause is suspected, the situation becomes emergent and immediate cranial computed tomography (CT) is indicated. If impending brain herniation is present, lowering of intracranial pressure is accomplished by intubation and hyperventilation (to cause cerebral vasoconstriction), administration of intravenous mannitol or hypertonic saline (to reduce cerebral fluid volume) and prompt surgical intervention (to remove a hemispheric mass or to remove cerebrospinal fluid (CSF) if obstructive hydrocephalus is present).

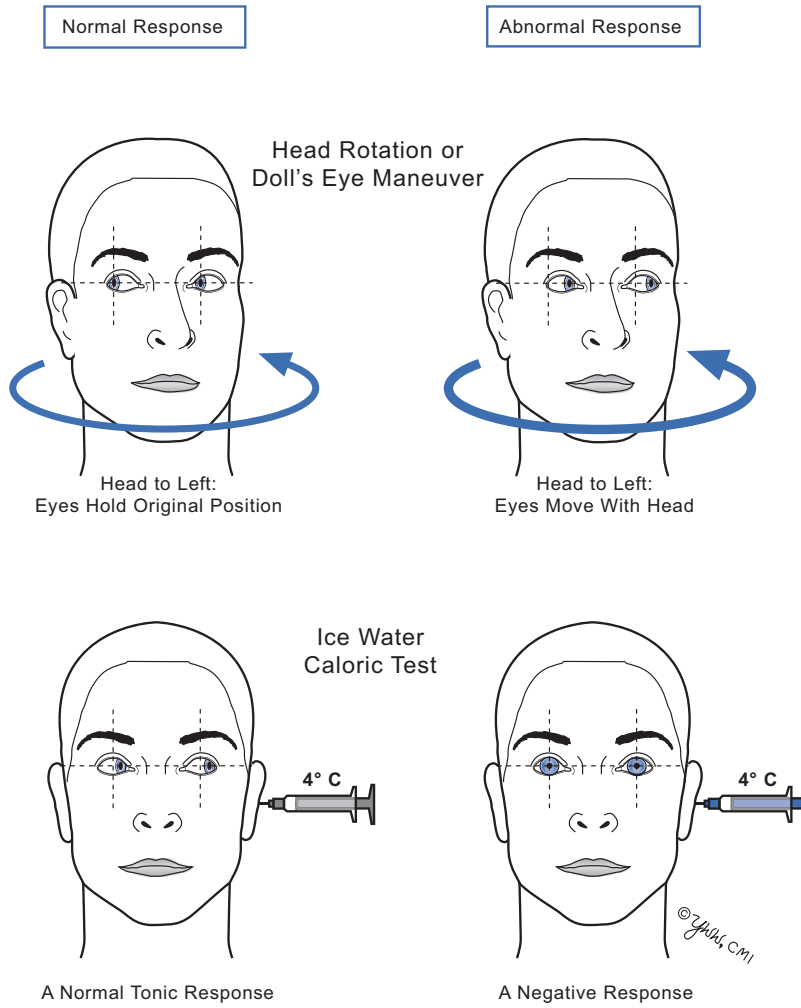

Fig. 16.1 Assessment of vestibulo-ocular reflex in coma

With infratentorial causes of coma, vital signs may rapidly worsen so intubation with mechanical ventilation and blood pressure supporting drugs may be needed. Neuroimaging can identify the cause but surgical intervention is seldom indicated. If the cause of metabolic coma is due to insufficient circulation, oxygen, or glucose to the brain, rapid correction of the etiology may reverse the situation. For many other causes including organ dysfunction and drug overdose, the patient should be stabilized, appropriate blood tests ordered to identify the etiology, and treatment focused to correct the underlying metabolic cause.

The outcome of a comatose patient varies with the etiology but in those with a structural brain lesion the mortality is high with severe neurologic sequelae in survivors. The following generalizations help predict outcomes from coma in patients without head trauma. Head trauma has a better prognosis (see Chap. 18 on traumatic brain injury and subdural hematoma).

- Coma seldom persists longer than 2 weeks. The patient dies, develops a persistent vegetative state (chronic condition in which s/he appears awake but has no evidence of cognition), or improves, opens eyes, and regains consciousness.
- Less than 1 % of patients regain independent function if they still have absent corneal,

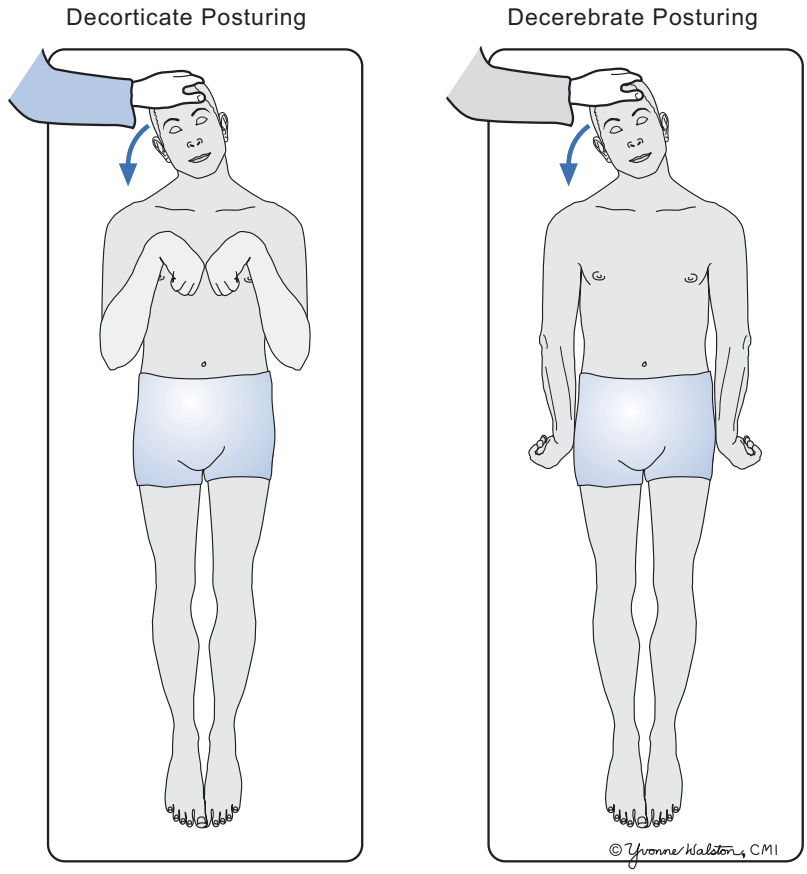

Fig. 16.2 Decorticate and decerebrate posturing reflexes

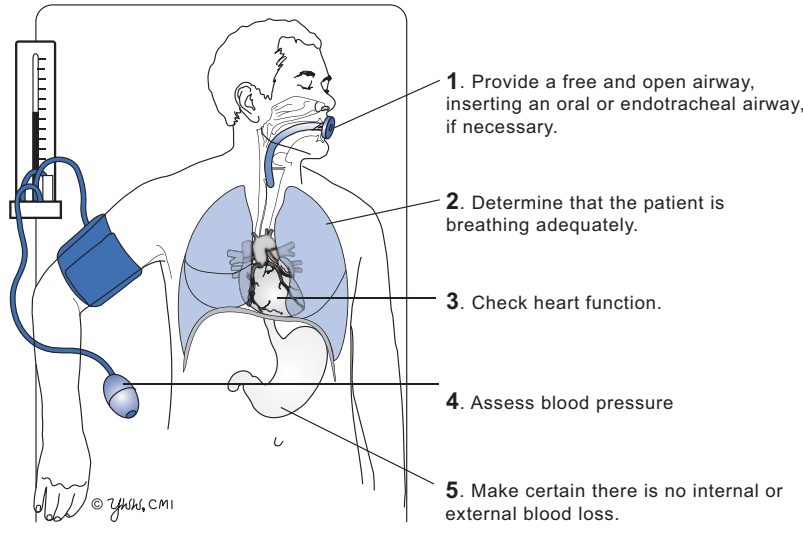

Fig. 16.3 Assessment of ABCs in coma

pupillary light, or vestibulo-ocular reflexes after one day of coma.
- Only 15% of patients comatose for over 6 h and 7% of patients comatose for 3 days recover with independent functioning.
- In metabolic coma, prognosis is best for patients with drug or endocrine causes and worst for anoxia or inadequate cerebral perfusion from any cause.

Table 16.4 Common clinical criteria for brain death

Coma, usually for at least 6 h
Absence of marked hypothermia (<34–36 °C) or sedative intoxication
Absence of purposeful motor responses other than spinal reflexes
Absence of brainstem reflexes (see Table 3)
Absence of respiratory drive (at a $PaCO_2$ that is 60 or 20 mmHg above baseline values)

Cerebral Death

Unfortunately many comatose patients progress to death. Human death always involves the permanent loss of the capacity for consciousness, combined with the irreversible loss of the capacity to breathe. The diagnosis of death is typically the legal responsibility of a medical practitioner and indicates a series of consequences that include no medical or legal requirement to provide life-sustaining technologies and ability to donate organs and to undergo an autopsy. It triggers end-of-life religious or social ceremonies, disposition of the body, the enactment of wills, etc.

Today, many patients are often mechanically- and chemically supported, making it important to know when brain functioning is permanently and irreversibly lost. As such, countries and states have adopted rules to diagnose brain death, which may vary slightly in detail. The U.S. Presidential Commission criteria for brain death heavily emphasize irreversible loss of brainstem functions. Thus, the current clinical criteria focus on absence of brainstem functioning that includes loss of spontaneous eye movements, midposition of eyes with fixed pupils, no response to caloric stimulation, paralysis of bulbar muscles, lack of gag or cough reflex, absence of purposeful limb movements to noxious stimuli, and absence of spontaneous breathing even when there is elevated PCO_2 blood levels (Table 16.4). If the coma etiology is known and irreversible, the decision is usually straightforward and often follows common clinical criteria for brain death without a need for laboratory tests. When the etiology is unknown, the diagnosis is somewhat more challenging. In particular, the patient must not be hypothermic (core body temperature below 34 °C) or intoxicated with sedating drugs (such as barbiturates) as marked hypothermia or deep intoxication can suppress brainstem reflex function and even produce a silent EEG giving the false impression of death. The coma should have persisted for at least 6–12 h in adults and longer in children. In children, an initial exam usually is followed by a confirmatory exam up to 24 h later. In adults, the confirmatory exam can be optional depending on state law. Presence of deep tendon reflexes implies only spinal cord segmental function that will soon disappear and does not negate a diagnosis of brain death. No patient with complete loss of brainstem function that meets all brain death criteria has ever recovered.

A series of confirmatory tests are available to establish brain death. These tests are optional in adults and seldom performed when the etiology is known. In infants, however, confirmatory tests are recommended. The most common test is an electroencephalogram (EEG), which demonstrates isoelectric silence (no detection of cerebral electrical activity when the EEG machine is at maximum sensitivity). When neurons and glia die, the cells swell (cytotoxic edema), increasing intracranial pressure and preventing cerebral arterial blood flow. Tests such as a cerebral arteriogram, CT or MRI angiogram or radionuclide study can be done to prove absence of cerebral blood flow. If there is a question about the presence of intoxicating drugs, quantitative drug blood levels are often obtained.

Although when the legal criteria for brain death are met and life support can be discontinued, it is important to have prior sensitive discussions with the family about understanding brain death

to help with their grieving. Social workers, religious members, friends, and family can be of tremendous help. Questions about organ donation can be answered usually by a member of the organ donation team who never participates in determining the brain death criteria.

Persistent Vegetative State

Persistent vegetative state (PVS) is a condition characterized by relatively intact brainstem function but no evidence of a functioning cerebral cortex. The UK Royal College of Physicians defines PVS as a clinical condition of unawareness of self and environment in which the patient breathes spontaneously, has a stable circulation, and shows cycles of eye closure and opening which may simulate sleep and waking. There is partial preservation of hypothalamic and brainstem autonomic functions but there is loss of sphincter control. Patients may show occasional random eye movements, swallowing, and grimacing but shows no signs of speaking or being aware of the environment. The EEG shows no changes in background activity when the patient is stimulated. Neuroimaging shows progressive cerebral atrophy over time. The neuropathology usually demonstrates diffuse necrosis of the cerebral white and gray matter associated with thalamic damage and relative sparing of the brainstem.

PVS lasting more than two weeks carries a very poor prognosis for moderate to good recovery and is considered permanent when the condition lasts more than 6 months.

Cardiac Arrest

Introduction

Anoxia from cardiac arrest is the third most common cause of coma after trauma and cerebrovascular disease. These three conditions can lead to post-anoxic coma, which usually develops following cardiac arrest, severe hypotension, or respiratory arrest. Cardiac arrest, the cessation of cardiac mechanical activity with absent signs of circulation, occurs in the USA 450,000 times annually. About 80% of cardiac arrests occur at home with a subsequent death rate of 90%. More than half of survivors are left with permanent neurologic sequelae. For in-hospital arrests, about 40% have circulation restored and 17% are discharged from the hospital. This improvement stems from better clinical recognition, cardiac arrest teams, defibrillators, and ICU monitoring of changes in cardiac rhythm, hypotension, and electrolytes.

Pathophysiology

Hypoxemia itself seldom causes neuronal death unless the arterial partial pressure of oxygen decreases to less than 25 mmHg. In the presence of severe hypotension, however, lesser degrees of hypoxemia can kill neurons. Normal cerebral blood flow (CBF) is 55 mL/min/100 g brain tissue. Reducing CBF to 25 mL/min/100 g brain tissue or lower impairs consciousness. CBF below 8 to 10 mL/min/100 g brain tissue causes neuronal death. Four major factors determine the amount of brain damage seen after cardiac arrest: (1) the duration of ischemia, (2) the degree of ischemia, (3) body temperature during the arrest with higher temperature associated with poorer prognosis, and (4) glucose levels (again, higher is bad).

Anoxic death of neurons occurs by several factors that cascade and include accumulation of lactic acid, increased concentrations of excitatory neurotransmitters such as glutamate, generation of oxygen-free radicals, and secondary microvascular occlusions worsening the local ischemia. Anoxic–ischemic encephalopathy begins one minute after cardiac arrest when phosphocreatine, a major source of high-energy phosphate, is depleted. This causes the sodium–potassium membrane pump to fail due to inadequate adenosine triphosphate (ATP). With mitochondrial energy failure, lactate production increases and calcium overload in mitochondria causes failure of respiratory function leading to cell death. Glutamate is released into the extracellular fluid caused by a failure of the glutamate buffering

mechanism. Glutamate then binds and activates N-methyl-d-aspartate receptors, which in turn produce osmotic cell swelling called cytotoxic edema. Subsequent activation of proteinases causes a breakdown of cytoskeleton elements. Thus, coma quickly develops from the global ischemia triggering widespread metabolic, neuronal, and glial failure leading to loss of neuronal membrane potentials and synaptic function failure. Secondary changes include diffuse brain swelling from the cerebral edema, leading to markedly elevated intracranial pressure and lack of cerebral arterial perfusion. The lack of cerebral perfusion can be demonstrated by a cerebral arteriogram.

Specific areas of the brain demonstrate anoxia vulnerability such as Sommer's sector of the hippocampus, cerebellar Purkinje cells, thalamus, basal ganglia, and parts of the brainstem. Neurons are more susceptible to hypoxia than oligodendrocytes and astrocytes. In the cortex, maximum damage occurs in the middle cortical lamina and is accentuated in arterial boundary zones or watershed areas between major arteries such as the middle and anterior or posterior cerebral arteries. When the brainstem is severely affected, the patient develops the syndrome of brainstem death. The spinal cord has a relative hypoxia resistance. Early histologic changes in neurons include lack of nuclear stainability, pale myelin sheath eosin stainability, and lack of cellular inflammation. Necrosis of the neuron then develops. The diffuse cerebral edema causes increased brain weight, diffuse softening, and dusky discoloration of involved areas. If the survival is prolonged, areas of encephalomalacia develop, which histologically contain lipid-laden macrophages.

Major Clinical Features

Unless cardiac function spontaneously occurs promptly, an untreated cardiac arrest progresses to death. The key to a successful cardiac resuscitation is rapidly to restore sufficient cardiac circulation and pressure along with adequate blood oxygenation to perfuse the brain and other critical organs.

Patients typically require monitoring in an ICU for subsequent development of cardiac arrhythmias, hypotension, or seizures. Eighty percent of survivors are comatose for hours to days. (See first part of this chapter for details.)

Seizures develop in 25% typically within 24 h of the arrest. Partial seizures or myoclonic seizures are the most common with generalized seizures less common. Generalized myoclonus characterized by sudden shock-like involuntary limb movements is common—often induced by tactile stimulation. It carries a poor prognosis and survivors with generalized myoclonus are severely incapacitated. Rare surviving patients can develop a variety of movement disorders including Parkinsonism, dystonia, chorea, and tics.

Major Laboratory Findings

Venous blood is tested for glucose, urea, carbon dioxide, bicarbonate, ammonia, sodium, potassium, chloride, calcium, and aspartate serum transaminase (AST). Arterial blood gases and carboxyhemoglobin tests for carbon monoxide exposure may be ordered when indicated.

During the cardiac arrest, the electroencephalogram (EEG) shows electrocerebral silence (isoelectric or "flat lined" EEG), which often continues after cardiac resuscitation. Thus, the EEG is usually done 24 h after resuscitation. The development of generalized EEG suppression or generalized epileptiform activity may occur and has a poor prognosis.

Neuroimaging immediately after a cardiac arrest often appears normal but by day three, the imaging often shows brain swelling and inversion of the gray–white densities.

Laboratory tests for brain death include an isoelectric EEG after several days demonstrating no electrical cortical function or the demonstration of no cerebral arterial perfusion above the foramen magnum due to cerebral edema, brain swelling, and markedly elevated intracerebral pressure. The lack of cerebral perfusion can be demonstrated by a cerebral arteriogram, MR or CT angiogram, or radionuclide brain scan.

A marker of hypoxic brain damage called neuron-specific enolase (NSE) is released from the brain into serum and CSF. NSE is an intracellular enzyme present in neurons and other cells of neuroectodermal origin. NSE serum elevation of greater than 33 μg/liter 1–3 days after cardiac arrest is associated with increased severity of post-anoxic neuronal injury but is not reliable for patients receiving therapeutic hypothermia.

Principles of Management and Prognosis

Optimal management of a cardiac arrest is to rapidly restore the heart beat and cerebral circulation. For in-hospital arrests especially on a cardiac monitored unit, rapid resuscitation is often accomplished within a few minutes. For out-of-hospital arrests, many uncontrollable delays occur. Once the patient is hospitalized, aggressive hemodynamic support is important to manage heart failure or myocardial infarction, control the blood pressure, correct electrolyte imbalances, and ventilate the patient for optimal oxygen delivery.

Post-resuscitation therapeutic hypothermia for out-of-hospital cardiac arrest is now endorsed by the American Heart Association. Two pivotal randomized studies have shown survival and quality of life benefit (16–21 % improvement over no hypothermia) for resuscitated patients when the initial cardiac rhythm is ventricular fibrillation. Currently, hypothermia is unproven for patients with other initial rhythms or asphyxia. Rapid hypothermia by several methods to cool the core temperature of the patient to 33–34 °C for 12–24 h with slow rewarming is standard at many hospitals. The benefit of hypothermia is believed to be through reduced cellular metabolism and less oxygen demand while maintaining acceptable ATP levels.

Poor prognostic signs following resuscitation for the comatose patient include no brainstem reflexes at any time, myoclonic status on day one, absence of pupil or corneal reflexes on days one to three, and absence of motor response other than extensor on day three. Elevated serum NSE on days one to three carries a poor prognosis unless the patient received hypothermia. Long-term outcomes from cardiac arrest range from death to persistent vegetative state to sufficient recovery for hospital discharge with mild to severe neurologic sequelae. Despite the wide range of outcomes, unfortunately, the overall prognosis is poor. For patients comatose for 6 h or less, consciousness returns in 35 % but for patients comatose after two weeks, full consciousness returns in only 13 % with the remaining progressing to a vegetative state or dying. Survivors in one study successfully resuscitated from cardiac arrest with initial atrial fibrillation after resuscitation had severe cognitive deficits in 60 % at 3 months and in 50 % at 1 year.

Recommended Reading

Posner JB, Saper CB, Schiff ND, Plum F. The diagnosis of stupor and coma, 4rd ed. Oxford, Oxford University Press; 2007. (Comprehensive review of coma and its causes)

Wijdicks EFM, Varelas PN, Gronseth GS, Greer DM. Evidence-based guideline update: determining brain death in adults. Neurology 2010;74:1911–8. (Reviews conditions necessary to fulfill criteria for brain death)

Monti MM, Laureys S, Owen AM. The vegetative state. Br Med J 2010;341:292–6. (Good review of what is and what is not a persistent vegetative state)

Young GB. Neurologic prognosis after cardiac arrest. N Engl J Med 2009;361:605–11. (Nice review of current status of cardiac arrest outcomes)

Disorders of the Developing Nervous System

17

A nine- month-old infant is referred to a child neurologist for evaluation after her pediatrician noted that the baby was not meeting developmental milestones. The baby was born at term with no complications and had a normal neonatal period. The baby was noted at three months to be "floppy" or hypotonic, and the neurologist also noted an exaggerated startle to auditory stimuli. Fundoscopic examination revealed a bright red fovea surrounded by a dull whitish retina (cherry red spot). This constellation of symptoms and signs was concerning for Tay–Sachs disease and a confirmatory blood test showed deficient levels of hexosamindase A enzyme. The child went on to develop seizures, lose vision, and regress developmentally. Death occurred at 3 years.

Overview

Amazing events in growth and development occur before birth as one cell develops into an infant. In spite of the immense complexity, most infants are born with a normal nervous system containing 50–100 billion functioning nerve cells. Unfortunately, 1–2% of infants are born with neurodevelopmental defects. About 40% of deaths in the first year of life are related to malformations of the central nervous system (CNS) and an unknown percent of spontaneous deaths in utero are from CNS maldevelopment. Although the cause of neurodevelopmental defects is unknown in 60%, defects can occur from several causes including genetic mutations, exposure to toxins or teratogens, central nervous system infections, metabolic deficiencies, and trauma. Table 17.1 lists some of the more commonly recognized causes.

Equally important as the cause of the CNS insult is the timing. By 3 weeks gestation, the primitive neural tube has begun to develop. CNS growth and maturation continues throughout the embryonic period (0–8 weeks), the fetal period (9–38 weeks), infancy, and well into late childhood. The characteristics of the malformation depend on the timing of the CNS developmental disruption although some insults, such as genetic mutations, may disrupt development over extended periods causing a variety of defects. In addition, multiple abnormalities may occur from a single primary deficit in early morphogenesis causing a cascading process of secondary and tertiary errors in morphogenesis. Insults that affect the CNS from week 3 to 6 usually produce major morphological abnormalities while insults occurring later may produce more subtle or localized dysfunction. Thus, it is possible to determine the latest time in gestation a malformation could occur but not the earliest. Table 17.2 presents the gestational timing of some neurodevelopmental milestones.

The basic steps of brain and spinal cord development are as follows: neurulation, neuronal and glial proliferation, migration, differentiation of neurons with axonal, dendritic and synaptic development, programmed cell death, and

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Table 17.1 Major recognized causes of neurodevelopmental defects of the nervous system

Genetic mutations
Mutations primarily affecting gray matter (neurons)
Tay–Sachs disease
Mutations primarily affecting white matter (myelin and their cells of origin)
Adrenoleukodystrophy
Krabbe disease
Unbalanced chromosomes (from duplications or deletions)
Down's syndrome
Fragile X syndrome
Toxins
Alcoholism in the pregnant mother
Organic mercury
Lead
Teratogenic drugs
Anticonvulsants (phenytoin, carbamazepine, valproic acid)
Thalidomide
Congenital infections
Rubella
Cytomegalovirus
Toxoplasmosis
Syphilis
Metabolic diseases
Phenylketonuria
Ionizing radiation
Defects uncommon unless radiation exposure is very high which causes fetal death

myelination. During neurulation, primitive cells destined to become neurons originate close to the neuroepithelium of the neural tube. These cells begin rapidly replicating by the fourth week producing cells that differentiate into bipolar neuroblasts. Some radial glia appear early and serve as scaffolding for neurons to migrate to the marginal layer, which will become the gray matter of the cerebral cortex. Ultimately the radial glia divide and become astrocytes. The migration of these post-mitotic neurons occurs in a precise orderly manner that is largely completed by the end of the fifth month but does continue at a slow rate until birth. This process appears to produce an excess number of neurons that are subsequently pruned to the appropriate number by a process of programmed cell death called apoptosis. Somehow neurons that do not establish correct neuronal connections by late pregnancy are triggered to die. Apoptosis does not elicit inflammation or gliosis, so there is no histologic evidence of their premature death.

Many terms describe abnormal brain tissue. The term dysplasia refers to abnormal cellular organization resulting in structural and functional consequences. *Dysplasias* may be localized (such as a hemangioma) or generalized, affecting a variety of structures from widespread distribution of the tissue defect. *Heterotopias* are portions of an organ displaced to an abnormal site within the same organ of origin, such as nodules of gray matter located in deep white matter due to incomplete neuronal migration. A *hamartoma* is a portion of tissue at the proper site but is architecturally disorganized, such as a focus of abnormal cortical lamination due to disorganization of pyramidal neurons. *Malformation* refers to a structural defect arising from a localized error in morphogenesis and may contain one or more of the features described above. Deformation occurs when normally formed tissue is secondarily damaged.

Anencephaly

Introduction

Anencephaly is the abnormal development of the brain and skull due to failure of the anterior end of the neural tube to close (e.g. neural tube defect (NTD)). The timing of the insult therefore occurs around week 4 of gestation. Due to the incomplete closure, the primitive neural elements are exposed to the amniotic fluid surrounding the fetus and thought to be relevant to the subsequent breakdown of this tissue.

Pathophysiology

The causes are unknown. The incidence of anencephaly in the USA is 1 per 1000 pregnancies with an estimated 1 in 10,000 infants born with anencephaly. Failure of anterior neuropore closure results in the absent cerebrum, cerebellum, and skull bones. The etiology of anencephaly is

Table 17.2 Milestones in pre- and perinatal development

Week of gestation	Major developmental event
3	Neural tube invaginates
4	Anterior then posterior ends of neural tube close
	Brain and head represent 50 % of total body length
	Rapid neuronal division into bipolar neuroblasts at rates up to 250,000 divisions/min
	Radial glia appear and migration begins
5	Lens placodes of eye develop
	Forebrain, midbrain and hindbrain become evident
	Neuronal migration largely complete
	Dorsal and ventral horns of spinal cord appear
	Peripheral nerves appear
6–8	Migration of neurons
	Ear develops
	Limbs develop
	All major organs under development
9–12	Gross brain structure established
	Glial development and migration appears
	Very rapid growth of axons and synapses
	Muscle contractions begin
13–20	Rapid brain growth
	CNS myelination begins
	α-Fetoprotein elevates in amniotic fluid and maternal serum if there is failure of proper neural tube closure
21–40	Primary cerebral fissures appear followed by secondary cerebral sulci
	Myelination continues
	Synaptic development continues
	Neuronal pruning of excess neurons by programmed apoptosis
Birth	Head is 25 % of total body length
	Peripheral nerve myelination almost complete but CNS myelination continues through age 2 years
	Cry vigorous, sucks and swallows liquids, yawns
	Suck, root, grasp and Moro reflex present
	Head control present
	Visual and auditory responses elicitable
Months after delivery	
2–5	Rapid brain growth continues with head circumference growing at 2 cm/month in first 3 months and 1 cm/month from 4–6 months
	Neurons develop more complex dendrites and synapses
	Oligodendrocytes and astrocytes in matrix zones continue to divide and migrate to about 6 months.
	Voluntary or social smile appears
	Head control improves
	Eye contact increases
	Turns to sounds
6–11	Rolls over, crawls, begins sitting
	Babbles, recognizes parents, says “Ma Ma”
	Head circumference grows at ½ cm/month
	Moro response and grasp reflex disappear

Table 17.2 (continued)

Months after delivery	Major developmental event
12	Neuronal dendrites continue growth but head circumference growth slows to ¼ cm per month
	Walks with hand held
	Uses pincer grip of thumb and forefinger
	Single words appear
	Babinski sign disappears
15	Walks independently
	Follows simple commands
18	Runs stiffly
	Knows about 10 words, identifies pictures
	Feeds self
24	Runs well, climbs stairs one step at time, opens doors
	Puts 3 words together (subject, verb, object)
	Tells immediate experiences

likely multifactorial, including both genetic and environmental factors. One gene that has been implicated is *MTHFR*, which codes for a protein involved in folate (or vitamin B9) processing. Accordingly, in the environmental realm, a deficiency of folate appears to play a role as well. Even though there may be a genetic contribution, most cases of anencephaly are sporadic.

Major Clinical Features

The most common phenotype has a lack of the cerebral and cerebellar cortices and variable loss of the basal ganglia and upper midbrain leaving in its place a small hemorrhagic, fibrotic mass of degenerating glia and neurons. The frontal, parietal, and occipital bones are absent leaving an open calvarium above the eyes. In addition, facial abnormalities and heart defects are common.

Major Laboratory Findings

Polyhydramnios (excess amniotic fluid) is a frequent feature. Sonograms are abnormal as early as 11 weeks and diagnostically very accurate at 14 weeks. The ultrasound reveals no brain tissue above the orbits and absent calvarium. In addition, there is marked elevation of serum and amniotic α-fetoprotein. α-Fetoprotein is synthesized by the fetal liver, circulates in fetal blood and is excreted in fetal urine into the amniotic fluid. It is then swallowed and digested by the fetal gastrointestinal tract. Thus, amniotic fluid and maternal blood normally contain little α-fetoprotein. The protein is elevated in fetal conditions such as open neural tube malformations, abnormalities in the fetal upper gastrointestinal tract, multiple fetuses, and fetal death. The optimal time to test amniotic fluid for α-fetoprotein is 14–16 weeks gestation while maternal serum testing occurs at 16–18 weeks and both are nearly 100 % elevated in anencephaly.

Principles of Management and Prognosis

Infants with anencephaly that make it to term (as the majority have fetal demise prior to term birth for a variety of reasons), typically die within days of birth. Even with this poor prognosis, living infants with anencephaly often make sucking and chewing movements and have simple limb movements demonstrating lower brainstem, spinal cord, and motor neurons are functioning.

Chiari Syndrome

Introduction

Chiari syndrome includes a developmental malformation of the brainstem, cerebellum, and spinal cord to varying degrees, resulting in a grading

of the malformations from 0 to IV (as described in detail below). Chiari type I and associated syringomyelia are the most common manifestations. The disease occurs in both genders with females affected slightly more frequently than males. Average age of presentation with symptoms is approximately 35 years but with a wide range from infancy to 60 years. The presentation can be highly variable from headaches to hydrocephalus, limb spasticity or cerebellar ataxia, and even lower cranial nerve dysfunction.

Pathophysiology

The key anatomical features of the specific Chiari malformation are characterized as follows:

Chiari type 0 malformation: syringomyelia ± cerebellar tonsil herniation

Chiari type I malformation: herniation of cerebellar tonsils > 5 mm below foramen magnum ± hydrosyringomyelia

Chiari type II malformation: herniation of cerebellar vermis, brainstem, and 4th ventricle through foramen magnum + myelomeningocele, hydrocephalus, ± hydrosyringomyelia (see Figs. 17.1 and 17.2)

Chiari type III malformation: occipital encephalocele + features of Chiari II

Chiari type IV malformation: cerebellar aplasia/hypoplasia + aplasia of tentorium

Major Clinical Features

Overall, the presentation of Chiari malformations can be varied—from asymptomatic (noted incidentally on brain MRI done for another reason) to severe deficits or coma due to hydrocephalus. When symptoms present in adulthood (25 to 45 years), the typical symptom of a Chiari type I is a suboccipital headache which worsens with coughing or bowel movements (Valsalva). This can extend to neck pain as well. Brainstem and cerebellar symptoms can present with vertigo or neurosensorial hearing loss. Ocular and breathing-related problems can also be a presentation.

In childhood, a Chiari type II malformation can present with progressive hydrocephalus, variable cerebellar ataxia, and lower cranial nerve CN 6–12 dysfunction with horizontal diplopia, facial weakness, deafness, sternomastoid muscle weakness and head lag, laryngeal stridor, and tongue atrophy. Spastic paraparesis in the arms from secondary cervical stenosis and cervical myelopathy may be present. The meningomyelocele causes variable paralysis and atrophy of lower leg and buttock muscles, loss of bowel and bladder control, and lumbar kyphosis. Cysts may develop in the cervical spinal cord producing syringomyelia with variable loss of sensation (especially pain and temperature) and atrophy of arm muscles.

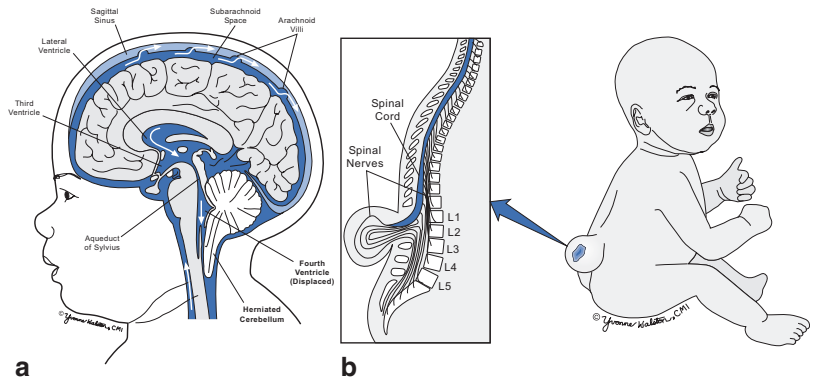

Fig. 17.1 Chiari type II malformation. **a** Cerebellar and medullary downward displacement **b** Meningomyelocele

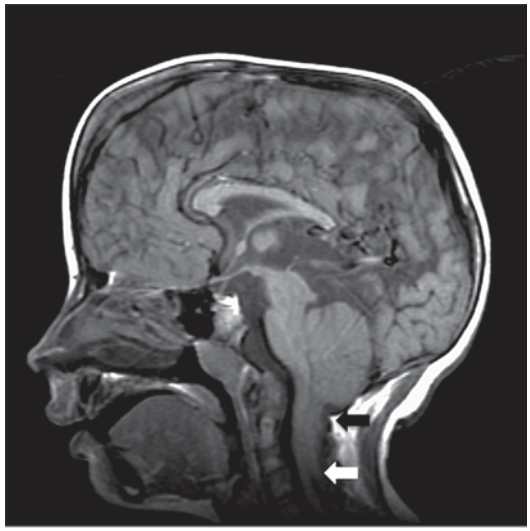

Fig. 17.2 Sagittal T1 weighted MRI of Chiari type II showing: narrowed 4th ventricle, beaked tectum, hypoplastic corpus callosum, and low cerebellum (*white arrow*) below the foramen magnum (*black arrow*) (Courtesy of Blaine Hart, MD)

Major Laboratory Findings

The diagnosis of Chiari II is confirmed in infants born with a meningomyelocele by MRI demonstrating the anatomical abnormalities detailed above.

Principles of Management and Prognosis

Therapy depends on the type of Chiari malformation as well as the severity of the symptoms at presentation. For incidental findings of Chiari type I by neuroimaging for other reasons, no interventions are recommended but the individual should be followed at regular intervals. Presentation with hydrocephalus as in Chiari type II requires alleviation of the increased intracranial pressure through a shunt (typically a ventriculoperitoneal shunt) and decompression of the posterior fossa may be required as well. Infections such as meningitis as well as CSF fistulas can be complications from these interventions. Motor and sensory symptoms due to abnormalities at the craniocervical junction or due to syringomyelia or meningomyelocele may respond to surgical treatment or decompression. Pharmacological analgesia for neuropathic sensory symptoms from the same lesions may also be indicated.

Phenylketonuria (PKU) (Phenylalanine Hydroxylase Deficiency)

Introduction

Metabolic disorders include derangements in metabolism of amino and organic acids. This includes storage diseases, mitochondrial enzyme defects, and leukodystrophies. These infants usually appear normal at birth but subsequently develop cerebral abnormalities. PKU is the most common disorder of amino acid metabolism and has an incidence worldwide varying typically between 1 per 10,000 and 1 per 20,000 births, although there are extremes with very high frequency and low frequency depending on carrier rate. Phenylalanine hydroxylase (PAH) deficiency is an autosomal recessive disorder that results in intolerance to the dietary intake of the essential amino acid phenylalanine and produces PKU children with profound and irreversible mental retardation when not treated. PKU is caused by mutations in the *PAH* gene on chromosome 12q23.2. Some mutations allow for partial PAH enzyme function and produce milder forms of the disease.

Pathophysiology

Phenylalanine is primarily metabolized in the liver by hydroxylation via phenylalanine hydroxylase to tyrosine. Mutations of the PAH enzyme cause abnormal elevations in plasma phenylalanine and low tyrosine levels. Normal plasma phenylalanine levels are less than 120 μmol/l, and affected infants are born with normal levels unless the mother has PKU not controlled by diet. After birth, dietary exposure occurs with consumption of either mother's or cow's milk that is rich in phenylalanine and cannot be metabolized to

tyrosine. When plasma phenylalanine levels rise above 1000 μmol/l, damage to the developing CNS occurs. Up to 1 g/day of excess phenylalanine and phenylpyruvic acid is then excreted in urine. PKU is inherited in an autosomal recessive manner.

Studies suggest that elevated brain free phenylalanine and decreased levels of large neutral amino acids (tyrosine and methionine) cause decreased protein synthesis, increased myelin turnover, and abnormalities in dopamine and norepinephrine neurotransmitter systems. The cerebral cortex that was histologically normal at birth develops abnormalities of myelination, dendritic growth and synaptic development—that is, systems that normally continue to mature after birth. In occasional untreated infants, degeneration of established white matter may develop.

Major Clinical Features

Clinically, infants are normal at birth. Over the first year of life (often within the first few weeks), infants develop eczematous skin rashes, progressive mental retardation, microcephaly, seizures, and behavior problems. Hypopigmentation of hair, skin, and iris (fair skin with blond hair and blue eyes) occurs due to inhibition of tyrosinase and lack of melanin production. Excretion of excessive phenylalanine and its metabolites creates a musty or mousy body odor. If PKU is not treated early, the mental retardation is irreversible. Untreated older children may develop spasticity, hyperactive reflexes, and paraplegia. There is increasing evidence that affected infants treated with careful phenylalanine-deficient diets grow to adulthood with an IQ in the broad range of normal. However, subtle cognitive deficits may still be present. Children experience delayed acquisition of speech, have more behavioral problems, and have some impairment of executive function on neuropsychological tests. Affected sibs have a lower IQ than unaffected sibs. Adults who go on a regular diet may also develop mild spasticity and subtle cognitive deficits so lifelong therapy is now recommended.

Major Laboratory Findings

The diagnosis is made by newborn screening in virtually 100% of cases, based upon the detection of hyperphenylalaninemia (levels above 1000 μmol/l) using the Guthrie microbial assay on a blood spot obtained from a heel prick 24 to 48 h after birth in the USA. The Guthrie screening test is usually confirmed by more specific methods such as tandem mass spectrometry which measures the ratio of phenylalanine to tyrosine (Phe/Tyr) which reduces false-positive results. Molecular genetic testing of the *PAH* gene exists but is not needed for diagnosis but can be used for prenatal testing (e.g., carrier status).

Neuroimaging is normal at birth and later detects irreversible abnormalities mainly in white matter. Histological changes in untreated cases include hypomyelination or demyelination of white matter, gliosis, and widespread neuronal loss with gross microcephaly.

Principles of Management and Prognosis

The goal of treatment is normalization of plasma concentrations of phenylalanine and tyrosine and the prevention of cognitive disorders. A diet restricted in phenylalanine should be instituted as soon as possible and continued for life. A phenylalanine-free medical formula with supplemental tetrahydrobiopterine is needed along with protein restriction, as protein restriction only is insufficient to provide sufficient nutrition and maintain plasma phenylalanine levels below 300 μmol/l (5 mg/dl). How high plasma phenylalanine levels can rise in adulthood before cognitive impairment occurs is unclear. However, noncompliance of dietary restrictions and markedly elevated plasma phenylalanine levels can result in decreased cognitive functioning and white matter abnormalities detectable on MRI. Plasma phenylalanine levels must be monitored closely and maintained below 300 μmol/l during pregnancy as high maternal phenylalanine levels can produce fetal abnormalities.

Tay–Sachs Disease Hexosaminidase A Deficiency (Acute Infantile Variant)

Introduction

Tay–Sachs disease is the classic example of a lipid storage disease and of a genetic disease that primarily affects gray matter (neurons of the brain and retina). Clinicians often divide degenerative diseases in infants and children into those primarily affecting gray or white matter (Table 17.3).

Tay–Sachs disease is a fatal autosomal recessive infantile disease due to severe deficiency of beta-hexosaminidase, an enzyme resulting in abnormal accumulation of glycosphingolipid GM2 gangliosides within neurons leading ultimately to neuronal death. Although cases have been reported in all ethnic groups, the incidence is markedly higher in Jewish communities of Central and Eastern European background (Ashkenazi Jews). Before current genetic testing, the incidence of Tay–Sachs disease in this population was 1 in 3600 births. The incidence of Tay–Sachs disease has dropped by over 90% since prevention efforts have been in place. The incidence in other populations is at least tenfold less. Less commonly, hexosaminidase A deficiency can present in a juvenile, chronic, or adult-onset form—which has later onset of symptoms, slower progression, and variability in the neurologic manifestations seen.

Pathophysiology

Hexosaminidases A and B are two catabolic enzymes that hydrolyze gangliosides with terminal β-N-acetylgalactosamine residues. In Tay–Sachs disease, there is a mutation in the hexosaminidase α-subunit such that the enzymatic activity of hexosaminidase B is normal but is nearly absent in hexosaminidase A. As a consequence, the ganglioside GM2 cannot be catabolized and accumulates within the cytoplasm of neurons eventually causing the neuron's death. In the retina, the fovea lacks ganglion cell bodies. Thus, accumulation of whitish GM2 gangliosides in ganglion neurons surrounding the fovea is seen with an ophthalmoscope as a "cherry red spot."

Pathologically, there is a large brain containing excessive neuronal glycolipids (up to 12% of the brain dry weight contains GM2 gangliosides). There is widespread loss of neurons with reactive gliosis. All remaining neurons are distended with glycolipid.

Major Clinical Features

Affected infants appear normal at birth. By 3 months, infants develop mild weakness, myoclonic jerks, and startle responses to sudden noises. By 9 months, the infant fails to achieve milestones and regression from previously attained motor gains. Weakness progresses rapidly. There is diminished visual attentiveness from loss of acuity, and a "cherry red spot" is seen in the retina on fundoscopy. Abnormal eye movements can occur as well. By 12 months, voluntary limb movements are minimal, vision is lost, and partial complex and absence seizures develop. Due to the gliosis described above, the head enlarges by 18 months of age. By year 2, the infant has decerebrate posturing, marked seizures, swallowing difficulties, and is in close to a vegetative

Table 17.3 Clinical features of diseases affecting primarily gray and white matter

Gray matter (neurons of brain and retina)	White matter (myelin and axons)
Loss of previously attained intellectual skills	Spasticity
Seizures	Sensory abnormalities
Aphasia	Ataxia and incoordination
Loss of visual acuity	Visual field defects
Memory loss	Visual loss
Variable muscle atrophy from loss of anterior horn neurons	

state. Bronchopneumonia leads to death before the age of 4 years.

Major Laboratory Findings

The diagnosis is established by demonstration of deficient hexosaminidase A enzymatic activity in the serum or white blood cells of a symptomatic individual in the presence of normal activity of the hexosaminidase B isoenzyme. There are greater than 100 described mutations of the *HEXA* gene with the majority associated with the infantile-onset disease (e.g., Tay–Sachs).

Neuroimaging shows an enlarged head from gliosis and not hydrocephalus. The electroencephalogram is abnormal early and shows paroxysmal slow waves and spikes.

Principles of Management and Prognosis

No treatment currently exists to replace the missing hexosaminidase A enzyme and the disease relentlessly progresses to death. Attempts have been made at enzyme replacement but the molecule was not able to cross the blood–brain barrier successfully. Experimental aims in the future include gene therapy and direct central nervous system enzyme replacement strategies. The goal of management is to provide supportive care, give adequate nutrition and hydration, minimize respiratory infections, and control seizures with anticonvulsants.

Since asymptomatic, heterozygote carriers can be detected by a simple, inexpensive, and sensitive serum hexosaminidase A enzyme assay, genetic screening as well as prenatal genetic tests are frequently done. Currently, Jews of Ashkenazi extractions are often tested when reaching adulthood. Prenatal testing is available when both parents are heterozygous or the mother is heterozygous and the father is unknown. The hexosaminidase A assay can be performed upon a chorionic villus sample at 10–12 weeks gestation or by amniocentesis at 16–18 weeks gestation.

Down Syndrome Trisomy 21

Introduction

Chromosomal abnormalities occur when there are too many copies, too few copies, or abnormal arrangements (duplications or deletions) of normal genes. At least 0.5% of all live births and 50% of spontaneously aborted fetuses in the first trimester are the consequence of chromosomal imbalances. The human genome is about 6×10^9 base pairs of DNA that is 2 m long if uncoiled. Each somatic cell has 22 pairs of homologous chromosomes that are identical in morphology and constituent gene loci plus 1 pair of sex chromosomes. Malformations are likely to develop if this genetic arrangement is significantly altered.

Most chromosomal disorders involving autosomal chromosomes are associated with multiple congenital abnormalities. Many of these individuals have in common some degree of intrauterine and postnatal microcephaly, mental retardation, seizures, and assorted ocular, gastrointestinal, and skin abnormalities. Only three autosomal trisomies (13, 18, and 21) survive to term and only trisomy 21 or Down syndrome survives past one year. Some patients with various chromosome deletions express only mild signs.

Down syndrome occurs around the world and has a prevalence of 90 per 100,000 live births and increases with maternal age above 35 years—although the majority of babies with Down syndrome are still born to mothers under the age of 35 years. In the USA, the rate of Down syndrome diagnosis has increased slightly from 1 in every 733 births to 1 in every 691 births.

Pathophysiology

About 95% of individuals with Down syndrome have trisomy 21 or three copies of chromosome 21 from nondisjunction during gamete formation in the mother. Four percent of cases have translocations where all or part of chromosome 21 is attached to another chromosome, usually 14,

and the remaining 1% are due to mosaicism. It is still unknown how the presence of additional chromosome 21 genes causes this complex but easily recognized syndrome. Chromosome 21 is the shortest chromosome, and genetic mapping of the human chromosome suggests it contains only 225 genes. Clinical features are identical in children with trisomy or translocation.

The brain of a person with Down syndrome is smaller by about 20% than someone without Down syndrome. This size difference is manifest even in development with detection of this reduced brain size at approximately 4- to 5-month-old fetuses. The brain is overall smaller but there is an enhanced decrease in the hippocampus, temporal lobe, and cerebellum. The gyri are simplified in appearance with primary gyri wider than normal and secondary gyri narrower. Reduced numbers of neurons in the cortex and hypomyelination are present and continue in subsequent growth. As the child grows older, there is significant reduction in linear growth and brain growth. Most adults have short stature and mild microcephaly.

Adults demonstrate basal ganglia calcifications and after the age of 30 years develop senile plaques and neurofibrillary tangles similar to those seen in Alzheimer's disease. By age 50 years, there is considerable loss of cortical neurons and brain atrophy.

Major Clinical Features

Newborns have hypotonia, hyperextensible joints, excess skin on the back of the neck, flat facial profiles, slanted palpebral fissures, over-folded helices, protruding tongues, short fifth fingers, and single palmar creases (Fig. 17.3). Congenital heart disease is present in 50%. Moderate mental retardation becomes apparent as the child grows. In addition, they may develop strabismus, nystagmus, small genitalia, and pectus excavatum. A small number of children with Down syndrome (around 10%) may have seizures. Developmental milestones are typically met but at a delayed timing, and developmental scales appropriate for children with Down syndrome have been developed. Some children have immunoglobulin imbalance and a susceptibility to respiratory infections and some, especially older children, develop hypothyroidism. Most males are infertile. In adulthood after the age of 30 years, a progressive dementia that has features of Alzheimer's disease often worsens the existing mental retardation.

Major Laboratory Findings

Prenatally, during the 11th to 13th week of pregnancy, the *first trimester combined* test is used. In this test, ultrasound is used to measure the back of the baby's neck known as the nuchal translucency screening test. The measurements from this test as well as blood tests measuring pregnancy-associated plasma protein-A and human chorionic gonadotropin are combined to screen for an elevated risk of Down syndrome.

In childhood, neuroimaging may demonstrate hypomyelination for age. In adults, basal ganglia calcifications are seen in 50% and brain atrophy is seen in older adults.

Karyotyping performed on blood lymphocytes or skin fibroblasts establishes the diagnosis

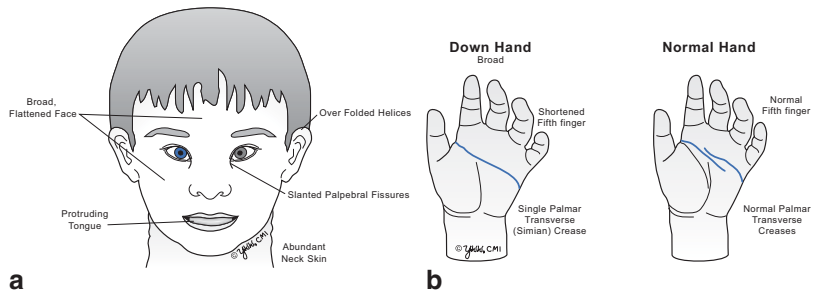

Fig. 17.3 Down syndrome features of face (**a**) and hand (**b**)

and determines whether the cause is trisomy 21 or translocation. Finding a translocation means that subsequent children of the mother or affected individual carry 50% risk of having Down syndrome.

Principles of Management and Prognosis

The goal of management is to prevent or minimize recognized malformations of heart, thyroid, and gastrointestinal tract. Infants should have careful cardiac, hearing, and thyroid evaluations. Children with serious cardiac defects greatly benefit from cardiac surgery. Respiratory and ear infections should be treated aggressively. Learning disabilities should be addressed and maximizing the potential of the individual should be the focus of any therapeutic interventions. Repeat testing in children and adults for problems of thyroid function, vision, hearing, and cardiac problems should be done. The mean life expectancy is 50 years.

Cerebral Palsy

Introduction

Cerebral palsy (CP) prevalence is estimated at 2 per 1000 live births—being the most common cause of disability in childhood. The highest prevalence is found in infants weighing between 1000 and 1500 grams at birth and highest in premature infants born before 28 weeks, and slightly more common in males than in females. The prevalence has been stable over time despite improvements in survival rates for pre-term infants. CP refers not to one disease process but is a group of disorders that can affect motor, cognitive, communication, and behavioral systems. Unlike a chromosomal abnormality like Down syndrome or an inherited metabolic abnormality such as Tay–Sachs, CP is a permanent, non-progressive brain injury. Although non-progressive pathophysiologically, co-occuring disorders such as musculoskeletal abnormalities, seizures, and functional limitations can change with growth and aging.

Pathophysiology

The brain injury in CP is thought to arise at some point in the prenatal, antenatal or early postnatal period. Prenatal risk factors that have been identified include the following: abnormal intrauterine growth; maternal infections and fever; multiple births; placental pathology; various genetic factors; intrauterine exposure to toxins; and cortical developmental malformations. In the perinatal period, hypoxia–ischemia may account for up to 6% of children with CP. Periventricular leukomalacia, fetal/neonatal stroke, and hyperbilirubinemia all can be a cause of CP in the perinatal period. In the postnatal infant, stroke, trauma, and infections can result in CP.

Major Clinical Features

The presentation of CP can vary from mild motor abnormalities with normal intelligence to severe quadriplegia with severe mental retardation. A delay in reaching motor milestones is a typical presentation of CP and a clinical diagnosis is typically reached by age 2 years. The classification of CP is made primarily on motor terms: spastic or pyramidal and non-spastic or extrapyramidal. Spasticity can manifest as a spastic hemiplegia (often arm more involved than leg), a spastic diplegia (with both legs affected) or spastic quadriplegia with all four limbs affected (Fig. 17.4). The extrapyramidal manifestations can be dyskinetic due to basal ganglia lesions or ataxic due to cerebellar lesions.

Major Laboratory Findings

CT scanning can be helpful due to ease of visualizing calcifications that can arise from intrauterine infections; however, MRI is more sensitive for assessing non-calcified lesions. In spastic hemiplegia, MRI could reveal injury to the white

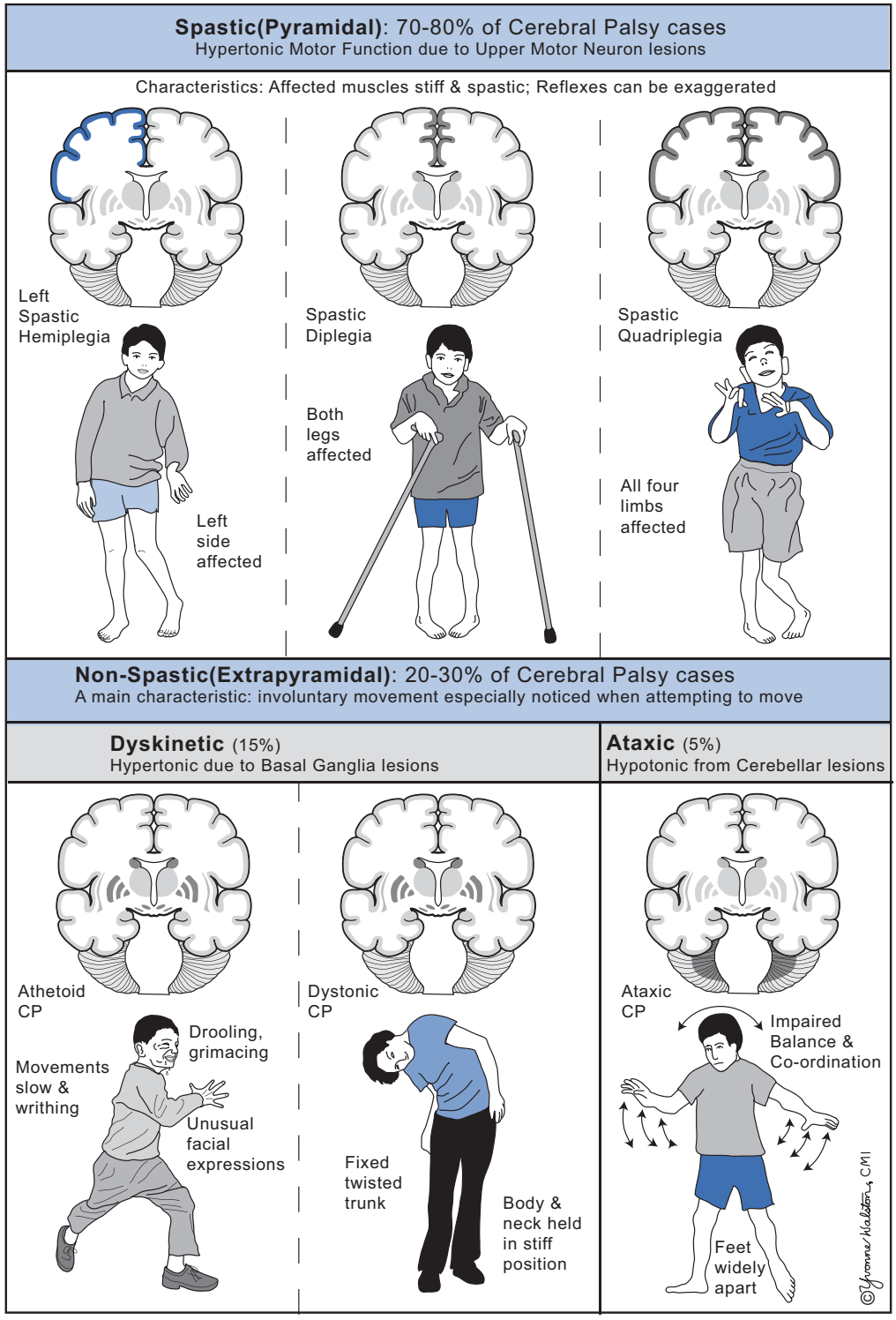

Fig. 17.4 Classification of cerebral palsy

matter unilaterally from an *in utero* insult or stroke. The most common MRI finding in spastic diplegia is periventricular leukomalacia (in up to 70 % of cases). Periventricular leukomalacia is a result of ischemic or oxidative stress to immature oligodendrocytes in the developing fetus. Accompanying dilation of the lateral ventricles can also be present as a result of the loss of periventricular white matter. For the dyskinetic forms of CP, gliosis in the thalamus and basal ganglia can be seen.

Principles of Management and Prognosis

As the definition of CP includes a motor presentation plus the presence of a static, non-progressive course, any clinical signs or symptoms that suggest a progressive course should be worked up to look for inherited metabolic, degenerative disease, spinal cord pathology, or muscular dystrophies. An MRI of the brain and sometimes the spinal cord is indicated. If an in utero or neonatal stroke is the suspected cause, workup for thrombophilic disorders is recommended.

Treatment is multidisciplinary in nature and very dependent on the needs of the individual affected with CP. Parents should be warned that some manifestations of the child's CP may not be apparent until those developmental milestones should be reached. Just as the etiologies vary, the prognosis and extent of disability from CP vary greatly.

Recommended Reading

Pina-Garza JE. Fenichel's Clinical Pediatric Neurology: A signs and symptoms approach (Expert Consult—Online and Print). 7th Ed., Saunders; 2013. (This and other pediatric neurology textbooks cover the many disorders of the developing nervous system in detail).

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Mitchell JJ. Phenylalanine hydroxylase deficiency. 2000 Jan 10 [Updated 2013 Jan 31]. In: Pagon RA, Adam MP, Bird TD, et al., (editors.) GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2013. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1504/. (A good website for concise and up-to-date information on various genetic diseases).

Kaback MM, Desnick RJ. Hexosaminidase A Deficiency. 1999 Mar 11 [Updated 2011 Aug 11]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2013. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1218/. (A good website for concise and up-to-date information on various genetic diseases).

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Traumatic Brain Injury and Subdural Hematoma

18

A 73-year-old man with a history of taking coumadin for his atrial fibrillation fell hitting the right side of his head. He did not lose consciousness, but saw "stars" for a few minutes. In the emergency department that day, his neurologic examination was normal and blood INR level was in the therapeutic range. His cranial CT except for a subcutaneous bruise over the right temple showed only mild brain atrophy. He was diagnosed as having mild traumatic brain injury and sent home with his wife to observe him. Three weeks later he complained of a mild right-sided new headache and the next week his wife noted he was developing weakness in the right arm and was more confused. A repeat CT scan now showed a chronic right subdural hematoma of 5 cm diameter that was shifting the right frontal lobe slightly across the midline of the falx. He underwent surgery with burr hole irrigation of the hematoma. The coumadin was discontinued for 1 month.

Traumatic Brain Injury

Introduction

Traumatic brain injury (TBI) is the most common cause of death and disability in young adults. Each year in the USA, 4 million people sustain TBI with a concussion: 1 million seek emergency room or outpatient care and 270,000 require hospitalization annually. The incidence of TBI is 200 per 1,000,000 individuals. Nearly 50,000 people die each year and another 80,000 have severe neurologic disabilities from TBI.

Young adult males are at highest risk for TBI but the syndrome can occur at any age including infants (shaken baby syndrome). In young adults, sports injuries and motor vehicle accidents are the leading causes while in older adults falls prevail.

TBI is graded as mild, moderate, and severe based on the Glasgow coma scale (GCS) after resuscitation (Table 18.1). GCS is easily administered and helps in acute management and prognosis of the patient. The scale is based on responses to eye opening, limb movements, and verbal responses to various stimuli with a score of 15 being normal. GCS scores rank the degree of injury as mild (13–15), moderate (9–13) and severe (3–8).

The mildest head trauma is a concussion leading to rapid but transient neurologic impairment. In very mild concussions, the patient may experience only a brief period of disorientation and amnesia for the event. Typically, patients will have a brief loss of consciousness after impact but a concussion can occur even without loss of consciousness. The loss of consciousness is associated with suppression of reflexes with a fall if they are standing, transient arrest of respiration, brief period of bradycardia, and a transient fall in blood pressure. Patients complain of headache, nausea and vomiting, confusion, disorientation, attention deficit, dizziness, and unsteadiness. Concussions are frequent, occurring in 15% of sports-related injuries. Having one concussion predisposes to repeated concussions from new

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Table 18.1 Glasgow coma scale

Eye opening		Motor response		Verbal response	
Response	*Score*	*Response*	*Score*	*Response*	*Score*
Spontaneous	4	Obeys	6	Oriented	5
To speech	3	Localizes	5	Confused	4
To pain	2	Withdraws	4	Inappropriate	3
None	1	Abnormal flexion (decorticate rigidity)	3	Incomprehensible	2
		Extension response (decerebrate rigidity)	2	None	1
		None	1		

sports injuries. These patients have normal neuroimaging.

Moderate to severe head trauma produces loss of consciousness for a longer duration, usually more than 5 min. Awakening is slow, confused, and often with retrograde and anterograde amnesia.

Pathophysiology

Brain damage from TBI is divided into two mechanisms: primary and secondary brain injury. Primary injury describes the initial structural injury to the brain as a direct result of the impact on the brain. It occurs at the moment of head trauma with several factors contributing to the brain damage. An acceleration–deceleration force transmitted to the head causes distortion of the brain in various areas depending on the part of head impacted first and the severity of the blow.

Diffuse axonal injury occurs in the majority of moderate to severe TBI patients when the patient has a low Glasgow coma scale score for over an hour. Axonal injury occurs from stretching or tearing the axon at the moment of impact primarily, but additional axonal destruction develops later when excess calcium entry and swelling further damages axon segments (Fig. 18.1). Common sites of axonal injury include medial frontal gyrus, temporal lobes, cerebral white matter, corpus callosum, cingulate gyrus, thalamus, and upper brainstem. Initially, an axon bulb (retraction bulb) develops followed in a few weeks by accumulation of microglia at the injury site. Wallerian degeneration of the axon tract occurs months after the initial injury.

Secondary brain injury begins at the time of brain trauma and progresses remote from the injury. It can develop from a compressive force like a depressed skull fracture or secondary intracranial mass from cerebral edema, parenchymal hemorrhage or extraparenchymal epidural or subdural hematoma. A mass lesion can lead to decreased consciousness from mass effect exerted *directly* by the lesion on the diencephalon,

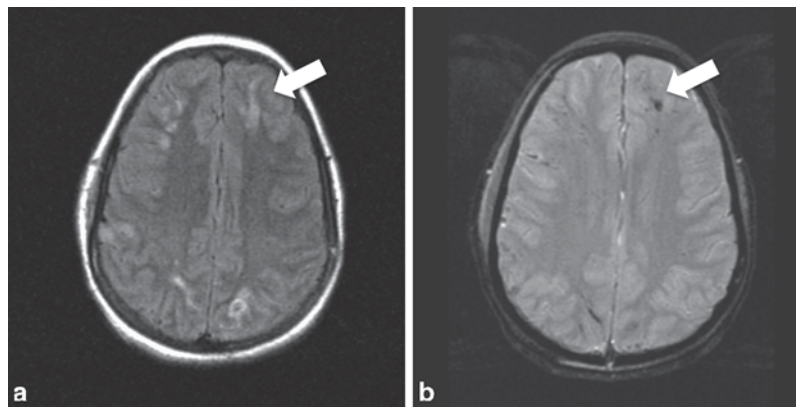

Fig. 18.1 **a** Axial MRI FLAIR sequence showing bright signal (*arrow*) of diffuse axonal injury and **b** Axial MRI gradient sequence showing dark signal (*arrow*) indicating hemorrhage in same area. (Courtesy of Dr. Blaine Hart)

mesencephalon, or brainstem or *indirectly* by increased intracranial pressure—both mechanisms could lead to herniation. Secondary brain injury also develops from a cascade of metabolic events including abnormal cellular metabolism, loss of autoregulated cerebral blood flow, disruption of extracellular and intracellular ions, and abnormal release of neurotransmitters. Axonal stretching and shearing often leads to acute release of neurotransmitters such as glutamate and causes abnormal neuronal firing releasing a potassium efflux, accelerated glycolysis, lactate accumulation, alterations in cerebral blood vessel blood–brain barriers, and cerebral edema.

Skull fractures portend considerable brain injury and are found in 3% of head trauma patients seen in emergency rooms, in over 50% of patients who are hospitalized, and in 80% of those who die. Over half the patients have a linear skull fracture, and 4% of these fractures are depressed from their normal location. Less common skull fractures may involve the petrous bone resulting in a CSF leak or blood accumulating behind the tympanic membrane, blood leakage into the mastoid area, blood leakage into periorbital tissues around the eyes, or CSF leakage through the nose (otorrhea) from a fracture involving the cribriform plate.

The pia-arachnoid membrane remains intact over a contusion but in a brain laceration, it tears producing bleeding into the subarachnoid space. Contusions and lacerations characteristically occur on the inferior surfaces of the frontal and temporal lobe poles where the brain comes in contact with bony protuberances of the skull base such as the frontal and temporal lobes. The crests of the gyri suffer the greatest injury. Contusions usually develop at the site of injury (coup) or in the brain diametrically opposite the site of injury (countercoup).

Diffuse vascular injury is commonly seen in severe TBI. Petechial hemorrhages are seen throughout the hemispheres, basal ganglia, and brainstem from shearing damage to small blood vessels. Intracerebral hematomas develop in 10–15% of patients, may be single or multiple, and often locate in the frontal and temporal lobes.

The effects of secondary injury may not present clinically until later. Brain swelling, an important cause of secondary injury, begins shortly after the trauma. Local edema develops at areas of brain necrosis from contusion, expanding intracerebral hematomas, or pockets of subarachnoid blood. As the intracranial pressure (ICP) elevates, diffuse brain ischemia may develop if the cerebral blood flow falls to critical levels and no longer perfuses brain tissue. Subdural or epidural hematomas may also contribute to increasing ICP. Once ICP reaches a critical level (above 20–25 mmHg), ischemic brain damage develops. One study found ischemic brain damage present in 90% of TBI patients (severe in 27%, moderate in 43%, and mild in 30%). The most common locations of ischemic damage were the hippocampus, basal ganglia, and cerebral hemispheres in the watershed territories (boundary zones between the anterior and middle cerebral arteries and middle and posterior cerebral arteries).

Clinical Features and Immediate Evaluation

Mild TBI (GCS 13–15) is the most common. These patients experience a simple concussion (brief loss consciousness without permanent brain damage) or may not lose consciousness but are stunned (see “stars”). They may not recall the event. Such patients may experience short-term memory and concentration difficulties that persist for days to months. In the emergency department, they have a normal neurologic examination and no signs of body injury. Some complain of immediate posttraumatic symptoms such as headaches, fatigability, insomnia, and nervousness, but these symptoms may also arise within a few days of the head trauma. These patients have a good prognosis and usually can be released from the emergency department after several hours of observation to a competent caregiver who will bring the patient back should he deteriorate.

For moderate to severe TBI, immediate attention to the patient at the scene of the trauma or in the emergency department is important. A quick

but thorough systemic trauma evaluation should be done according to advanced trauma life support guidelines. Care should be taken to evaluate the potential of spine or neck injury as 10% of patients with moderate to severe head trauma also have spine injuries. A Glasgow coma scale (GCS) should be done. Monitoring of blood pressure, heart rate, respiration rate, and oxygen saturation is important.

Information about the cause of head trauma, location of head impact, and duration of unconsciousness should be obtained from witnesses. The head should be examined for signs of penetrating injuries and focal subcutaneous swelling. Signs suggestive of a basal skull fracture include periorbital ecchymoses or "raccoon eyes", CSF drainage from the nose (otorrhea), blood behind the tympanic membrane in the middle ear (hemotympanum), bleeding from the external auditory canal, ecchymoses over the mastoid bone (Battle's sign), and anosmia. Corneal reflexes, extraocular eye movements, symmetrical facial grimacing during pain, clarity and content of any vocalization, and ability to swallow should be checked. Pupils should be examined for symmetry in size and function. A unilateral fixed dilated pupil may suggest brain uncal herniation unless there has been direct eye trauma. Strength, tone, coordination of limb movements, brief sensory examination, deep tendon reflexes, and Babinski signs should be evaluated.

In moderate TBI (GCS 9–12), the patient often is stuporous, poorly verbalizes, and opens their eyes to pain. Other signs of trauma (skin lacerations, fractures, etc.) are common. These patients require immediate care with special attention to possible neck injuries and should be taken to an emergency room for further observation and neuroimaging. Recovering patients frequently complain of headaches, poor recent memory, inability to concentrate, unsteadiness, or vertigo for varying lengths of time.

In severe TBI (GCS 3–8), the patient is comatose, unable to open his/her eyes and follow verbal commands. The presence of trauma elsewhere in the body is common. These patients may have severe bleeding, hypotension, and hypoxia that require emergency management. It is common for these patients to worsen over hours as secondary injury events develop. Once comatose, patients may remain unresponsive for hours, days, or weeks. A few patients never regain consciousness and evolve into a persistent vegetative state (permanent coma with return of spontaneous breathing and some other brainstem reflexes).

A few patients will have initial loss of consciousness followed by a lucid interval, followed by a secondary deterioration of consciousness. The initial loss of consciousness is due to the impact of the head trauma and the second is due to an epidural hematoma. This scenario develops in about half of patients with epidural hematoma; the others do not regain full consciousness before deterioration. An epidural hematoma develops most frequently from a linear skull fracture that causes laceration of a branch of the middle meningeal artery (Fig. 18.2).

Major Laboratory Findings

Neuroimaging in the emergency room is usually done to evaluate for neck fractures, skull fractures, and intracranial hematomas. Most often this involves initial cervical spine X-rays followed by a cranial non-contrasted CT. If a depressed skull fracture (bone completely beneath the skull vault and often penetrating into the brain) is detected, surgery is required. Open fractures where there is a connection from the skin surface to brain increase the risk of intracranial infection (subdural infection (empyema), meningitis, or brain abscess). The risk of a subdural or epidural hematoma is low (1:1,000) if no fracture is identified but rises to 1 in 30 if a fracture is seen. Since secondary brain injury may be delayed, repeat CT scans are often required if new signs develop. An MRI is often done later to more carefully evaluate the extent of intraparenchymal brain damage such as small contusions and areas of diffuse axonal injury.

The electroencephalogram (EEG) immediately after injury shows suppression of electrical activity over the injured brain that returns as generalized, large amplitude, slow waves (delta). Depending on the severity of TBI, the EEG can normalize during recovery.

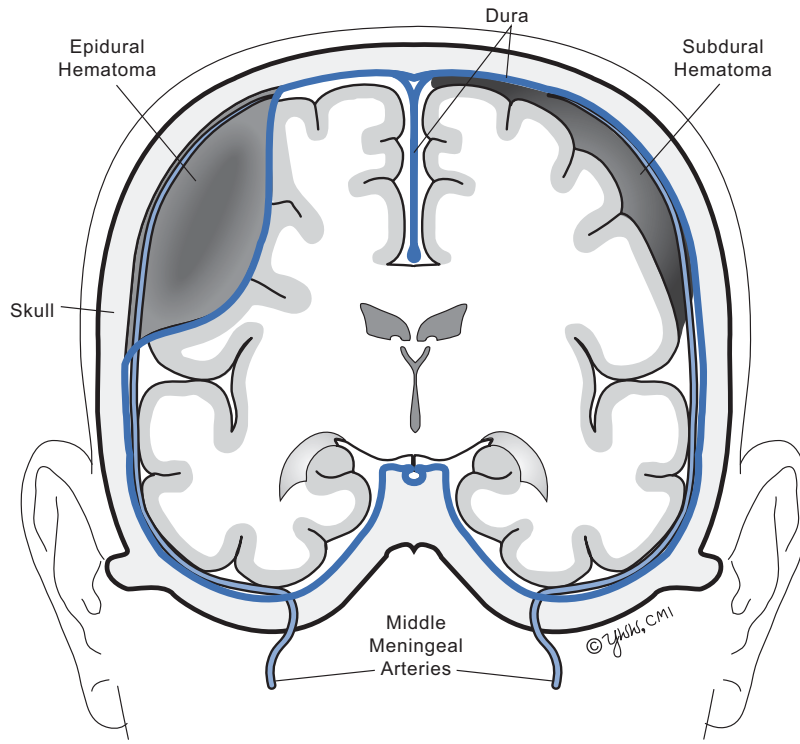

Fig. 18.2 Diagram of epidural and subdural hematomas

Principles of Management and Prognosis

Optimal treatment of the TBI patient has yet to be established. The amount of primary brain injury is determined at the time of trauma. However, outcome can be improved by minimizing secondary brain injury. One important way is to control increased intracranial pressure and prevent cerebral ischemia. Diffuse cerebral ischemia occurs when the cerebral perfusion pressure is inadequate. This is particularly important since TBI often results in loss of cerebral autoregulation of blood pressure so brain perfusion becomes dependent on cerebral perfusion pressure. Cerebral perfusion pressure is defined as mean arterial pressure-intracranial pressure. Thus, a fall in systemic blood pressure or a rise in intracranial pressure decreases cerebral perfusion pressure. Brain ischemia occurs when the cerebral perfusion pressure is less than 70 mmHg that corresponds to a cerebral blood flow of less than 40 ml/100 gram brain/minute. Studies have shown that hypotension (systolic blood pressure < 90 mmHg), elevated ICP (above 20–25 mmHg), and hypoxia (arterial PaO_2 < 65 mmHg with digital pulse oximetry oxygen saturation of < 90 %) are the major causes of diffuse brain ischemia. Elevated ICP comes from intracerebral hemorrhages, extracerebral hematomas, and cerebral edema. Normal intracranial pressure is 0–10 mmHg and above 20 mmHg is considered sufficiently abnormal to treat.

If surgical lesions are identified (subdural or epidural hematoma, large intracerebral hematoma, or depressed skull fracture) by CT, the patient usually goes to the operating room (Fig. 18.3). Since measurement of ICP is important in the management of severe TBI, many neurosurgeons place an intracranial pressure monitor to follow ICP changes.

The goal is to maintain intracranial pressure below 20 mmHg but most medical management methods reduce ICP only temporarily. Elevation

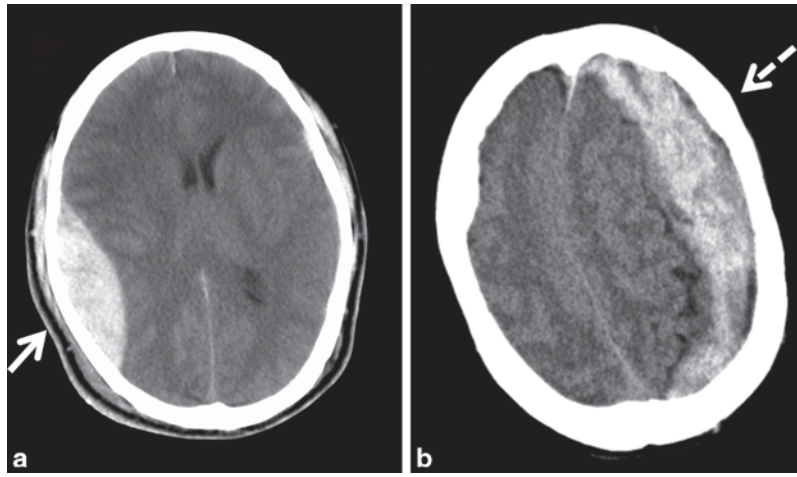

Fig. 18.3 **a** Axial head CT showing epidural hematoma with convex shape (*arrow*) and exerting mass effect and **b** Axial head CT showing acute subdural hematoma with concave shape (*dashed arrow*) also showing mass effect with midline shift. (Courtesy of Dr. Blaine Hart)

of the head to 30° may help. Mannitol given in intravenous boluses will lower ICP and can be continued until the serum osmolality reaches 320 mmol/L. Above 320 mmol/L, mannitol loses its effect and serum electrolytes become deranged. Hyperventilation will reduce ICP but its use is controversial since it does so by lowering arterial PCO_2 and constricting cerebral blood vessels. Long-term use of hyperventilation is thought to worsen diffuse cerebral ischemiaand hence prognosis. Drainage of CSF through the ventricular pressure monitor catheter but not a dural pressure monitor will also reduce ICP. If the ICP cannot be controlled by usual medical management or by surgical removal of hematomas, hypothermia or high-dose barbiturates to suppress cerebral metabolism can be tried. Typically, the barbiturate infusion is continued for 48 h and tapered down. Hypothermia is done by decreasing the core temperature to 34–35 °C for 24–48 h with slow rewarming over 2 days. Corticosteroids have not been shown to be beneficial.

Patients with prolonged coma will require nasogastric feeding to maintain nutrition. Since subdural and epidural hematomas may develop late, repeat CT scans may be necessary if the ICP rises or the patient deteriorates.

About 5% of TBI patients will experience a generalized seizure during their hospitalization but prophylactic use of anticonvulsants has limited benefit. Following hospitalization, 12% of patients subsequently develop posttraumatic epilepsy (partial or partial with secondarily generalized seizures) occurring 1–60 months after the trauma that usually can be well controlled with anticonvulsants.

The prognosis of TBI depends on its severity. In moderate TBI with a GCS score of less than 12 on admission, the fatality rate is 20% and rises to 40% for a GCS score of 8 or less. Other poor early prognostic indicators include the following: age over 60 years, hypotension on admission, unreactive pupils or a fixed dilated pupil, markedly abnormal CT findings, multiple traumatic injuries, and prolonged coma. Rehabilitation from TBI is slow and difficult. Patients may complain of headaches, poor concentration, cognitive deficits, and impulsivity. In adults with severe TBI, unemployment at 5 years is about 70% compared to a 14% pre-injury unemployment rate. In children who survive severe TBI, loss of cognitive skills and impaired concentration can result in behavioral and learning problems.

Repetitive brain concussions in sports injuries are now reported to cause a progressive brain encephalopathy characterized by progressive decline in memory and cognition, depression, poor impulse control, aggressiveness, parkinsonism, and late dementia. Brain neurodegenerative changes include brain atrophy and accumulations of hyperphosphorylated tau proteins.

Spinal Cord Trauma

Spinal cord injury occurs in 11,000 new patients per year in the USA. The classic picture is complete spinal cord transection at a high cervical level. Patients experience respiratory insufficiency, quadriplegia, anesthesia below the affected spinal cord level, transient loss of reflexes below the affected level, loss of rectal and bladder sphincter tone with urinary retention and ileus, Horner syndrome (ipsilateral ptosis, miosis, and anhydrosis), and neurogenic shock (hypotension without compensatory tachycardia). After about three weeks, there is return of the intrinsic spinal cord neurons without supraspinal center modulation. Although the level of paralysis and sensory loss continues, there is hyperreflexia with Babinski signs, and increased muscle tone (spasticity) in the paralyzed muscles. Autonomic hyperreflexia may develop with intermittent massive firing of sympathetic neurons after distention, stimulation, or manipulation of the bladder or bowel accompanied by a marked increase in blood pressure. Tracheotomy and mechanical ventilation will depend on the level of the cervical spinal cord transection, but is typically necessary when an injury occurs above C4.

Chronic Subdural Hematoma

Introduction

A subdural hematoma (SDH) may be acute, subacute (signs appear within 1–3 weeks of head trauma), or chronic (signs appear more than 3 weeks after trauma). Acute SDHs due to tearing of bridging pial veins and arteries develop within hours to a week following moderate to severe TBI and can also occur in patients with bleeding diatheses after minor trauma. Presenting symptoms of SDH are lethargy, stupor, pupillary dilatation, limb weakness, and finally coma. Emergency surgical drainage is indicated when acute SDH causes neurological deficits, including impairment in consciousness. In chronic SDH, patients develop a hematoma that follows a mild head trauma or even after an event where head trauma is not apparent. The signs and symptoms vary from the presentation of acute SDH and will be discussed below.

The incidence per year of SDH is rare in small children, lowest in young adults (1/100,000 and usually follows moderate to severe TBI), and highest in the elderly (7/100,000). In young adults, the male-to-female ratio is 3:1 while in the elderly it is 1:1. Chronic SDH mainly develops from head trauma (motor vehicle accidents, falls from syncope, ataxia, or weakness, seizures, and child abuse), but can occur in patients with bleeding problems (anticoagulation, thrombocytopenia, liver failure, alcoholism), dural lesions (sarcomas, arteriovenous malformations, metastatic cancer), and low CSF volume (CSF shunts, renal dialysis, and excess diuretics).

Pathophysiology

A SDH begins in the subdural space between the dura mater and arachnoid mater of the meninges. The dura intimately adheres to the inner table of the skull and consists of a thick layer of fibroblasts and extracellular collagen. Inner border cells connect directly with the outer layer of the arachnoid membrane. The arachnoid is more vascular and contains blood vessels with tight junctions that arise from meningeal vessels in the internal carotid and vertebral artery system. Blood leakage from tears of arachnoid venules initiates the hematoma.

In infants and small children whose brain is growing, the cerebral cortex abuts tightly against the dura, preventing movement of the brain away from the skull. As such, blood vessels are not likely to be stretched, making subdural hematomas rare. At the other end of the age spectrum, there is a slowly progressive, age-dependent, atrophy of the brain that occurs during adulthood. From age 50 to 80 years, the normal brain shrinks by 200 gm in weight and the space between the brain and skull increases by 10% of total intracranial space. In addition, many degenerative brain diseases accelerate brain atrophy. Since the skull does not involute with aging, the smaller brain enables independent movement of the brain and the skull during head trauma that can lead to a shearing or tearing of small arachnoid venules.

If the patient is taking anticoagulants, there may be prolonged oozing of blood into the subdural space.

Once present, the subdural blood may expand rather than shrink, as a bruise would do elsewhere in the body. Within days, fibroblasts from adjacent blood vessels begin forming a capsule around the hematoma. The outer layer of the hematoma capsule generally contains numerous macrocapillaries that have wide vascular lumens of 40–80 μm diameter with endothelial gap junctions up to 2 μm. The new capillaries usually lack a pericyte, complete basement membrane, and surrounding smooth muscle cells. As such, the thin, fragile outer membrane is vulnerable to future microbleeds allowing plasma and erythrocytes to enter the subdural capsule from repeated minor head trauma. The microbleeding triggers fibrinogen to degrade into fibrin degradation products from hyperfibrinolysis in the hematoma fluid. Thus, evidence suggests that chronic subdural hematoma growth develops from recurrent microhemorrhages in outer capsule macrocapillaries. Excessive, repeated activation of both coagulation and fibrinolysis results in increased fluid in the capsule.

Over weeks to months, a hematoma may continue to expand until it eventually sufficiently displaces the underlying brain to cause signs and symptoms. Untreated, the SDH will continue to shift intracranial structures until coma and brain herniation occurs. However, in many other SDHs, there is stabilization of the clot with slow clot resolution eventually over months, producing a thin fibrous membrane next to the dura. The majority of SDHs develop over the lateral aspect of the cerebral convexities but they rarely can occur in the posterior fossa.

Major Clinical Features

In a chronic SDH, signs and symptoms slowly develop over weeks. Headache occurs in over 90% of patients and may be lateralizing, constant, and relatively mild. As intracranial pressure increases, patients often note light-headedness, drowsiness, unsteady gait, and a deterioration of mental status with confusion, lethargy, and memory disturbances. This is particularly common in the elderly. Lateralizing signs next begin with a hemiparesis, occasionally aphasia, and rarely an homonymous hemianopia. Focal or generalized seizures occur in 10%. The signs and symptoms of a chronic SDH are not specific and 40% are initially misdiagnosed as other diseases such as Alzheimer's disease, vascular dementia, stroke, depression, or brain neoplasm. In general, SDH should be considered in the elderly who have progressive deterioration of mental status, hemiparesis, and new-onset headache.

Major Laboratory Findings

Neuroimaging is the key to the diagnosis. The CT scan demonstrates an oval hematoma between the dura and brain and, depending on the age of the hematoma, has differing densities (Fig. 18.4). Acute SDH looks hyperdense relative to brain. Beginning one week later, subacute SDH appears as isodense (same density as adjacent brain) and is recognized by lateral ventricle compression

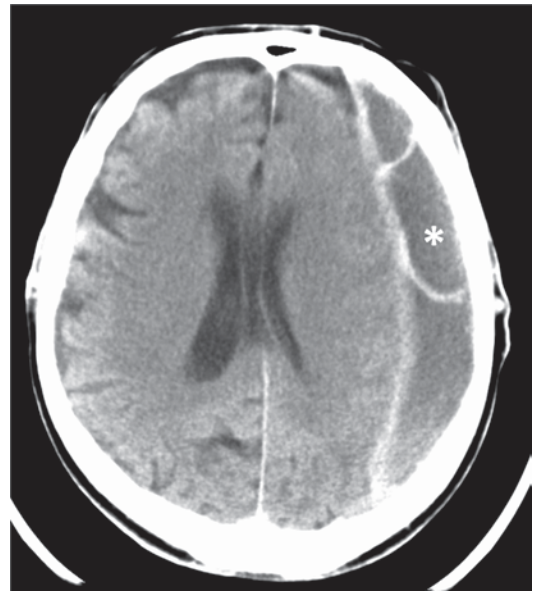

Fig. 18.4 CT scan of chronic subdural hematoma with mixed densities, hyperdense, and isodense (*asterisk*). (Courtesy of Dr. Blaine Hart)

and shifting, medial displacement of gray–white junction, and loss of sulcal spaces that normally are seen against the skull table. Chronic SDHs between two or more weeks after the bleed are hypodense (75%) or have mixed densities (25%), suggesting recurrent bleeding into the hematoma. An acute SDH on T-2-weighted MRI images is hypointense, reflecting the presence of deoxyhemoglobin. Over the next several weeks, both T-1- and T-2-weighted images appear hyperintense because of methemoglobin formation in the clot. Eventually, the chronic SDH appears hypointense on T-1-weighted images. MRI scans are better to detect exact outer and inner membranes and thin resolved chronic SDH membranes adjacent to the dura than non-contrasted head CT scan. The EEG typically shows non-diagnostic suppression of activity and slow waves in the area of the hematoma.

Principles of Management and Prognosis

Typical management of a symptomatic SDH is placement of two burr holes with irrigation of the hematoma without removal of the hematoma membranes. A craniotomy, with removal of the hematoma and membranes, may be done when SDH is recurrent or associated with a tumor or infection. Elderly individuals with brain atrophy are prone to SDH recurrences because the brain atrophy prevents the brain from re-expanding to the inner table of the skull. SDH in the elderly are typically followed by serial CT scans as long as there is no major shift of midline structures, no marked new neurologic signs from baseline, or if the SDH was an incidental discovery on neuroimaging done for another indication.

Recommended Reading

Karrar EE, Mansour N, Bhansali A. Cranial and spinal cord trauma: current concepts. Dis Mon 2011;57:543–57. (Good review of pathophysiology and current management of TBI)

Chen JC, Levy ML. Causes, epidemiology, and risk factors of chronic subdural hematoma. Neurosurg Clin N Am 2000;11:399–406. (Entire issue devoted to chronic subdural hematoma)

Neurologic Complications of Alcohol and B12 Deficiency

19

A 48-year-old man who has a history of alcohol abuse and hypertension is brought in by ambulance to the emergency room after having a seizure witnessed by his roommate. On exam, the patient is confused and agitated but there is no seizure activity. After 30 min, the patient becomes less confused but remains tremulous. His blood alcohol level is zero. Neuroimaging was normal. After the patient is more cooperative, he reports that his last drink of alcohol was 2 days ago in an attempt to go "cold turkey". The neurologist diagnoses him with an alcohol withdrawal seizure.

Who could have foretold, from the structure of the brain, that wine could derange its functions.
Seneca, 1st Century AD, Rome

Neurologic Complications of Alcohol

Overview

Alcoholism, the addiction to alcohol, is characterized by a craving of alcohol and a tolerance to its intoxicating effects. Worldwide, alcoholism has an enormous impact to society, as it is the number one abused drug in the world. In the USA, there are over 8 million people affected by alcoholism. In the emergency room, up to 40% of people evaluated have alcohol in their systems. When subsequently admitted to the hospital, withdrawal from alcohol can complicate the medical admission. The cause of alcoholism remains poorly understood but genetic factors appear to play a role, as alcoholism is seven times more frequent in first-degree relatives of alcoholics than in the general population. Adoption studies in Sweden found that alcoholism in a biologic parent was more important than growing up in an environment with alcoholism in the adopted parents. Identical twins have a higher concordance for alcoholism than fraternal twins.

Ethanol enters the circulation within minutes of consumption and is rapidly distributed throughout body tissues. The liver metabolizes over 95% of alcohol via alcohol dehydrogenase that converts ethanol to acetaldehyde, which in turn is metabolized by aldehyde dehydrogenase to acetate. In the average adult, alcohol metabolizes at a rate of 8 g/h (~ 8 oz beer/hour). Alcohol consumption at faster rates leads to increasing alcohol levels in blood and brain.

The effects of ethanol on the nervous system are numerous and complex. Which brain interactions are responsible for specific ethanol syndromes remain unclear. Ethanol inserts into cell membranes increasing membrane fluidity possibly interfering with signal transduction. Significant components of the withdrawal syndrome after chronic alcohol use reflect reduced neurotransmission in the inhibitory type A gamma-aminobutyric acid (GABA) pathways and enhanced neurotransmission in glutamate (N-methyl-D-aspartate) pathways. Alcohol withdrawal causes complex decreases in GABA

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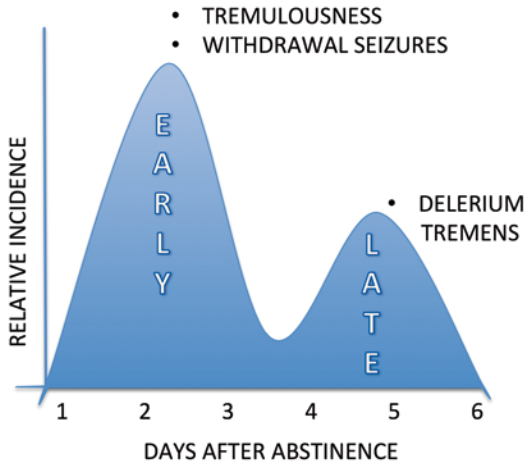

Fig. 19.1 Time course of alcohol withdrawal

receptor binding, resulting in loss of presynaptic inhibitory control. In addition, increased dopaminergic transmission may cause hallucinations and increased autonomic activity during the withdrawal syndrome. Hypomagnesia and hypocalcemia frequently occur during alcohol withdrawal and likely contribute to CNS hyperexcitability by altering neuronal action potentials.

Complications of alcoholism involve many organs, but damage to the CNS and peripheral nervous system (PNS) is particularly common. This chapter will review the major neurologic complications from alcohol intoxication and withdrawal (Fig. 19.1).

Intoxication and Alcoholic Coma

Ethanol readily crosses the blood–brain barrier, enabling the brain alterations to begin soon after drinking. Signs of intoxication in nonalcoholic persons begin at blood levels about 60 mg/dl, and gross intoxication occurs at levels of 120–150 mg/dl. In alcoholics, intoxication may not occur until blood levels are as high as 150 mg/dl. Signs of intoxication consist of varying degrees of euphoria, exhilaration, excitement, loss of restraint, irregular behavior, slurred speech, incoordination of movement, gait ataxia, irritability, and combativeness. While the biochemical effects are incompletely understood, the net result appears to be excitation of brain activity. There are a variety of metabolic abnormalities that may accompany alcohol intoxication, including hypoglycemia, lactic acidosis, hypokalemia, and hypophosphatemia. Other systemic manifestations of alcohol intoxication can include tachycardia, peripheral vasodilation, and volume depletion—leading to low blood pressure and inability to maintain body temperature causing hypothermia.

At higher blood levels, brain functions deteriorate with the development of lethargy, stupor, and coma, suggesting ethanol now produces inhibition of brain activity. Alcoholic coma is seen at blood levels around 300 mg/dl, and respiratory failure develops at levels of >400 mg/dl. Comatose patients often require intubation and mechanical ventilation until the alcohol is cleared from the systemic circulation.

Alcohol Withdrawal Syndrome

In the setting of chronic alcohol use, if alcohol intake is abruptly reduced, within hours as blood alcohol levels fall or are absent, an alcohol withdrawal syndrome can develop. Early alcohol withdrawal is characterized by autonomic hyperactivity (tremulousness, sweating, nausea, vomiting, and anxiety). Later alcohol withdrawal can include those early symptoms and also result in excessive neuronal excitation (confusion, agitation, delusions, hallucination, and seizures).

Stage 1 alcohol withdrawal is characterized by tremulousness, feeling anxious, and sometimes nausea and vomiting. Tremor ("shakes" or "jitters") develops in over 50% of individual in withdrawal. The tremors begin about 6 h after the last drink and worsen over the next 2–3 days (Fig. 19.1). The tremor is present at rest and with action. It is 6–8 Hz and irregular in character. Patients may also have an increased startle response. The mental status remains relatively clear but the patients feel uncomfortable. The tremor can be treated with benzodiazepines. It is also often "self-treated" by additional alcohol consumption (e.g. "an eye-opener") to resolve the tremulousness sensation. Some patients will go on to further stages of withdrawal. Risk factors

for a more severe withdrawal course include prior withdrawal episodes, advanced age, male sex, comorbid conditions (e.g. liver disease), and higher daily intake of alcohol.

Stage 2 alcohol withdrawal occurs at 1–2 days after the last alcohol consumption. The tremulousness may worsen and be accompanied by agitation and hyperactivity. The autonomic symptoms of tachycardia, hypertension, and diaphoresis begin, and the tremor described above becomes more apparent. Patients are typically lucid at this stage but may have disordered sleep and experience insomnia. Stage 2 can worsen into stage 3 withdrawal which incorporates the features of stage 2 but includes seizures (described below). At 3–5 days from last alcohol consumption, stage 4 alcohol withdrawal or *delirium tremens* can occur. This is discussed later in this chapter.

The Clinical Institute Withdrawal Assessment Scale for Alcohol, Revised (CIWA-Ar) is commonly used to assess patient symptoms during alcohol withdrawal in the medical setting. It contains ten items and requires interaction from the patient. Stage 1 alcohol withdrawal is a score of less than 10. A score of greater than 10 is suggestive of more severe withdrawal that likely will require evaluation and possible admission to a medical facility.

Alcohol Withdrawal Seizures

Alcohol withdrawal seizures occur in nearly 5% of individuals who have been steadily drinking for years and then abruptly stop. For example, undiagnosed alcoholics who are hospitalized may experience a seizure the day after admission. The primarily generalized seizure occurs 7–72 h after alcohol cessation with a peak of 12–48 h (Fig. 19.1). Patients tend to have 1–4 seizures over several hours. Status epilepticus is rare.

Alcohol withdrawal seizures are partly a diagnosis of exclusion. The mechanism for withdrawal seizures is unknown but thought to result from a hyperactive brain (due to alcohol withdrawal), accompanying low serum magnesium, and elevated arterial pH from respiratory alkalosis. In keeping with this, half of patients withdrawing from ethanol have an abnormal electroencephalogram (EEG), manifesting myoclonic or convulsive responses to flashing lights.

Fifty percent of patients brought to the ER with possible alcohol withdrawal seizures have another identifiable etiology. These patients often have a seizure aura (implying a focal origin for the seizure), history of serious head trauma while intoxicated, atypical seizures, abnormal neurologic exam, or signs of systemic infection. Neuroimaging studies can identify subdural hematomas, hemispheric contusions or infarctions, intracerebral masses (brain abscess, neurocysticercosis, tumors, vascular malformations), or meningitis. Neurologic exam should not show acute signs that cannot be attributed to chronic alcohol usage. The blood alcohol level should be zero or very low and the CSF exam, if done, is normal. Some patients have known epilepsy whose seizure was actually triggered by drinking alcohol and stopping their anticonvulsant medications.

Administration of benzodiazepines (lorazepam or diazepam) usually prevents further seizures during the critical withdrawal period. Phenytoin administration does not prevent seizures. Patients who permanently stop drinking do not have future seizures. Controversy exists as to whether administration of anticonvulsants prevents subsequent alcohol withdrawal seizures. Since patients often stop their anticonvulsants during drinking spells, the combination of alcohol and anticonvulsant withdrawal may actually increase their risk of future seizures.

Delirium Tremens

Delirium tremens (DT) or stage 4 alcohol withdrawal syndrome is a serious but uncommon complication of alcohol withdrawal (less than 8% of hospital admissions for alcoholism) and presents with profound delirium and autonomic nervous system overactivity. Patients have marked confusion, agitation, hallucinations, tremors, and sleeplessness. Signs of increased autonomic nervous system activity include fever, tachycardia, dilated pupils, and profuse sweating.

Clinical signs begin 2–5 days after alcohol withdrawal and may be preceded by withdrawal seizures (Fig. 19.1). Life-threatening events include high fever, dehydration, hypotension, cardiac arrhythmias, and secondary complications of trauma (from the agitation) or alcohol-associated medical conditions (liver failure, gastrointestinal bleeding, systemic infection, or pancreatitis).

Treatment aims at reducing agitation and maintaining fluid and electrolyte balance. Lorazepam given repeatedly intravenously or intramuscularly is required for sedation. Repeated doses of sedating medications like lorazepam are helpful in reducing withdrawal symptoms but can lead to respiratory failure requiring intubation and respiratory support. Patients require replacement of up to 4–10 L of fluid per 24 h to prevent dehydration and circulatory collapse. Serum potassium and magnesium levels are usually low and require correction.

The duration of DTs lasts 2–7 days with most cases ending by day 3. Recovering patients regain alertness and ability to cooperate but seldom have any memory for the acute illness. The mortality rate is 10%.

Wernicke's Encephalopathy and Korsakoff's Syndrome

Introduction

Wernicke's encephalopathy and Korsakoff's syndrome are linked to abnormal low levels of thiamine (vitamin B_1) in the CNS. Chronic alcoholic patients tend toward malnourishment. People with alcoholism may obtain as much as half their daily caloric intake from ethanol, resulting in serious nutritional deficiencies including thiamine, niacin, folate, and protein. Hence, these two disorders are not linked to the direct toxic effects of alcohol or alcohol withdrawal. Thiamine is required for all tissues and is found in high concentration in the brain, heart, skeletal muscle, liver, and kidney. Thiamine is absorbed in the small intestine and transported to the brain by an energy-dependent transport system. A series of phosphorylation reactions produce thiamine diphosphate, a required cofactor in carbohydrate and amino acid metabolism. Thiamine-dependent enzymes are involved in the biosynthesis of neurotransmitters and in the production of reducing equivalents used in oxidant stress defenses.

Manifestations of thiamine deficiency can involve the brain (Wernicke–Korsakoff syndrome), peripheral nerves (dry beriberi), or the cardiovascular system (wet beriberi).

Pathophysiology

Neuropathologic findings in Wernicke's encephalopathy include demyelination, glial and vascular proliferation, hemorrhage, and necrosis. These principally affect gray matter regions of the medial thalamus, hypothalamus, tegmentum of the pons and medulla, and cerebellum (particularly the Purkinje and granule cells of the anterior–superior vermis). Korsakoff's psychosis shows pathologic brain changes including hemorrhages and necrosis in the dorsomedial nucleus of the thalamus and/or the mammillary bodies.

Major Clinical Features

Wernicke's encephalopathy is an acute condition that presents with the classical triad of oculomotor abnormalities, gait ataxia, and a confusional state. The ocular signs consist of nystagmus that is both horizontal and vertical, paralysis of external recti, and paralysis of conjugate gaze. Nystagmus and weakness of both the lateral rectus muscles are the most common with total ophthalmoplegia being rare. The ataxia of gait typically produces a wide-based stance and an unsteady, lurching gait. Ataxia of limbs remains less pronounced, and many patients have normal finger-to-nose and heel-to-shin tests.

Most patients experience a quiet confusional state characterized by apathy, inattentiveness, and indifference to surroundings. Speech is minimal. Drowsiness is common and may progress to stupor if untreated. Twenty percent of patients experience mild disorders of perception or hallucinations.

Wernicke's encephalopathy can evolve into Korsakoff's syndrome, which is a unique mental state in which memory is impaired out of proportion to other cognitive functions in an otherwise alert, fluent, and responsive patient. A selective disorder of memory, Korsakoff's syndrome typically follows one or more episodes of Wernicke's encephalopathy. Impaired memory for previously established recent events (retrograde amnesia) and the inability to incorporate new memories (anterograde amnesia) appear but immediate recall stays preserved. Patients are unaware of their memory deficits, and confabulate or invent material to fill gaps in memory gaps.

Major Laboratory Findings

MRI abnormalities vary in acute patients and include T2-weighted abnormalities in the periaqueductal region, medial thalamus, and mammillary bodies (Fig. 19.2). Later, the T2-weighted abnormalities disappeared and atrophic changes occur in the mammillary bodies and cerebellar vermis with enlargement of the third ventricle.

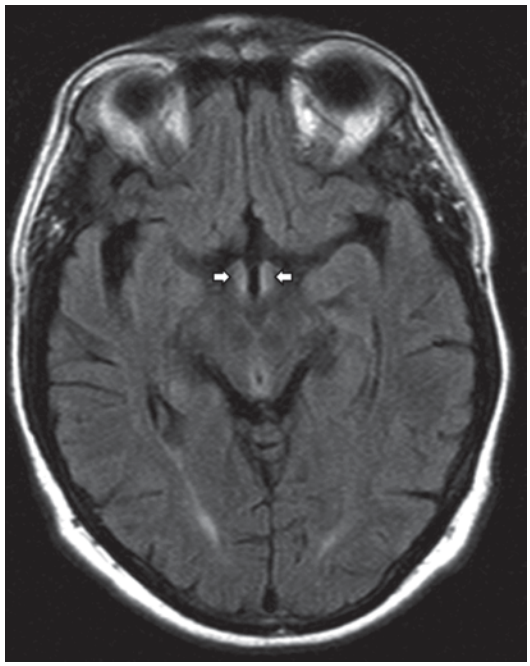

Fig. 19.2 Axial MRI FLAIR sequence of a 50-year-old alcoholic who presented with confusion, ataxia, nystagmus, and diplopia, showing bright signal in the mammillary bodies (*arrows*). (Courtesy of Dr. Blaine Hart)

Principles of Management and Prognosis

Early diagnosis of Wernicke's encephalopathy is critical as administration of intravenous thiamine can correct the acute neurologic problem. In fact, it is prudent to administer parenteral thiamine to every alcoholic patient seen in the ER or hospitalized since administration of glucose can precipitate the onset of Wernicke's encephalopathy. It is less clear whether thiamine can reverse the memory deficit seen in Korsakoff's syndrome. Poor prognostic factors include severe clinical features, delayed thiamine administration, T2-weighted abnormalities on MRI, and cerebellar or mammillary body atrophy. In countries using thiamine-enriched flour in bread, the incidence of Wernicke–Korsakoff syndrome has fallen but not disappeared.

Alcoholic Cerebellar Degeneration

Chronic alcoholism often leads to slowly progressive gait ataxia similar to that seen in Wernicke's encephalopathy. This is a wide-based, unsteady, short-stepped, and lurching gait. Patients often run their hands against the side of buildings or walls to improve their ambulation. Limb ataxia is usually mild. MRI shows atrophy of the superior cerebellar vermis, and pathology demonstrates a loss of cerebellar Purkinje cells and other neurons, maximally in the superior vermis and vestibular nuclei (Fig. 19.3). Once the gait ataxia develops, no treatment has been shown to reverse it.

Alcoholic Polyneuropathy

A distal symmetrical sensorineural polyneuropathy is common in chronic alcoholism. The etiology of the neuropathy remains unclear although

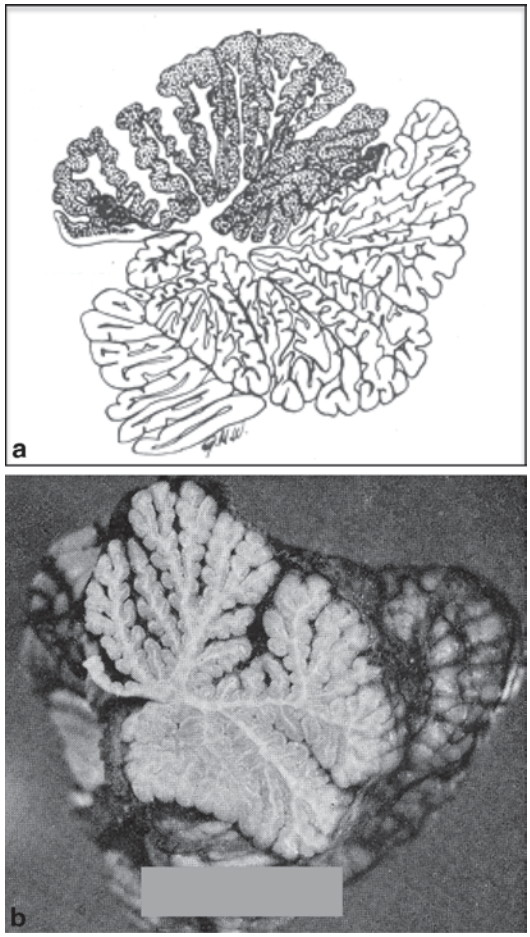

Fig. 19.3 Alcoholic cerebellar degeneration: **a** Illustration of cerebellar atrophy affecting the superior vermis (shaded area) and **b** photograph of autopsy specimen reflecting same pattern of atrophy in an alcoholic patient. (Courtesy of Dr. Mario Kornfeld)

direct effects of alcohol on the peripheral nerve and nutritional/vitamin deficiencies have been proposed.

The majority of patients have slowly progressive symptoms of paresthesias, burning dysesthesias, numbness, and muscle cramps in their feet and lower legs. On exam, there is loss of ankle jerks, diminished vibratory sensation in the feet, and varying degrees of foot numbness and weakness. Loss of pain sensation appears less commonly. As the disease advances, leg weakness and gait apraxia occur from loss of position sense in the feet and possibly concomitant alcoholic cerebellar degeneration. Axonal degeneration, the principal pathologic process, occurs although segmental demyelination can occur. If alcohol consumption stops, the neuropathy may improve. Use of simple analgesics and tricyclic antidepressant medications may alleviate the burning dysesthesias.

Fetal Alcohol Syndrome

Introduction

Alcohol is the most common human teratogen. Of the 60% of women who drink alcohol, 16% report drinking during their pregnancy and 4% report drinking more than seven times a week. The prevalence of fetal alcohol syndrome (FAS) in the USA is estimated at 0.5–2 per 1000 live births.

Pathophysiology

The pathophysiology of FAS while incompletely understood has several generalizations. Human and animal studies find that (1) consumption of 1 or more alcoholic drinks per day is highly associated with FAS, (2) alcohol exposure in the first trimester of pregnancy leads to the characteristic congenital malformations of the face and midline brain, (3) third trimester alcohol exposure decreases brain weight and numbers of neurons, and (4) peak blood alcohol concentrations are more critical than the same dose of alcohol at a lower peak level. The threshold amount of alcohol consumption needed to produce fetal toxicity remains unknown. As such, total abstinence from drinking alcohol is currently recommended for pregnant women or women planning pregnancy.

How alcohol damages the developing fetal brain is poorly understood but alcohol can kill developing neurons. In early development, excessive cell death in the midline of the developing embryo may account for midline brain defects (agenesis of corpus callosum) and craniofacial abnormalities. In late fetal development, the loss of neurons is more widespread, producing a low

Table 19.1 Characteristic features of fetal alcohol syndrome

Facial abnormalities	Short palpebral fissures
	Ptosis (droopy eyelids)
	Flat midface
	Smooth philtrum
	Thin upper lip
Growth retardation	Low relative birthweight
	Growth retardation despite adequate nutrition
	Low weight relative to height
CNS neurodevelopmental abnormalities	Microcephaly
	Agenesis of corpus callosum
	Cerebellar hypoplasia
	Neurologic signs that may include poor fine motor coordination, hearing loss, and clumsy gait
Behavioral abnormalities	Learning disabilities (poor abstract reasoning, math skills, judgment, concentration, and memory)
	Poor school performance
	Poor impulse control
	Hyperactivity
	Poor social interactions
Birth defects	Congenital heart defects
	Skeletal and limb abnormalities
	Ophthalmologic abnormalities
	Sensorineural hearing loss
	Cleft lip or palate

brain weight. Hypotheses of the mechanism by which ethanol kills neurons include formation of toxic acetaldehyde by alcohol dehydrogenase metabolism of ethanol, free radical formation that causes cellular damage in the developing brain, and disruption of the L1 cell adhesion molecule (CAM) that is important in the developing brain.

Major Clinical Features

Infants with fetal alcohol syndrome demonstrate several characteristic abnormalities that involve growth retardation, craniofacial structure, neurodevelopmental abnormalities, behavior problems, and occasional birth defects (Table 19.1 and Fig. 19.4). The average IQ score in FAS is 66 with a range of 16–105. These IQ scores are higher than those seen in Down's syndrome (25–65) and fragile X syndrome (30–55). Nearly 60% of FAS children develop significant behavioral problems compared to 25% for Down's syndrome children. The cognitive, behavioral, and psychosocial problems persist into adulthood.

Major Laboratory Findings

Clinicians have created categories such as alcohol-related birth defects and fetal alcohol effects or alcohol-related neurodevelopmental disorder for infants damaged by ethanol who do not meet all the criteria for FAS. Presently, there is no laboratory test that establishes the diagnosis.

Principles of Management and Prognosis

Patient management begins with an early diagnosis that enables medical intervention, psychological help, educational evaluation and access to special education and related services such as speech and language programs, access to community resource programs. Helping the mother and other family members enables family preservation and helps prevent drinking during subsequent pregnancies.

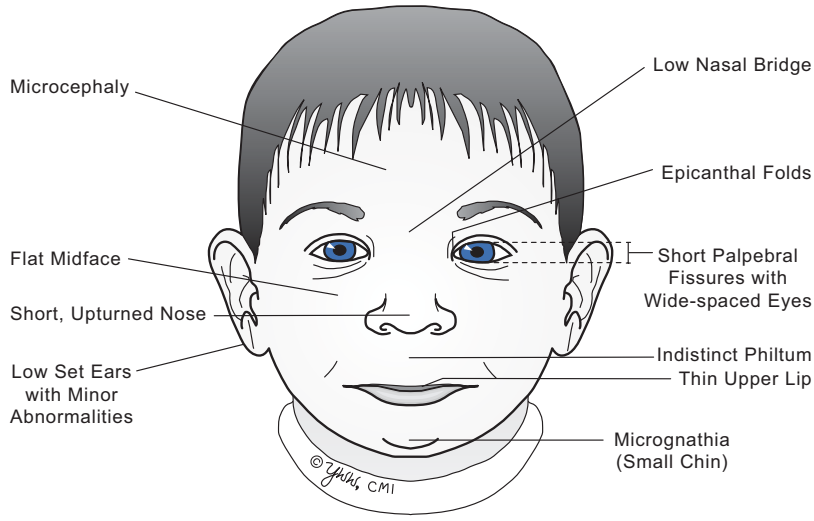

Fig. 19.4 Fetal alcohol syndrome facial features

Vitamin B_{12} Deficiency (Subacute Combined Degeneration)

Introduction

Cyanocobalamin or vitamin B_{12} is an essential water-soluble vitamin that must be acquired from our diet. Meats and liver are rich in this vitamin and it is lacking in vegetables. B12 contains a single cobalt atom and serves as an enzyme cofactor for two important enzyme-catalyzed reactions in mammals that have impact on the generation of new blood cells and normal neurological functions.

Absorption of B12 is highly complex and involves the salivary glands, stomach, pancreas, and small intestine. B12 in food is bound to proteins. Once liberated from food proteins by gastric acid and pepsin, it is tightly bound in the stomach by R-proteins, which are produced by salivary glands. After binding, the R-protein–B12 combination is carried into the small intestine where pancreatic proteases degrade the R-proteins releasing free B12. At that time, intrinsic factor, originally produced by parietal cells in the stomach, attaches to B12 and transports it across cells in the intestinal wall. Once B12 enters the circulation, it is again bound by a serum protein called transcobalamin II where it enters cells via a specific receptor. Because of this complex process, a variety of diseases can cause B12 deficiency such as pernicious anemia from absence of intrinsic factor due to loss of stomach parietal cells, small intestine malabsorption syndromes due to bacterial overgrowth, or lack of B12 in the diet as in prolonged strict vegetarians. The normal diet contains 5–15 μg/day with a daily requirement of only 2 μg. In addition, B12 is heavily stored in the human liver allowing for absence of newly absorbed B12 of 2–3 years before symptoms develop. As such, B12 deficiency rarely develops from a dietary deficiency and mainly results from abnormalities involving the stomach and less often from primary small intestine malabsorption. Pernicious anemia occurs in 80% of patients and results from absence of intrinsic factor either from atrophy of the gastric mucosa or from autoimmune destruction of parietal cells.

Clinical signs of B12 deficiency occur in both sexes mainly in adults with a peak incidence in ages 40 years and above. The true incidence of neurologic symptoms in patients with B12 deficiency is unclear. However, the easy availability of obtaining a serum B12 level has led to many more early diagnoses and treatment before major signs and symptoms develop.

Pathophysiology

B12 deficiency results in macrocytic anemia and neurologic signs. A deficiency of either B12 or folate impairs production of tetrahydrofolate. In the bone marrow, this causes a defect in DNA synthesis that prevents cell division and allows limited synthesis of large erythrocytes. Thus, both folate and B12 deficiency causes macrocytic anemia. However, only lack of B12 and not folate results in nervous system damage. It is thought that B12 deficiency reduces production of S-adenosylmethionine from methionine and is the critical step causing neurologic damage.

Spinal cord pathology begins in the cervical and thoracic dorsal columns and extends into the lateral columns. Early lesions consist of swelling of myelin sheaths with minor axonal changes. Fibers of large diameter are predominately affected. Later, as the myelin breaks down, macrophages invade, inflammatory lymphocytes appear, axons die, and Wallerian degeneration develops along with some neuronal deaths. Oligodendroglia appear normal and nerve roots are seldom damaged. Gliosis develops in older lesions and the spinal cord becomes shrunken in the dorsal aspect.

Patients also develop a peripheral neuropathy. Available electrophysiological studies suggest a mixed axonal-demyelinating neuropathy develops with slow motor nerve conduction velocities, reduced sensory nerve potentials, and fibrillations in distal muscles. Limited histopathologic studies of peripheral nerves in humans and experimental monkeys suggest loss of large myelinated axons and degeneration of distal sensory nerves.

Clinical Features

Signs and symptoms of B12 deficiency may develop over weeks or have an insidious onset over a few months. The first clinical sign of B12 deficiency is typically an alteration of sensation. Paresthesias and numbness of the legs and occasionally arms develop in about 90% of patients. Diminished vibration and proprioception sense in the feet and rises up to the knees along with occasional signs in the hands also develop in 90%. These patients often cannot tandem walk and have a positive Romberg sign. A broad-based unsteady ataxic gait may develop. Diminished temperature and pain appreciation in the feet develop in 30%. Leg weakness may develop as the sensory signs progress.

Lateral column signs with hyperactive reflexes, Babinski signs and leg weakness and spasticity develop as the disease progresses. An autonomic bladder with incontinence and impotence may also occur. Cognitive abnormalities develop in about 25–40% of untreated patients when administered neuropsychological tests. These patients develop difficulties in short-term memory, episodic and visuospatial memory, attention, and abstract reasoning.

Major Laboratory Findings

The patient has a moderate anemia. A key characteristic of the anemia is that mean corpuscular volume of peripheral blood cells is enlarged (MCV >100 fl). Oval-appearing erythrocytes and hypersegmented (six or more segments) neutrophils often are seen on a peripheral smear.

About 95% of patients have serum B12 below 200 pg/mL by radioimmunoassay or corresponding abnormally low values using non-radioimmunoassays. In patients with pernicious anemia, 90% have serum antibody against parietal cells and 60% have antibody to intrinsic factor. Achlorhydria determined by absence of gastric acid is common. Serum homocysteine and methylmalonic acid levels are commonly elevated.

MRI of the cervical and thoracic spinal cord in some patients demonstrates increased T2 signal in the dorsal horns and variable increased signal intensity in the lateral columns. Lesions do not enhance with gadolinium.

The diagnosis of B12 deficiency can be complicated at times especially if the patient is also folate deficient. Since folic acid has been added to all enriched grain products, macrocytic anemia from folate deficiency is uncommon. A straightforward diagnosis can be made if the patient has compatible neurologic symptoms and signs, low serum B12 levels (below 200 pg/mL), and the presence of macrocytic anemia with hypersegmented neutrophils seen on a peripheral blood

smear. However, the neurologic signs of B12 deficiency can develop in a patient without any anemia.

Principles of Management and Prognosis

Treatment is usually initiated with IM injections of B12 for 1–3 months to restore B12 levels followed by oral synthetic B12 (1000 mg daily). The high oral doses of B12 allow adequate absorption of the vitamin without intrinsic factor. Although deficiency in folic acid may mimic some of the macrocytic anemia features of B12 deficiency, it should not cause the neurologic abnormalities. Prognosis depends on the intensity and duration of symptoms but most patients experience improvement in the anemia and their sensory symptoms within the first 2 months. About half of the patients make a complete recovery and most make some improvement in their disability including improvement in cognition.

Recommended Reading

Carlson RW, Kumar NN, Wong-Mckinstry E, et al. Alcohol withdrawal syndrome. Crit Care Clin. 2012;28:549–85. (Up-to-date review of clinical features of alcohol withdrawal syndrome and current management)

Zahr NM, Kaufman KL, Harper CG. Clinical and pathological features of alcohol-related brain damage. Nat Rev Neurol. 2011;7:284–94. (Comprehensive review of Wernicke encephalopathy and Korsakoff syndrome)

Manji H. Toxic neuropathy. Curr Opinion Neurol. 2011;24:484–90. (Nice review of toxic neuropathies, including alcohol neuropathy)

Thackray HM, Tifft C. Fetal alcohol syndrome. Pediatr Rev. 2001;22:47–55. (Excellent review of clinical and laboratory features of FAS)

Reynolds E. Vitamin B12, folic acid, and the nervous system. Lancet Neurol. 2006;5:949–60. (Comprehensive review of the subject including recent findings in cognition)

Green R, Kinsella LJ. Current concepts in diagnosis of cobalamin deficiency. Neurology. 1995;45:143501440. (Oldie but very informative)

Disorders of Pain and Headache

20

A 19 yr old woman in class notes odd, flashing lights appearing on the right side of her vision in both eyes that persist even when closing her eyes. They disturb her vision but do not occlude all vision. Over 5 min the flashing lights disappear. Shortly afterwards she develops a pounding left-sided headache, nausea, and notes that bright lights make the headache worse. The headache becomes severe enough that she seeks medical help. She is diagnosed with a migraine with aura and is given a triptan orally that resolves the headache over the next two hours. These headaches recur once or twice a month.

Background

In 1906, Sherrington, an early pioneer in neurophysiology, described a noxious stimulus as one with an intensity and quality sufficient to trigger reflex withdrawal, autonomic responses, and pain. He also recognized that nociceptive pain is like an early warning system that detects the presence of potentially damaging stimuli. The pain sensation is mediated in the periphery by high threshold primary sensory neurons called nociceptors, which transmit sensory information via nociceptive pathways in peripheral nerves that communicate to nociceptive-specific projection neurons in the spinal cord and regions of the brainstem. Nociceptive signals are then relayed via the spinothalamic and trigeminothalamic tracts to the thalamus, primary somatosensory, anterior cingulate, and insular cortices. In addition to acute pain perception from peripheral tissue injury and inflammation, reversible adaptive changes in the sensory nervous system lead to the generation of pain hypersensitivity. This hypersensitivity is hypothesized to be a protective mechanism that ensures proper healing of damaged tissue. We know this pain system is important. Individuals with congenital or acquired loss of pain sensation have a high incidence of permanent damage to their face and limbs from lack of pain as they do not have awareness of the injury that occurs under normal pain conditions.

For a large majority of individuals, this pain system works well and pain spontaneously subsides as the damaged area heals. For certain people, however, pain may persist and become permanent, more severe, and even incapacitating. The pain can expand from the region of original discomfort, show hypersensitivity to painful triggers, and change in character in how the pain is perceived. This abnormal pain is called neuropathic pain (NP). NP is common and can impair

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Table 20.1 Major causes of neuropathic pain

Focal (or multifocal) lesions of peripheral nervous system	*Entrapment syndromes such as carpal tunnel syndrome*
	Ischemic neuropathy
	Herpes zoster and post herpetic neuralgia
	Trigeminal neuralgia
	Vasculitis syndromes
Polyneuropathies	*Diabetes mellitus*
	HIV neuropathy
	Amyloidosis
	B_{12} deficiency, beriberi
	Hereditary sensory neuropathies
	Toxic neuropathies
	Toxins (arsenic, thallium, acrylamide, clioquinol, ethylene oxide)
	Drugs (*antiretrovirals*, *cisplatin*, *oxaliplatin*, disulfiram, ethambutol, isoniazid, nitrofurantoin, thalidomide, *vincristine*, metronidazole)
	Alcohol
	Malignant (paraneoplastic syndromes, multiple myeloma)
Central nervous lesions	Spinal cord injury, syringomyelia
	Brain infarction or malformation bleeds, esp. in thalamus and brainstem
	Brain tumors, abscesses*, subdural hematoma, meningitis*
Complex mixed pain syndromes with both tissue damage and neuropathic pain	*Disk protrusion producing low back or neck pain with radiculopathy*
	Cancer pain
	Postsurgical operations
	Regional pain syndromes such as complex regional pain syndrome, causalgia
	Phantom limb pain or amputation stump pain
Headache[a]	*Tension*
	Migraine
	Uncommon (cluster, occipital neuralgia, temporal arteritis)

Italics indicates common causes

[a] Chronic headache pain is not always considered neuropathic pain

quality of life, interfere with normal sleep, and often trigger depression or anxiety. Approximately 166 million American adults or about 18% of the population are affected with NP. It is estimated that over 50% of office visits to a primary care provider are for pain-related problems.

NP most commonly originates following damage to peripheral nerves, but NP can be due to central nervous system causes (Table 20.1). Typically, the pain has both positive and negative elements. There is often diminished or loss of primary sensations producing thermal hypoesthesia, pinprick hypoalgesia, and diminished vibration sensation that indicates loss of myelinated and unmyelinated sensory fibers coming from the area of sensory loss. These negative symptoms are coupled with positive abnormal hypersensitive symptoms in the affected area such as paresthesias, dysesthesias, paroxysmal pains, hyperalgesia, and allodynia. *Allodynia* is characterized by painful sensations to the involved skin area triggered by light touch, warming or cooling the skin, or blowing air over the skin, creating sensations that are not normally painful. *Paresthesias* are non-painful crawling or tingling sensations of skin while *dysesthesias* are uncomfortable burning, shock-like, or shooting sensations. If only **Aδ** fibers fire ectopically, the result is painless

paresthesias, like hitting the ulnar nerve at the elbow. If **C** fibers or both fiber types ectopically fire, the individual may experience dysesthesias or allodynia. *Hyperalgesia* develops when the nociceptor input is amplified peripherally or centrally, yielding more pain than would otherwise be expected.

Normal Pain Pathways

Pain pathways appeared at different times in evolution. The most primitive system uses specific polymodal nociceptors that are activated by a specific type of high-intensity mechanical, chemical (such as chili, garlic, mustard, horseradish), or thermal stimulus. Thus, nociceptor nerves differ from other sensory nerves that respond to innocuous stimuli with a lower threshold to firing. The majority of nociceptive nerve fibers are small-diameter, unmyelinated C fibers that conduct slowly at 0.5–2.0 m/s The axon endings are free nerve terminals with no extracellular matrix capsule. These fibers fire continuously without decay if the noxious stimulus is maintained. Activation of nociceptive C fibers is appreciated as a burning, uncomfortable, and poorly localized pain.

The cell bodies of all C fibers are located in the dorsal root ganglia. A single axon emerges from each cell body, with the axon immediately bifurcating into two fibers, one projecting to the periphery innervating various body regions (e.g. the skin), while the other fiber projects to the central nervous system (spinal cord, or brainstem for the head and neck). The centrally projecting nerve terminals communicate to nociceptive-specific projection neurons in the superficial layers (lamina I and II) of the spinal cord dorsal horn of several rostro-caudal adjacent segments. Centrally projecting C-fibers additionally contact excitatory and inhibitory interneurons present in lamina II. Many inhibitory interneurons are spontaneously active, maintaining tonic inhibitory control over dorsal horn processing. C-fiber terminals release glutamate and substance P as their excitatory neurotransmitters. The incoming signal may be diminished or inhibited by interactions from endorphin-releasing interneurons (endogenous opioids), or influenced by inhibitory or facilitatory axons descending from supraspinal regions such as the somatosensory cortex, hypothalamus, midbrain periaqueductal gray, and pons.

Nociceptive spinal neurons that become activated by pain-related stimuli project to various sites in the brainstem and thalamus before reaching the cortex for the conscious perception of pain. The most important ascending pathways for pain processing consist of direct spinal projections to the thalamus, direct spinal projections to homeostatic control areas in the medulla, and projections to the hypothalamus and ventral forebrain.

The most recent evolutionarily pain pathway conducts nociceptive signals from the body to the brain in a similar manner to C-fibers following noxious mechanical, thermal, or chemical input that ultimately reach the cerebral cortex, resulting in conscious awareness of pain. These peripheral pain fibers are small-diameter, thinly myelinated Aδ fibers that conduct at 5–30 m/s. Thus, this pathway system is more rapid than the primitive C-fiber pathway and yields more precise localization of the pain source. Stimulation generates signals that are felt as sharp, pricking, localizable pain. The axons usually have dynamic firing rates that decline with time even if the stimulus is maintained (known as accommodation). As with C-fibers, Aδ fibers travel through the dorsal root ganglion, terminate in the superficial layers of the dorsal horn of the adjacent segments of spinal cord, and release excitatory neurotransmitters such as glutamate. Again, interneurons modulate further transmission of the pain signal. Second-order axons in the spinothalamic pain pathway cross the spinal cord midline and travel to the contralateral spinothalamic tract to terminate at the thalamus (ventral posterior lateral and central lateral nuclei). Third-order axons then travel to the somatosensory cortex, somatosensory, anterior cingulate, and insular cortices. How pain signals reach conscious perception is poorly understood.

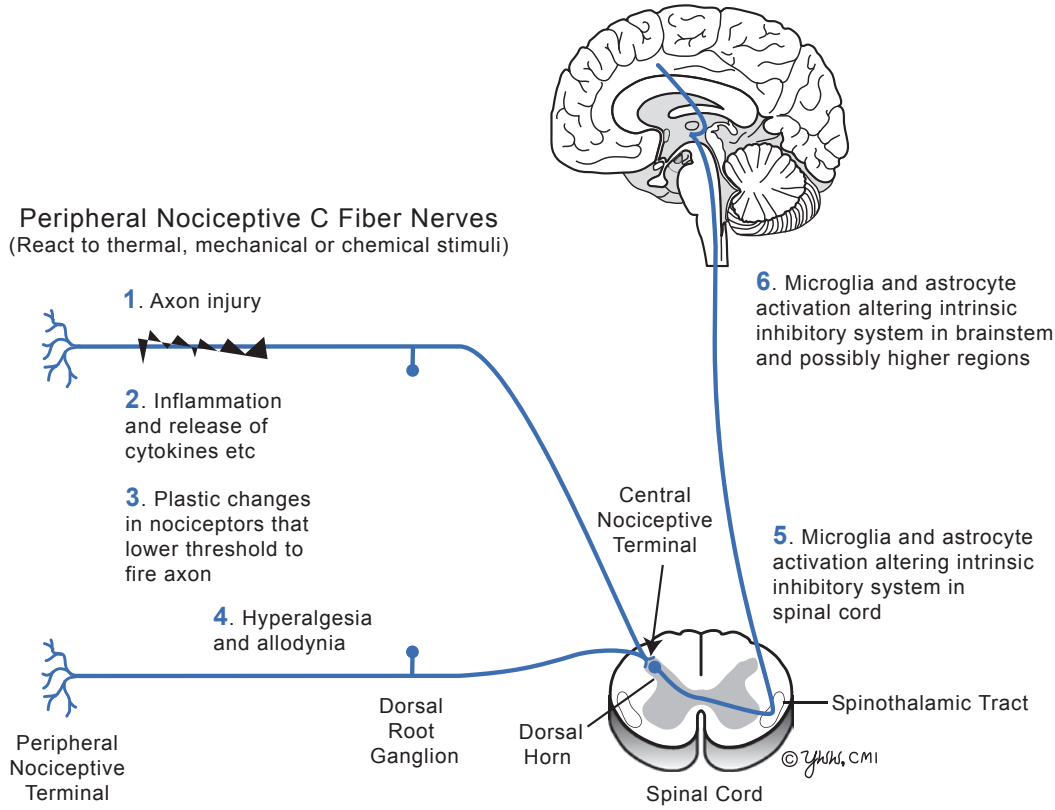

Fig 20.1 Current basic concepts of neuropathic pain development

Neuropathic Pain Mechanisms

The pathophysiologic knowledge of NP is expanding, but the steps that initiate the process are still poorly understood. Physiologic changes producing NP develop at several anatomic locations including the damaged nerves, dorsal root ganglia, spinal cord dorsal column root entry zone, brainstem, thalamus, and cerebral cortex. It appears that the anatomic location of the pathologic changes varies from person to person yet often produces similar symptoms and appears to respond similarly to the pain medications.

Peripheral sensitization begins with stimulus-evoked plasticity of the peripheral nociceptors initiated from inflammatory mediators released from injured nerves and inflammatory cells that sensitize the nociceptive terminal (Fig. 20.1). Cytokines, Substance P, bradykinin, serotonin, and prostaglandin sensitize injured and adjacent nociceptors to lower their threshold to fire—amplifying the intensity of the pain signal and expanding the skin area involved. The number of sodium channels increases in the damaged and adjacent intact sensory nerves, making the axon depolarize more easily. The net result of the peripheral nociceptive nerve plasticity is hypersensitivity and allodynia.

At the spinal cord dorsal horn, brainstem, and thalamus, several complex events develop. Microglia, the resident macrophages of the central nervous system, become activated in the brainstem and possibly higher, releasing their cytokines, thus affecting the complex interaction of dorsal horn fibers. Adjacent astrocytes also become activated in the spinal cord and at the anterior cingulate cortex. Activated astrocytes surrounding the pain-related synapse affect pain transmission by inducing synaptic neuroplasticity that intensifies nociceptive transmission and eventually produces gliosis. The role of microglia and astrocytes in causing NP is growing in

importance. In addition, negative feedback from inhibitory cortical fibers descending to the secondary dorsal horn pain neurons is diminished. Finally, changes in the central nervous system appear capable of inducing pain signals that did not originate in the peripheral nervous system. These are called central pain syndromes (Table 20.1).

Predisposing factors for chronic pain development have been identified and include genetic factors, poor coping skills, depression, intensity of the original tissue damage, and female gender.

In summary (Fig. 20.1), NP usually begins following injury to peripheral nociceptive axons resulting in local inflammation that induces complex plastic changes in the peripheral nociceptor resulting in a lower threshold for the injured axon and adjacent axons to fire. At the spinal cord dorsal horn and brainstem, secondary changes develop from the activation of microglia and astrocytes that alter the normal negative feedback control of pain signals, which adds to aberrant pain signal transmission and often perpetuates pain, even when the peripheral nerve injury has recovered.

Neuropathic Pain Management

As the physiology of NP is becoming better understood, there is improved understanding of how the conventional pain medications may work (Table 20.2). Unfortunately, we have not yet found methods to prevent or terminate the entire NP process. The most commonly administered, evidence-based, first-line medications for chronic pain are tricyclic antidepressants (amitriptyline and nortriptyline), gabapentin, opioids, and lidocaine patches. Each medication has multiple side effects so the drug type and dosage must be individualized for each patient. In general, always begin at a low dose and slowly increase to effectiveness over 1–2 weeks to reduce the side effects. It is useful to warn the patient that takes several weeks before the medications show benefit.

It is frustrating that in spite of a wide variety of available pain medications, less that 50% of chronic pain patients achieve satisfactory pain relief with any drug combination.

Headache

Overview

For most types of head pain, the first and second divisions of the trigeminal nerve bring noxious signals to the brain and to awareness. Only certain parts of the central nervous system are innervated by pain fibers, including proximal cerebral vessels (especially internal carotid, proximal anterior, and middle cerebral arteries), dural blood vessels, large veins, sinuses, dura at base of brain, bone, and several cranial nerves (5,7,9,10). In addition, the scalp, skull muscles, sinus mucosa, and teeth are innervated by pain fibers. The brain parenchyma, ependyma, choroid plexus, pia, and dura over the convexity of the brain, however, are insensitive to pain. Somatic pain usually localizes to the exact area of injury (i.e. scalp laceration),

Table 20.2 Medications for chronic pain and their proposed mechanism of action

Medication for chronic pain	Proposed mechanism of action
Tricyclic antidepressants Amitriptyline Nortriptyline Desipramine	Inhibition of reuptake of serotonin and/or norepinephrine, blocking sodium channels, and anticholinergic
Selective serotonin and norepinephrine reuptake inhibitors (SSNRI) Duloxetine Venlafaxine	Inhibition of both serotonin and norepinephrine reuptake
Opioid agonists	μ-receptor agonism in spinal cord dorsal horn and brainstem
Anticonvulsants Carbamazepine Topiramate Valproate	Blockade of sodium channels at multiple locations
Topical lidocaine	Blockade of sodium channels in peripheral nerve axons

Table 20.3 Important questions in headache evaluation

Is there a headache warning (aura)?
Is there an antecedent event (head trauma or dental/facial infection)?
Headache location
Headache intensity (mild, moderate, or severe or a Likert scale of 0–10)
Headache frequency
Pain character (constant pressure or throbbing; sharp or dull)
Headache duration (minutes, hours, days, or constant)
Headache triggers (coughing, sneezing, eating cold food, alcohol consumption, etc.)
Age of onset of headaches
Presence of family history of similar headaches?
Presence of other neurologic symptoms including nausea, vomiting, weakness, loss of face sensation, hearing changes, vertigo, etc.

Table 20.4 Red Flags (signaling possible serious cause of headache)

Worst headache of my life
Sudden onset of headache in an individual not prone to headaches
Headache progressing in severity over days to weeks
Focal neurologic signs present such as stiff neck, paralysis, asymmetrical pupillary responses, cranial nerve abnormalities, hemianopia, etc.
Headache associated with new confusion or delirium
Papilledema
New headache in an older person
New headache in person immunosuppressed by drugs or disease
Headache worsened by exercise or valsalva maneuver
Headache associated with fever or elevated white blood count

while the pain from headache is more diffuse and localizes only to large regions of the head.

There are over 250 causes of headache. In general, a simple classification divides headaches into primary and secondary. Primary headaches (like tension-type, migraine, and cluster) are those headaches where pain is the primary symptom and no structural damage occurs to the brain. Secondary headaches (from tumor, infection, subdural hematoma, etc.) develop from structural damage to the skull or central nervous system masses causing secondary meningeal origin pain. Secondary headaches often produce other neurologic signs and symptoms.

The evaluation of a patient with headache usually requires a careful history with attention to its characteristics (Table 20.3). The exam should be thorough with attention for the presence of papilledema, neck stiffness, cranial nerve signs (especially the trigeminal nerve), or signs of sinus or tooth/mouth infection. For the headache to be considered primary, the neurologic exam should be normal. If the neurologic exam is abnormal, the headache may be secondary and the result of structural damage of the face, skull, meninges, or brain. If a secondary etiology of the headache is suspected and of recent origin, neuroimaging should be considered.

There are a number of symptoms that are considered "red flags" and should prompt concern that the headache is not benign but a more serious type of headache (Table 20.4). When these "red flags" are encountered, timely neuroimaging is usually recommended.

Tension-type Headache

Introduction

Tension-type headaches (TTH) are the most common type of headache with a lifetime prevalence of 78 % and a yearly prevalence in adults of 38 %. TTH are commonly divided into *infrequent episodic TTH* with less than 12 headache days per year (prevalence 50 %), *frequent episodic TTH* with 12–180 headache days per year or less than 14 headaches per month (prevalence 25 %), and *chronic TTH* with over 180 headache days a year with at least 3 headaches a week (prevalence 3 %). The prevalence peaks between 30–40 years of age and declines in the elderly. There is seldom a genetic predisposition. Simple TTH occur about equally in men and women, but women have more chronic daily headaches. Elderly individuals with cervical arthritis may experience TTH.

Pathophysiology

Remarkably little is understood about the pathogenesis of TTH. The old hypothesis that TTH occur from muscle contraction with secondary ischemia is no longer held. Patients with muscle

Table 20.5 Clinical differences between tension-type and migraine headache[a]

Symptom	Tension type	Migraine
Onset	Slow over hours	More rapid
Visual aura	No	20 %
Pain character	Constant pressure	Throbbing
Location	Bilateral, often in neck, frontalis and temporalis muscles	Unilateral
Nausea/vomiting	Uncommon	Common
Photophobia	Uncommon	Common
Duration	Hours to years	Hours to 2–3 days
Neurologic signs	No	Only if complicated migraine
Relief from sleep	Occasionally	Frequent

[a] Not all headaches demonstrate all properties. Some migraines are bilateral and non-throbbing and some tension-type headaches will develop migraine-like symptoms if the headache becomes intense or prolonged. It is common for migraine patients to also develop tension-type headaches

hypertonia (such as Parkinson's disease, dystonia, etc.) are not necessarily headache-prone. There are no significant differences in electromyographic recordings from the forehead or neck muscles between TTH, migraine, and normal controls. Scalp and neck muscles from TTH patients do not show muscle pathology, inflammatory cells, or biologic markers of muscle damage, such as elevated serum creatine kinase or lactate. Nevertheless, cranial and neck muscles somehow appear to play a role in the pathogenesis. TTH patients have more focal areas of muscle tenderness (tender points) than do controls, even when they are not experiencing a headache. Patients with chronic TTH have more tender and painful frontalis, temporalis, pterygoid, masseter, and trapezius muscles. TTH patients are more likely to develop neck or head pains following static muscle exercises. Subjectively measured muscle pain thresholds are lower in patients with chronic TTH than in controls or than patients with episodic TTH.

While the pathogenesis of episodic TTH remains unclear, it is thought to be based in the peripheral nervous system with evidence mounting that secondary pain sensitization develops in patients with chronic TTH similar to that recognized in neuropathic pain described above. A convergence of sensitized pain signals occurring in the caudal nucleus of cranial nerve V may trigger a cascade of secondary neuroplastic changes.

A number of studies have shown that stress, poor sleep habits, and mental tension are precipitation factors for TTH. Patients with chronic TTH report more everyday stressful events that are described in more detail than controls. They tend to interpret their headache symptoms as threatening their physical integrity, ascribe more weight to them, and feel they interfere more with their daily life. Yet, personality profiles of individuals with only episodic TTH are normal and differ from those with chronic TTH. How these psychological differences contribute to chronic TTH is unknown.

Major Clinical Features

The typical patient with TTH complains of constant, non-pulsating pain (75 %), bilateral pain (90 %), which is localized over the frontal, temporal, and posterior neck muscles (Table 20.5). Usually the headache is not aggravated by physical activity, light, or sound. Nausea and vomiting are uncommon. The headache begins as a dull pain, often in the neck, that slowly progresses in intensity and cranial area over several hours. If the headache becomes intense, it may occasionally become unilateral and throbbing in nature. The headache may last from a few hours to over a day. On exam, scalp and neck muscles may be tender to palpation. The neurologic exam during and between headaches should be normal.

Major Laboratory Findings

Patients with TTH have normal neuroimaging exams, routine blood tests, and electroencephalograms.

Principles of Management and Prognosis

Management of TTH patients is divided into acute treatment and prophylaxis. Most patients treat mild to moderate TTH with simple over-the-counter analgesics, such as aspirin, acetaminophen, and non-steroidal analgesics. Studies have generally found that all three types are about equally effective, especially if taken early in the headache. Muscle relaxants (such as benzodiazepines) and triptans are seldom effective. Narcotics may give temporary pain relief but often do not terminate the headache.

Non-pharmacological treatments are often effective and include hot and cold packs to the head or neck and hot baths or showers. Acupuncture and spinal manipulation therapy lack excellent randomized clinical trials demonstrating efficacy.

If the headache becomes severe, treatment is often difficult as simple analgesics are seldom effective. Stronger analgesics and medications aimed at inducing sleep are often needed.

If headaches become frequent (>15 days/month), prophylactic treatment is indicated. Non-pharmacologic approaches include regular aerobic physical exercise (walking, jogging, or swimming for 45–60 min 5 times a week), gentle neck stretching exercises, and psychological treatments. Psychological therapy includes relaxation techniques in training the patient to recognize the signs of tension and relax to abort the headache and cognitive-behavioral therapy that teaches the patient to identify and modify thoughts and beliefs which generate stress and aggravate the headaches. A combination of psychological therapy and pharmacological therapy with a tricyclic drug has been shown to be superior to either alone.

Randomized controlled studies have shown several medications taken daily are beneficial in reducing the severity of the headaches and their frequency. The first-line drug is a tricyclic antidepressant (nortriptyline or amitriptyline) in low to moderate daily doses. It is usually started at a low dose at night (because of sedation) and slowly increased over weeks. It takes several weeks for the prophylactic effect to begin with a reduction in the number and severity of the TTH. Second-line medications include venlafaxine and possibly topiramate and SSRI medications. Prophylactic medications are usually given for 6 months and slowly tapered. Attempt to reduce the amount of acute analgesics to minimize the rebound headache effect.

A 12-year European follow-up study reported 45% had a complete remission of their frequent episodic and chronic TTH with 84% considered to have made a significant improvement. This is in keeping with the data showing the prevalence of TTH reduces with aging. Nevertheless, it is important to explain to the patient they can expect to develop some recurring headaches, and they need to develop their own patterns of coping with the recurrent headaches.

Migraine

Introduction

Migraine headaches are a common and often debilitating disorder that affects 28 million Americans with a prevalence rate of about 18% for adult women and 6% of men. The syndrome is characterized by recurrent attacks of headache that vary widely in intensity, duration, and frequency. It is associated with varying amounts of nausea, vomiting, and photophobia. Migraine usually begins during adolescence or young adulthood but an increasing number of children are recognized to experience occasional migraines during ages 5–10 years. After the age of 50 years, migraines begin to subside spontaneously. There is a dominant genetic predisposition to migraines but specific genes have not been identified.

Patients who experience auras before the headache are classified as *migraine with aura* or *classical migraine*. Patients without auras are classified as *migraine without aura* or *common migraine*. Patients who develop prolonged auras or headaches with neurologic signs that persist are classified as *migraine with prolonged aura* or *complicated migraine*. Occasional patients will experience a visual aura without the headache (*migraine equivalent*).

Pathophysiology

The etiology of migraine is unknown and its pathophysiology is incompletely understood. Early theories focused on intracranial blood vessels that were thought to vasoconstrict during the migraine aura and then to dilate during the headache. There is now considerable evidence that active vasoconstriction is not the cause of the aura but extracranial arteries do dilate during the headache phase. A second theory focused on brain changes as the etiology of migraine. The current theory combines both and is called the neurovascular or trigeminovascular theory. This theory focuses on the roles of meningeal blood vessels, peripheral trigeminal nerve afferent fibers with their brainstem connections, and the brain in producing a migraine.

About 15 % of migraine headaches begin with an aura, which is a direct cortical event. Considerable evidence finds that the spreading cortical depression of Leao begins with cortical hyperexcitability and depolarization primarily of occipital cortex neurons in one hemisphere that slowly advance at 2–5 mm per minute accompanied by localized hyperemia lasting up to 4 min. The hyperpolarized neurons then become relatively depolarized triggering a spreading oligemia region lasting 1–2 h that can be detected by neuroimaging. These visual cortex changes correlate with the visual symptoms that appear simultaneously. If the spreading depression advances into the parietal lobe, patients may develop paresthesias of the contralateral hand and face and even difficulty concentrating and confusion. It is unknown what initiates the aura or how the aura triggers the headache but some scientists argue that migraine could be part of a class of channelopathies that causes intermittent CNS signs such as seizures, periodic paralysis, etc. However, current studies find that many patients with common migraine without aura never develop areas of cortical spreading depression.

The migraine headache phase depends on the activation of trigeminal afferents that transmit nociceptive impulses from meningeal blood vessels. The exact triggers affecting the trigeminal nerves are poorly understood but vasoactive neuropeptides, such as substance P, neurokinin A, nitric oxide, and calcitonin gene-related peptide, are released from unmyelinated trigeminal nerve axons. These vasoactive peptides may produce sterile inflammation inducing more trigeminal stimulation that then travels to the brainstem and trigeminal nucleus caudalis and finally upward to the thalamus, anterior cingulate cortex, and somatosensory cortex. Serotonergic, dopaminergic, and glutamatergic systems are suspected to be involved. One theory argues that recurrent migraine headaches may act to produce central neurogenic sensitization allowing for the pain to persist for hours. Neuroimaging and sonograms show during the headache the external carotid and middle meningeal arteries commonly dilate stretching the surrounding trigeminal pain fibers to cause the pounding nature of the headache with each arterial pulsation. Central brain connections of the trigeminal nerve in the brainstem are thought to activate autonomic responses such as nausea and vomiting. Again, what process initiates the trigeminovascular system to begin the migraine or how the migraine terminates is unknown.

Major Clinical Features

Migraine attacks usually occur 1–2 times a month. There might not be a recognized trigger preceding a migraine but for many, common triggers include consumption of alcohol, excessive salt intake, menstrual periods, use of birth control pills or conjugated estrogen tablets, sleep irregularities, stress or even resolution of stress. Although certain foods are often suspected to be a trigger, controlled studies have generally not supported the suspected food.

Migraine headaches are divided into 4 phases—*prodrome*, *aura*, *headache*, and *post-headache*. Occasionally patients have a prodrome and are aware a migraine attack is coming hours before the headache begins. These vague symptoms are often described as irritability, mood changes, fluid retention, polyuria, photophobia, or unusual drowsiness.

About 15 % of patients experience an aura that begins 5 to 20 min before the headache phase.

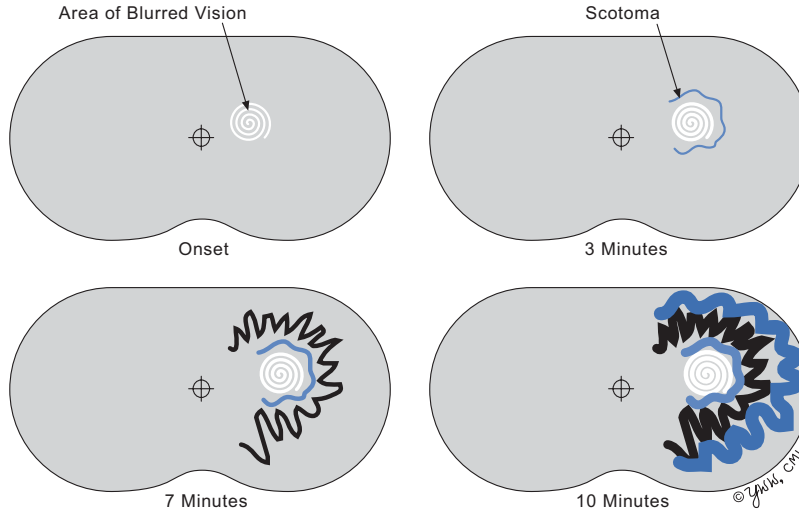

Fig 20.2 Classical migraine aura

The aura of most patients is visual but a few patients have sensory, motor, or aphasic auras. The visual aura usually begins as a vague diminishing or blurriness (not total loss) of vision (like "looking through a glass of water") with varying amounts of flickering dots of bright white or colored lights that often expand and move into the periphery of one visual field and then disappear (Fig. 20.2). A key identifier of an aura is that the flickering lights do not disappear when the eyes are closed. In contrast, most ocular causes of visual disturbance disappear with closure of the eyes.

The headache is usually unilateral (in frontal or temporal area), pounding or pulsating, and severe (Table 20.5). The time from headache onset to severe headache is usually less than one hour. About a quarter of patients will describe their severe headache as bilateral or non-throbbing. Nausea and vomiting, photophobia (increased pain from bright light), and phonophobia (increased pain from loud noises) are common. During the headache phase, some find concentration and higher cortical functioning difficult even if the pain is controlled with medication. Patients often avoid further stimulation of the central nervous system and frequently seek a dark, quiet room to rest as sleep often relieves the headache. The headache typically lasts 4–24 h, and occasionally up to 3 days. As the headache subsides, some patients experience post-migraine lingering symptoms of fatigue, difficulty in concentrating, and residual nausea for up to a day.

Some children and a few patients with migraine experience brainstem symptoms such as vertigo, dysarthria, limb incoordination, abdominal pains, and bilateral limb paresthesias that are accompanied by an occipital headache that is called a basilar migraine or vestibular migraine.

Major Laboratory Findings

The diagnosis of migraine is usually based in an adult patient by a typical history and a normal neurologic exam. There is no diagnostic test for the disease. Routine blood and CSF exams are normal. PET and fMRI scans during an acute migraine may demonstrate focal areas of mildly reduced blood flow in the occipital cortex that are not diagnostic.

Principles of Management and Prognosis

Management of patients with migraine headaches is divided into treatment of the acute headache and prevention of frequent headaches.

For many patients, the acute migraine pain responds well to simple analgesic treatmentat the time of an attack. Drugs, such as aspirin, acetaminophen, ibuprofen, or naproxen, should be taken as soon as the headacheis recognized. A variety of other drugs are aimed at inducing sleep, a potent terminator of migraine. In some patients, vomiting, nausea, and gastroparesis may prevent systemic absorption of oral medications, making oral treatment ineffective or its benefit delayed. Narcotics are difficult to use as they often diminish the headache just for the half-life of the narcotic but fail to terminate the headache. Narcotics also commonly make the patient's nausea worse.

Treatment of the headache pain dramatically improves with triptan medications that can be delivered by the subcutaneous, nasal, sublingual, and oral routes. Triptans are receptor agonists that act at the 5-HT_{1B} receptor located on meningeal blood vessels and trigeminal nerve endings. Triptans appear to inhibit neuropeptide release by presynaptic trigeminal nerve endings in the meninges, curtailing localized aseptic perivascular inflammation, and have direct vasoconstriction action of meningeal vessels counteracting the vasodilatation from the perivascular inflammation, and inhibit central neurotransmission in the trigeminal nucleus caudalis by activation of receptors on central axonal projections to the trigeminal nerve with secondary inhibition of second-order neurons of the trigeminocervicalcomplex. Triptan medication works best if administrated early in headache. Subcutaneous formulations deliver pain relief within 1–2 h in about three-fourths of patients while oral tablets deliver pain relief in 2–4 h in slightly fewer patients. There is not much difference in effectiveness of the triptan brands. Triptans currently are contraindicated in patients with complicated migraines producing hemiparesis or in patients with ischemic heart disease and should be discontinued if they elicit angina after taking the triptan. Excessive use of triptans for more than 4–6 headaches a month is associated with the development of medication overuse daily headaches.

Two older ergot alkaloids, ergotamine and dihydroergotamine, are also beneficial to terminate an acute migraine. These are serotonin antagonists and have a high affinity for the 5-HT_{1A} and 5-HT_{1D} trigeminal nerve receptors.

Most medications used for migraine prophylaxis were discovered by serendipity and their mechanisms of action are unclear. Prophylactic therapy to reduce the frequency of migraines is usually directed to patients with 3–4 or more migraines a month. Studies have shown several medications significantly reduce the frequency of migraines. Recommendations by the American Academy of Neurology and other headache organizations include divalproex sodium, topiramate, propranolol, timolol, nortriptyline, amitriptyline, and venlafaxine. The FDA has approved botulinum toxin injections for chronic migraine treatment but the mechanism of action is unclear. Prophylactic drugs must be taken daily and have a variety of mild to moderate side effects but often reduce migraine frequency by about 50%. Non-pharmacologic therapy is also beneficial and aims at encouraging daily regular aerobic exercise, keeping regular sleeping hours, and avoiding alcohol, excess caffeine, or abrupt caffeine withdrawal.

The long-term prognosis is generally good as migraines decrease in frequency beginning around age 50 years unless the patient is taking vasodilator medication for angina (nitroglycerin tablets) or estrogen for menopause. Rare ischemic strokes have been reported associated with migraine but many of these patients have **c**erebral **a**utosomal **d**ominant **a**rteriopathy with **s**ubcortical **i**nfarcts and **l**eukoencephalopathy (CADASIL) caused by mutations of the notch 3 gene.

Medication-Overuse Headache

Introduction

Medication-overuse headaches (MOH) are frequent, often daily, chronic headaches in a patient with one type of headache who overuses medications such as triptans, butalbital, opioids, and other analgesics. MOH occur most frequently in migraine patients but may develop in patients with tension-type headaches and cluster headaches. The prevalence is increasing in the USA and Europe. In adults, the prevalence ranges

around 1% but can reach over 10% in migraine patients. Today 30 to 50% of patients attending headache clinics suffer from MOH.

Pathophysiology

The pathophysiology of MOH is unknown. It is clear that heavy daily analgesic use is not the sole cause. For example, patients with rheumatoid arthritis who consume large amounts of aspirin do not develop frequent headaches unless the patient already has a known headache syndrome. The frequency of using a medication to induce MOH varies by the offending drug. Triptans, opioids, butalbital, and ergotamines are the most common triggers and often induce MOH by their use more than ten times a month for at least three months. Simple analgesics are a less common trigger usually requiring their use more than 15 days a month.

Major Clinical Features

Patients typically have a primary headache illness such as migraine, tension-type, or cluster headache for which they are taking the overuse medication. As a consequence, MOH patients typically develop a daily headache often beginning in the morning, possibly from offending medication withdrawal. The headache location often varies from day to day but frequently involves neck pain. The patient generally has non-restorative sleep and may have concomitant depression or anxiety. Autonomic features such as nasal stuffiness and rhinorrhea are common in heavy opioid usage and are often confused for a sinus condition. At times the MOH headache pattern is difficult to distinguish from chronic tension-type headaches. The problem is that these recurring symptoms encourage the patient to take more of the overuse medication.

MOH patients have an increased incidence of subclinical obsessive–compulsive disorder, mood disorders, and history of overuse of other medications or recreational drugs. There is limited evidence that patients may have a genetic predisposition to developing MOH.

The neurologic exam is normal unless the underlying illness causes the clinical signs.

Major Laboratory Findings

MOH patients typically have normal neuroimaging, electroencephalograms, and routine laboratory tests. There is no specific test to establish the diagnosis.

Principles of Management and Prognosis

There are several principles for effective management. One should educate patients about the genesis of their problem without accusing them of being addicts. The clinician should wean the patient off the medication either by slow taper or by abrupt withdrawal (unless the drug is an opioid or butalbital). Most studies have shown no differences between the two methods, so the tapering method is more often done. The challenge is to control the transiently increased daily headaches during the withdrawal. The patient can be started on prophylactic medications immediately during the withdrawal period. The choice of medications depends on the underlying primary headache cause. Finally, the provider needs to allow the patient to use acute treatment medication for severe headaches, but the dose and amount need to be carefully regulated to prevent a relapse. Use of a headache diary may help the patient adhere to the regimen and better recognize the headache improvement.

Most patients improve when weaned and appropriately treated with prophylactic medications. Relapse rates are similar whether the withdrawal is done in an outpatient or inpatient setting and range around 25% at one year.

Recommended Reading

Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol. 2010;9:807–819. (*Review of current ideas about neuropathic pain*)

Woolf C, Ma Q. Nociceptors–Noxious stimulus detectors. Neuron. 2007;55:353–64. (*Excellent review of normal and neuropathic nociceptive pain*)

Fumal A, Schoenen J. Tension-type headache: current research and clinical management. Lancet Neurol. 2008;7:70–82. (*Nice review of tension headaches and current thoughts on pathogenesis and treatment*)

Cutrer EM. Pathophysiology of migraine. Semin Neurol. 2010;30:120–30. (*Current review of what is known about migraine headaches*)

Evers S, Marziniak M. Clinical features, pathophysiology, and treatment of medication-overuse headache. Lancet Neurol. 2010;9:391–401. (*Well-written review of the status of medication-overuse headache*)

Disorders of the Vestibular System

21

A 50-year-old woman in previous good health with no history of dizziness awoke with severe room-spinning vertigo. Within minutes she became nauseated and started to vomit. She had to crawl to the bathroom as she was ataxic requiring her to hold on to a chair to keep from falling to the right. In bed she found closing her eyes reduced the intensity of the vertigo that was in a horizontal plane. Focusing her eyes on a single target helped the vertigo, and moving her head made it worse. She had no tinnitus or muffled hearing. She stayed in bed for 3 days and relied on her husband for sips of liquids. On the third day, she was hospitalized by her physician who diagnosed vestibular neuritis. She was given IV fluid rehydration, antiemetics, and a vestibular suppressing medication and was discharged the next day. Over the next 2 weeks her balance improved back to normal but rapid head movements triggered brief vertigo for a month.

Overview

Vertigo, from the Latin, "I turn," is the sensation that either the individual is moving or the environment is moving in a rhythmic back and forth sensation that is associated with nystagmus. Dizziness and vertigo are common complaints. Dizziness severe enough to interfere with daily activities ranks as the third most common complaint for which older adults seek medical attention.

Dizziness, a nonspecific term, implies a sense of disturbed relationship to the space outside oneself. Patients frequently use such words as imbalance, off-balance, swaying, floating, light-headedness, impending faint, giddiness, fuzzyheaded, reeling, and anxious to describe dizziness. The evaluation of dizziness challenges the problem-solving ability of the clinician since the causes are many. Table 21.1 lists the major causes of dizziness and vertigo. In the elderly, more than one cause is often present (multifactorial). Careful questioning is necessary to further define the type of dizziness which usually can be divided into 4 categories: Vertigo, dysequilibrium, presyncope, and other.

Vertigo, the illusion of rotation or body movement through space, implies dysfunction of the vestibular system.

Dysequilibrium is common and mainly experienced when standing and often relieved by sitting or lying down. The imbalance or unsteadiness usually develops from diminished sensory input from the proprioceptive, visual, and vestibular system or abnormal input from key motor centers, such as the basal ganglia and cerebellum.

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Table 21.1 Major causes of dizziness and vertigo

Vestibular system (25%)	*Benign paroxysmal positional vertigo*
	Meniere's disease
	Vestibular neuritis
	Chronic labyrinthine imbalance from poorly understood causes
Proprioceptive system (15%)	*Distal sensory peripheral neuropathy* (diabetes, alcohol, toxins)
	Pernicious anemia (B_{12} deficiency)
	Spinocerebellar ataxia
	Human immunodeficiency virus myelopathy
Visual system (<1%)	Recent or unrecognized diplopia or mature cataracts
	Macular degeneration or diabetic retinopathy
	Glaucoma
Brainstem/cerebellum (25%) Structural (1%)	*Infarction* (lateral medulla or midline cerebellum)
	Tumor (glioma, ependymoma, etc.)
	Degenerative (multisystem atrophy)
	Congenital (Arnold-Chiari malformation)
Metabolic (24%)	*Cardiovascular* (orthostatic hypotension, vasovagal, cardiac arrhythmia, heart failure, severe anemia)
	Endocrine (hypo/hyperglycemia, hypothyroidism)
Psychophysiologic (5%)	Anxiety with hyperventilation
Adverse drug effects (30%)	Over 150 drugs have >3% incidence of dizziness and vertigo but those listed below are the major drug types
Vestibulo-toxic drugs that cause permanent vestibular hair cell damage	*Aminoglycoside antibiotics* (*gentamycin*, kanamycin)
	Cancer chemotherapeutics (cisplatin, chlorambucil)
Central nervous system drugs	*Sedatives* (benzodiazepines, sleeping pills)
	Psychoactive (major antipsychotics, lithium, tricyclics)
	Anticonvulsants (phenytoin, carbamazepine)
Circulatory drugs	*Antihypertensives* (prazosin, ganglionic blockers, beta blockers)
	Vasodilators (isosorbide, nitroglycerin)
	Antiarrhythmics (mexiletine, flecainide, amiodarone)
	Loop diuretics (furosemide, ethacrinic acid)
Herbal medicines	Dizziness is a side effect of many herbs

(%) refers to the approximate distribution of causes.
Italic refers to the most common cause in each category

When there is a mismatch in brainstem from one or more of the key sensory systems for balance, patients feel a sense of dysequilibrium.

Presyncope is the feeling of light-headedness or of impending faint that may be associated with a feeling of unsteadiness. Some patients perspire, have palpations, and demonstrate pallor. The symptoms result from hypoperfusion, or changes in blood chemical composition to the brainstem, and are rarely a symptom of focal cerebrovascular disease. Orthostatic hypotension and cardiac arrhythmias are the most common causes.

Other causes of dizziness include medication side effects and psychiatric conditions with hyperventilation.

Normal Balance

Normal balance comes from appropriate brainstem and cerebellar integration of three sensory systems: vestibular, visual, and proprioceptive (Table 21.2). Incorrect sensory signals or inappropriate integration of the sensory signals gives rise to dizziness and vertigo.

The vestibular system comprises end organs adjacent to each cochlea (three semicircular canals (SCC), utricle, and saccule), vestibular nerves, and vestibular nuclei located in the dorsal medulla at the floor of the fourth ventricle and midline cerebellum (Fig. 21.1). The vestibular system divides into two major components. First,

Table 21.2 Components of normal balance

Vestibular system
Detects changes in gravity and adjusts body posture
Maintains eyes steady during head movement
Proprioceptive system
Knowledge of position of feet
Detection of leg and foot movement (sway)
Visual system
Detection of head movement from horizon
Feed back ("retinal slip") information on integrity of vestibulo-ocular reflex
Vestibular nuclei in brainstem and cerebellum
Integrates signals from vestibular, visual and proprioceptive systems sending information to SCC, eye muscles and cerebral cortex to make appropriate changes in posture and eye movements

the vestibulo-spinal system alters body position in response to changes in gravity. Changes in gravity location are detected by the bending of hair cells in the macula of the utricle and saccule when there is movement of otoconia (tiny calcium carbonate crystals imbedded in a gelatinous matrix). Impulses sent via the vestibular nerve to vestibular nuclei are processed and then transmitted to anterior horn cells of antigravity muscles to maintain stable body posture. Changes in posture usually occur without an individual's awareness.

Second, the vestibulo-ocular system maintains steady eye position in space during head movement. Angular acceleration is detected by one or more pairs of the semicircular canals that are located at right angles to each other. Head rotation bends SCC hair cells in the endolymph sending a change in the baseline frequency of nerve signals to brainstem vestibular nuclei. The signals are integrated resulting in appropriate signals transmitted via CN 3, 4, and 6 to move the eyes equally in the opposite direction of head rotation. Thus, during head movement, the world does not appear to move. Individuals with vestibulo-ocular reflex (VOR) dysfunction complain of vertigo when they move their head.

The visual system locates the horizon and detects head movement from the horizon. It also sends feedback (retinal slip) information to the vestibular nuclei regarding the integrity of vestibulo-ocular reflex. The visual system is comprised of eyes, optic nerves, lateral geniculate nuclei,

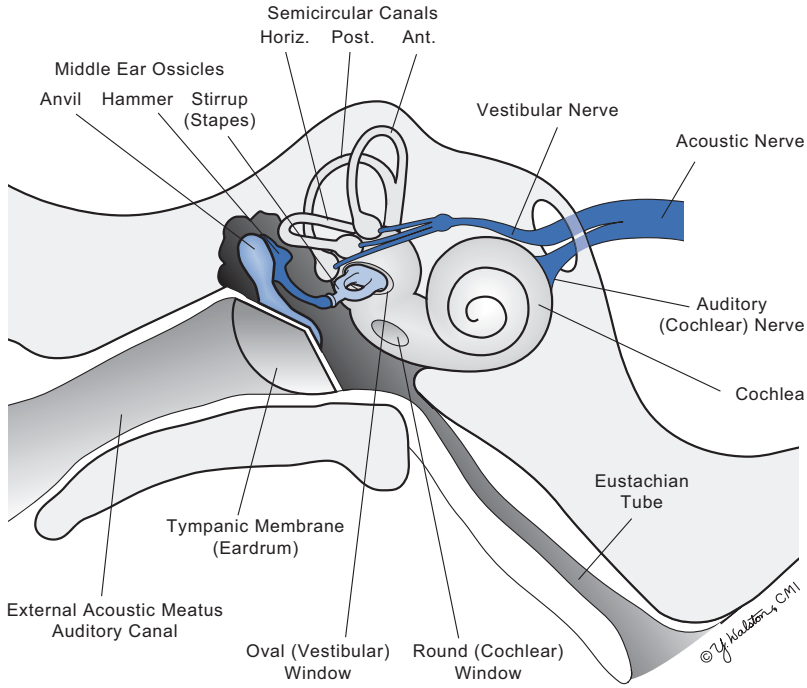

Fig. 21.1 Anatomy of the inner ear

optic radiations, visual cortexes, and pathways from the lateral geniculate bodies and occipital cortex to vestibular nuclei. The visual system seldom causes primary dizziness. However, it is the major compensating system when other sensory systems are impaired. As such, patients commonly have good balance during the day but feel off balance, dizzy, and fall at night when they have diminished vision.

The proprioceptive system delivers knowledge on the foot position detecting and compensating for leg and foot movement (sway). Joint position sensors located in the feet transmit changes in the foot position via small myelinated peripheral nerves to the spinal cord. Information then rises to the vestibular nuclei via the posterior columns. Nerve impulses sent from joint position sensors in the feet are important to maintain balance while standing and walking. Dysfunction of this system does not lead to vertigo but to a feeling of dizziness and being off balance (disequilibrium) when standing and walking that improves with lying or sitting.

In summary, vestibular nuclei integrate signals from vestibular, visual, and proprioceptive systems to trigger appropriate changes in posture to maintain balance and to alter the eye position in order to keep the world steady during head movement. Paired vestibular nuclei in dorsal lateral medulla, flocculus, and nodulus cerebellar lobes receive and integrate afferent sensory signals. Efferent signals travel via the medial and lateral vestibulo-spinal tracts to anterior horn neurons of antigravity muscles and to the sensorimotor cortex for conscious knowledge of the body position and balance.

Dizziness and vertigo are symptoms, not diseases. The key to diagnosis is to determine which system(s) is responsible for the symptoms. The history, associated symptoms, and physical exam lead to the involved system (Table 21.3). If the vestibular system is involved, additional localization questions include: Does the problem lie in the vestibulo-ocular reflex or vestibulo-spinal system and is the dysfunction peripheral in the end organs (common) or central in the brainstem/cerebellum (uncommon)?

Frequently, the history and exam are sufficient to establish the cause of the vestibular dysfunction. However, laboratory tests and neuroimaging may be helpful in some circumstances. Neuroimaging is not capable of demonstrating inner ear membranous structures such as cristae or macula and is of little value for many primary vestibular diseases. However, thin CT sections through the temporal bones can identify a temporal bone fracture, tumor, or infection that damages the inner ear. MRI can identify middle ear infections, tumors including an acoustic neuroma, masses involving the cerebellopontine angle, and structural damage to the brainstem or cerebellum. Electronystagmography (ENG) or videonystagmography (VNG) records eye movements and nystagmus in response to a variety of maneuvers similar to those done in the office (Table 21.3). ENG also determines the integrity of the horizontal semicircular canal (but not other canals, utricle or saccule) following irrigation of the external auditory canal with cool and warm water. ENG helps when one wants to determine if the vestibular dysfunction is bilateral as in drug toxicity and hereditary diseases or unilateral as in vestibular neuritis, Meniere's disease and temporal bone destruction. Examination of the cerebrospinal fluid is seldom helpful unless a meningeal tumor or infection is suspected.

Principles of Vertigo Management

Symptomatic treatment should be given for acute severe vertigo until the severe symptoms subside. Chronic administration of these drugs for mild vertigo may actually delay natural recovery and is especially sedating in the elderly. Patients with brief recurrent vertigo episodes seldom benefit from drugs. Patients with dizziness from proprioceptive, visual, or metabolic brainstem causes are not helped by antivertigo medications. Simply treating the vertigo symptom is insufficient and specific treatment should also be directed toward the etiology of the dizziness.

Table 21.3 Key elements of the office evaluation of dizziness or vertigo

History	
	Dizziness or vertigo?
	Constant or intermittent?
	Duration of dizziness (seconds, minutes, hours, days, weeks)
	Circumstances of onset (e.g. head trauma, infection, new drug usage, etc)
	Triggers or exacerbating factors (head movement in particular direction, diabetic missing meals, getting out of bed, etc)
	Is the course of vertigo improving, stable, or worsening?
	Syncope? (if yes, problem is not dizziness or vertigo)
Associated diseases, signs and symptoms	New hearing loss or tinnitus—vestibular
	Diplopia, new glasses, cataracts—ocular
	Pain, numbness or paresthesias in feet, bilateral leg weakness—proprioceptive
	Facial weakness, numbness, stiff neck, unequal pupils, diplopia—brainstem, structural
	Diabetes mellitus, hypothyroidism, cardiovascular disease—brainstem, metabolic
Exam	
Vestibulo-ocular system	Vestibulo-ocular reflex test: subject looks at distant target while slowly rotating the head horizontally or vertically. An abnormal test is when target moves and examiner sees late saccades to catch up with target Head shaking test: subject rapidly rotates head horizontally (like saying "no") for ten cycles and then looks forward. Abnormal test is horizontal nystagmus present after stopping head shaking and patient feeling dizzy Dix-Hallpike maneuver: Sit patient on exam table with back towards the end. Turn head 45 degrees laterally and rapidly lay patient down with head hanging below the table for 30 seconds. Abnormal test is presence of directional-rotary nystagmus often after a short delay with subject reproducing their dizzy symptoms
Vestibulo-spinal system	Tandem gait: subject walking a straight line with feet in front of each other. Abnormal test is when they sway and side step. Normal test suggests system is intact but abnormal test has many causes including orthopedic leg problems, proprioceptive or cerebellar dysfunction Romberg test: subject asked to stand with feet together with eyes open and closed. Abnormal test is when they can stand with eyes open but not closed and implies dysfunction in proprioceptive or vestibular system
Nystagmus (described in direction of the fast phase)	Slow phase is from vestibular activity and fast phase is from cerebral cortex action to correct slow phase Nystagmus from vestibular end organ dysfunction is horizontal or direction-rotary occurring in mid position or 45 degrees off center that is worsened by removal of fixation (such as by Frenzel +30 lenses) Nystagmus from central vestibular cause is pure rotary or pure vertical, long lasting and independent of fixation Gaze evoked nystagmus is symmetrical, high frequency, low amplitude horizontal nystagmus seen at end of far lateral gaze in both directions and is usually due to drugs such as alcohol, benzodiazepam, phenytoin, and sedatives
Hearing tests	Inspection of the external auditory canal with otoscope Ability to hear whispers or finger rubs in each ear and hear low frequencies such as 128 cps tuning fork If hearing loss, determine if sensorineural (air conduction greater than bone conduction) or middle ear conductive (bone conduction better than air conduction)
Proprioceptive system	Position and vibration sensitivity in feet Romberg test and tandem gait
Visual system	Extraocular muscle exam for diplopia Simple visual acuity Fundoscopic exam for cataracts
Brainstem and cerebellum	Cranial nerve exam (especially CN V, VII, IX)
Cardiovascular	Heart rate and rhythm and presence of murmurs Lying and standing blood pressure
Pulmonary	Respiratory rate resting and with some exercise Auscultation of lungs

Benign Paroxysmal Positional Vertigo

Introduction

Benign paroxysmal positional vertigo (BPPV) or benign positional vertigo is the most common type of vertigo with about 2.5 % of adults experiencing it at some point in their lives. Overall the incidence is 60/100,000 individuals/year but the incidence rises to 120/100,000/year in individuals over age 50 years. Most cases develop from peripheral SCC dysfunction but a few are of the central brainstem origin.

Pathophysiology

The signs and symptoms of BPPV develop from abnormal movements of endolymphatic fluid in a posterior semicircular canal due to the presence of agglomerated debris. In most cases, the debris is otoconia breaking loose from the macula of the utricle. Gravity causes loose otoconia to fall downward into the posterior SCC (Fig. 21.2). With rotation of the head in a vertical plane, the debris in one SCC briefly alters the dynamics of the vestibulo-ocular reflex in one SCC compared to the opposite side causing transient vertigo.

Major Clinical Features

Most patients experience transient vertigo lasting less than 30 s when rotating their head upward (i.e., to place an object on a high shelf) or downward (i.e., to tie their shoes). The sensation is unexpected and often disconcerting to the patient. There is no associated nausea, vomiting, hearing loss, tinnitus, or other neurologic signs. Attacks occur 1–5 times a day. If the movement that precipitated the episode is repeated several times, the vertigo fatigues—becoming less intense, shorter in duration and then enters a refractory period for hours when the movement does not trigger dizziness. About 20 % of cases follow minor head trauma but most have no recognized precipitating factor.

Between attacks, the patient is asymptomatic and has normal balance and coordination. The Dix-Hallpike maneuver, performed in the office, can often trigger their vertigo (Fig. 21.3, Table 21.3). The maneuver should reproduce the

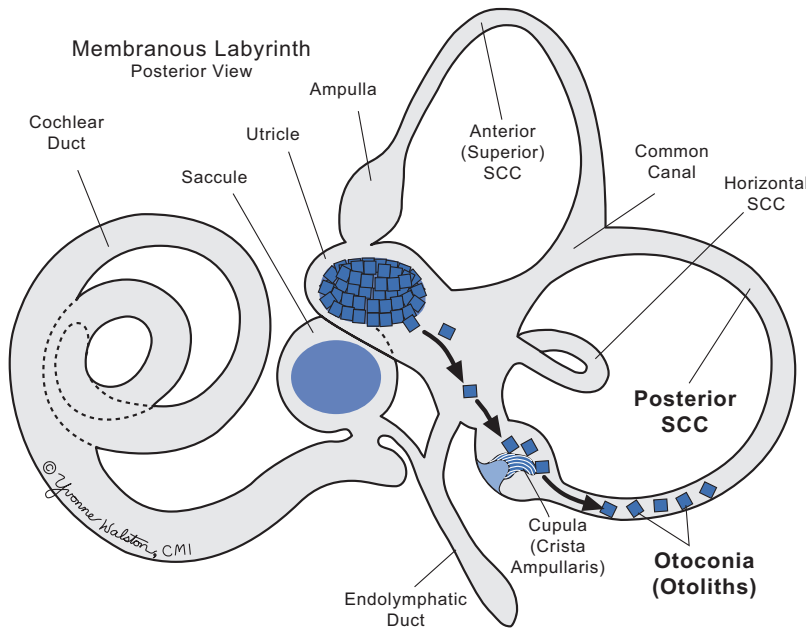

Fig. 21.2 Benign paroxysmal positional vertigo

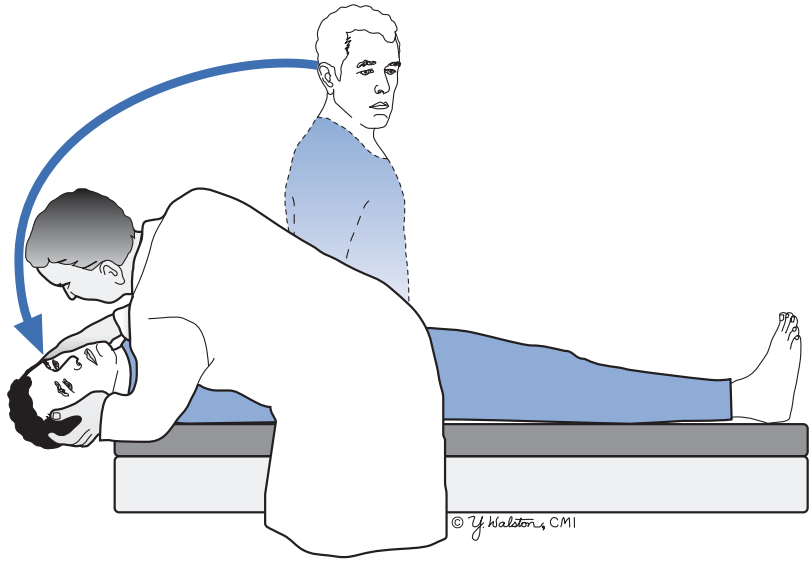

Fig. 21.3 Hallpike maneuver

patient's vertigo symptoms. The examiner looks for directional-rotary nystagmus to appear 1–5 s after the patient's head is hanging below the table. The diagnosis of BPPV is made based on a characteristic history and a positive Dix-Hallpike maneuver.

Major Laboratory Findings

Neuroimaging and ENG tests are not helpful and are normal.

Principles of Management and Prognosis

Most episodes of BPPV spontaneously resolve within 1–2 months but a few can persist for prolonged periods. In over two-third of patients, BPPV can be terminated or greatly improved by the otoconia-repositioning maneuver or Epley maneuver. In this maneuver, the posterior SCC canal debris moves by gravity around the SCC to deposit back in the utricle where it is then absorbed. This is accomplished by repeating the maneuver with the ear side down that triggered the vertigo (Fig. 21.4). Over a period of 2 min, the head is held in this position, slowly rotated to midline, then rotated to the opposite side, and finally the patient is rotated to a sitting position. The otoconia-repositioning maneuver eliminates or reduces BPPV over 60% of the time. However, recurrences may develop presumably due to more otoconia falling into the posterior SCC.

Vestibular Neuritis

Overview

Vestibular neuritis is considered the second most common cause of vertigo in the elderly. Cases occur equally in both sexes with an increasing incidence after age 40 years.

Pathophysiology

Available histopathology is limited but has shown degeneration of the superior vestibular nerve branch going to the horizontal canal with associated neuronal death in parts of the vestibular ganglia. The etiology is unclear but the vertigo arises from a mismatch of horizontal semicircular canal signals reaching the vestibular nuclei.

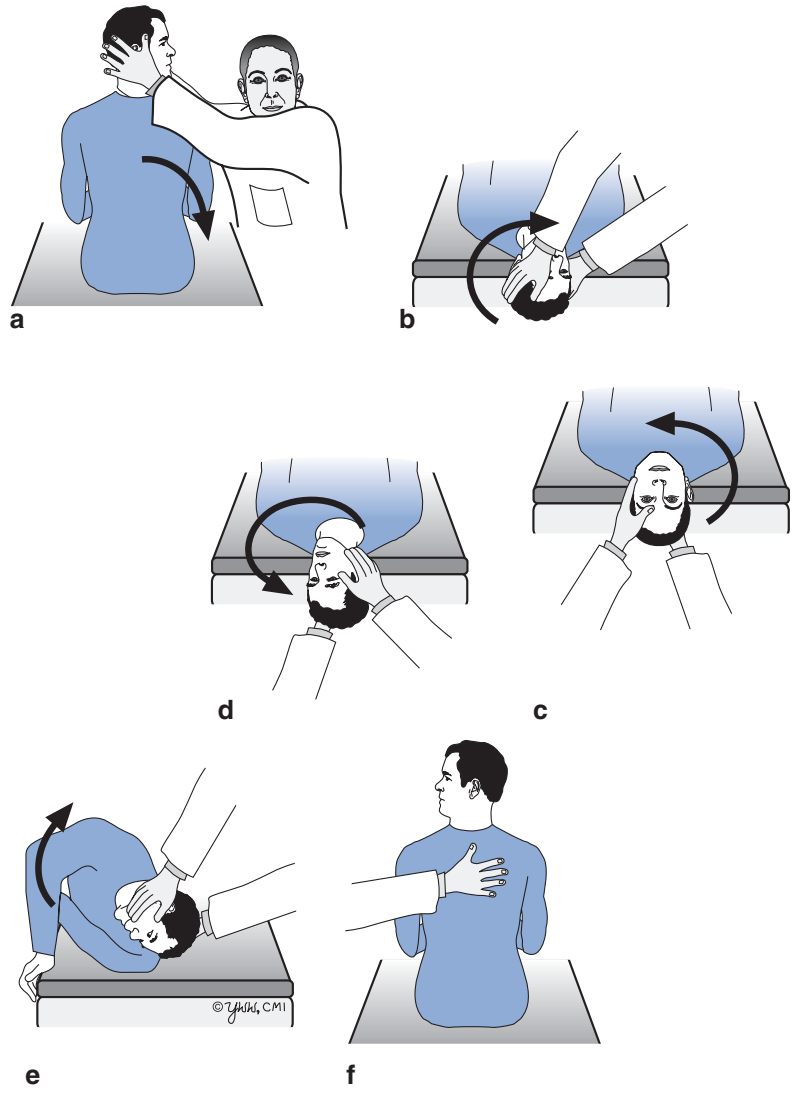

Fig. 21.4 Epley maneuver

Clinical Features

About half the patients describe an upper respiratory illness in the preceding 2 weeks. The onset is abrupt without warning and the vertigo is usually severe (see case history in the Introduction). Patients note a horizontal spinning sensation that causes severe ataxia sufficient to prevent walking without falling. Nausea and vomiting are common and often severe. There is no objective hearing loss but some patients note fullness in one ear. On exam, the patients typically have a horizontal nystagmus with the slow phase toward the involved ear since this is a destructive disease. Since nystagmus is named according to its quick phase (the cortical recovery phase), the nystagmus would be described as away from the involved ear. Falling and tilting are usually toward the side of the involved ear.

Major Laboratory Features

If caloric tests are performed in a vestibular laboratory, there usually is paresis or hypofunction of the horizontal semicircular canal on the involved

side. Neuroimaging is usually normal as is the CSF.

Management

Since the etiology is unknown and the illness is self limited with spontaneous recovery, management is mainly symptomatic. Reassurance that the patient does not have a stroke helps reduce anxiety. Patients often require IV fluid rehydration and IV administration of antivertigo and antiemetics such as promethazine. Early administration of corticosteroids such as methylprednisolone or prednisone is reported to shorten the duration of symptoms but not the extent of clinical recovery. Addition of acyclovir does not offer improvement.

The illness is self-limited as the severe vertigo ends in a few days and symptoms subside over 1–3 weeks. In general, patients should reduce and stop antivertigo medication as soon as they can tolerate the vertigo since these drugs may slow the rate of spontaneous recovery. Recurrences are uncommon but patients may note occasional brief positional triggered vertigo spells for a month.

Meniere's Disease or Endolymphatic Hydrops

Introduction

Meniere's disease or endolymphatic hydrops is less common than BPPV but more incapacitating. The yearly incidence is about 15 cases per 100,000 depending on the definition used. The illness affects both sexes and most ages except children with the peak from 40 to 60 years.

Pathophysiology

Temporal bone studies demonstrate characteristic endolymphatic hydrops with pathological expansion of endolymphatic fluid at the expense of the perilymphatic system. Secondary endolymphatic membrane ballooning and distortions develop in the cochlea, utricle, and saccule. Evidence of rupture with healing of endolymphatic membranes is common. There is variable damage to cochlear or vestibular hair cells depending of the duration of the disease.

Acute attacks are thought to occur when an endolymphatic membrane ruptures, transiently allowing potassium-rich endolymph and potassium-depleted perilymph to mix. The resulting abnormal stimulation of vestibular and cochlear axons leads to permanent hearing and vestibular function loss over time.

The etiology is unknown in over 90 %. The remaining cases appear as delayed consequences of otitic syphilis, mumps labyrinthitis, head trauma, or meningitis. Five percent of patients have a family history of Meniere's disease.

Major Clinical Features

Abrupt attacks of vertigo develop without warning or occasionally are preceded by an aura of increasing tinnitus, fullness in the ear with muffled and diminished hearing on that side. No triggers are known. The vertigo, characterized as a horizontal spinning sensation, is accompanied by horizontal nystagmus, nausea and often vomiting. Since Meniere's disease is irritative in nature with the nystagmus toward the involved ear since the slow phase of the nystagmus comes from the inner ear is away from the involved ear. The severity of vertigo varies by attack but is often severe enough to prevent walking. Associated tinnitus (roaring or whistling sound) and diminished or muffled hearing affect the involved ear. Occasional patients suffer from sudden brief drop attacks where they feel they are pushed to the floor. Vertigo attacks usually last up to several hours but the patient may feel exhausted and unsteady for a day. The typical frequency of attacks is a few times a month with a range of twice a week to twice a year. The patient slowly and progressively loses hearing in the involved ear.

Major Laboratory Findings

The progressive hearing loss begins with low frequencies (peak loss at 250–500 cycles per second) such that speech discrimination (which is 500–3,000 Hz) is affected early. As the disease progresses, all frequencies are lost. Finding low frequency hearing loss is helpful as most other cases of acquired sensorineural hearing loss, such as hearing loss in elderly (presbycusis), involve high frequencies. In over 50%, caloric testing demonstrates a diminished or absent caloric response in the involved ear. Neuroimaging and CSF are normal in idiopathic cases.

Principles of Management and Prognosis

There is no cure for the disease. Acute vertiginous attacks are difficult to symptomatically treat as nausea and vomiting prevent use of oral medications and the vertigo often ends in 30 min–4 h. Rectal medications, such as promethazine suppositories, lessen the vertigo and nausea but will make the patient sleepy. Since the clinical course and frequency of attacks are variable, determination of effective drugs to reduce the frequency of attacks has been difficult. The most commonly administered treatments are aimed to reduce production or enhance absorption of endolymph and include low salt diets and daily diuretics (hydrochlorothiazide or acetazolamide). However, studies have yet to confirm clear benefit in preventing attacks. In patients with frequent severe attacks who fail medical treatment, gentamycin locally instilled in the middle ear through the tympanic membrane has been successful in destroying vestibular hair cells with the reduction of attack severity but at the price of variable loss of hearing in that ear in up to 30% of treated patients. Surgical approaches to shunt endolymph or destroy vestibular nerves are unproven.

Spontaneous vertigo attacks usually subside over 5–10 years when the disease progresses to where the patient is deaf and has no caloric response. Unfortunately, 15% of patients develop Meniere's disease in the opposite ear.

Video Legend

This video shows the office examination of the vestibular system in a healthy 30 year-old woman

Segment 1: Vestibulo-Ocular System Exam
- Dix-Hallpike
- Epley Manuever
- Head shaking test

Segment 2: Eye Movement Exam
- Nystagmus evaluation
- Smooth pursuit eye movements
- Fistula test: evaluation for nystagmus
- Valsalva: evaluation for nystagmus

Recommended Reading

Baloh R. Dizziness, hearing loss, and tinnitus. Philadelphia: FA Davis; 1998. (Excellent straightforward book on causes of vertigo)

Fife TD. Benign paroxysmal positional vertigo. Semin Neurol. 2009;29:500–8. (Excellent review of this syndrome and the Epley maneuver)

Goddard JC, Fayad JN. Vestibular neuritis. Otolaryngol Clin North Am. 2011;44:361–5. (Brief up-to-date review)

Gates GA. Meniere's disease review 2005. J Am Acad Audiol. 2006;17:16–25. (Good clinical, pathophysiology, and management review)

Sleep Disorders

22

A 22 year-old previously healthy college student began developing irresistible urges to sleep during his classes, often falling asleep for 20 min at a time. He was doing well in his classes, not taking recreational drugs, and had normal sleep hours, but soon found his nocturnal sleep becoming fragmented. About 1 month later he suddenly collapsed among a group of friends laughing at a joke. He did not lose consciousness and found himself on the ground weak with garbled speech for a minute. These attacks recurred every few days whenever he expressed laughter or anger. One morning he awoke with a vivid dream and felt paralyzed for several minutes. He went to the student health center where he was initially thought to be having seizures. He subsequently was referred to a neurologist who diagnosed narcolepsy with cataplexy.

Overview

Sleep is a fundamental behavior found in the entire animal kingdom and is a state that alternates with wakefulness. It occurs in a recumbent posture, has a low level of motor output, a raised threshold to respond to sensory stimulation, and dreaming (Table 22.1). In contrast, wakefulness is characterized by an active and deliberate sensorimotor discourse with the environment. Sleeping is a precisely orchestrated complex state characterized by mutually exclusive phases. In a typical night there are 4–5 cycles of nonrapid eye movement (NREM) and rapid eye movement (REM) sleep. The NREM stages of sleep (stages 1–4) have distinctive electroencephalogram (EEG) characteristics. During NREM sleep, there is usually little movement, dreaming is rare, and muscles are not paralyzed. Stage 4 sleep is considered the deepest stage of sleep (hardest to be aroused), has many slow delta waves seen on the EEG, and occurs mainly in the early hours of sleep.

REM sleep is characterized by: Rapid and random movement of the eyes, dreaming often with vivid dreams, low muscle tone, and a rapid, low-voltage EEG. REM sleep in adult humans typically occupies 20–25 % of total sleep or about 90–120 min of a night's sleep. In a normal night, REM sleep does not begin during the first hour of sleep and is of shortest duration early in sleep with longer duration toward morning.

The neurophysiology of sleep is complex and is considered here only in brief overview. Key brain anatomy for generating REM sleep is in the pontine tegmentum and adjacent portions of the midbrain. Destruction of these areas prevents REM sleep. These brain areas and the hypothalamus contain REM-on neurons that are maximally active during REM sleep and REM-off neurons which are minimally active during REM sleep. During REM sleep; REM-off neurons stop firing and thus fail to stimulate motor neurons, which in turn causes REM muscle atonia. As such, limb and face muscles do not move but the diaphragm

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Table 22.1 General characteristics of sleep and wakefulness

	Non REM sleep	REM sleep	Wakefulness
Sensation and perception	Absent or dull	Vivid but internally generated	Vivid but externally generated
Movement	Limited, episodic and involuntary	Dream commanded	Continuous and voluntary
Thought	Uncommon	Illogical	Frequent, logical, and additive
Electromyogram	Minimal activity, random	Suppressed motor activity except for diaphragm	Active and purposeful to specific muscles
Electroencephalogram	Varies with stage of non REM sleep	Active and variable	Mixed frequencies with alpha background
Possible evolutionary functions	Conservation of energy, repair of injury, defense from predators, heat saving	Memory and motor learning consolidation	Active learning, communication, working, eating, mating

functions normally. In addition to muscle atonia, the heart rate and respiratory rate become irregular similar to behavior during the waking hours. In addition, the body temperature is poorly regulated and falls toward environmental temperature. Erections of the penis occur called nocturnal penile tumescence.

NREM sleep is generated by neurons in the preoptic region of the hypothalamus and adjacent basal forebrain. Stimulation of these regions produce sleep onset and in contrast lesions in the same area produce insomnia.

Neurons in the posterior hypothalamus are important in maintaining the waking state. These neurons are tonically active during wakefulness, greatly reduce their discharging in NREM sleep, and are almost silent in REM sleep. Neurons that fire in a similar profile are also present in the locus coeruleus, raphe nuclei, and hypocretin containing neurons of the hypothalamus.

Our body maintains many daily rhythms involving physiological and behavioral processes that are controlled by a network of circadian clocks linking the brain and peripheral organs. Fundamental circadian rhythms have several components: Photoreceptors and visual pathways that transduce photic entraining information, pacemakers that generate a circadian signal, and output pathways that couple the pacemaker to effector systems.

The master clock in our body is located in the suprachiasmatic nuclei (SCN) of the hypothalamus. The SCN clock is autonomous and spontaneously cycles about every 24 h. However, it receives exogenous input to modify it to follow environmental time whose daylight changes by season as well as other factors such as mealtime, locomotor activity, and chronobiotic drugs. However, the most efficient synchronizer is the daily light–dark cycle. Specific wavelengths of blue light (roughly 460–480 nm) are detected by a newly discovered photopigment, melanopsin, which is present in a small percentage (1–2 %) of the retinal ganglion cells. The axons of the melanopsin-containing retinal ganglion cells project directly to the suprachiasmatic nuclei (SCN) via the retinohypothalamic tract in the optic nerve so the visual cortex is not involved.

Critical to afferent control of circadian rhythms of other tissues is the pineal gland. This gland is an unpaired neuroendocrine organ situated in the midline of the brain. Its primary function is to transduce light and dark information to the whole body physiology via release of the hormone melatonin. The light–dark cycle of the pineal gland is under the control of the SCN via a multisynaptic pathway that eventually terminates on pinealocytes. Amazingly, this pathway travels down to the thoracic sympathetic neurons in the intermediolateral cell column. The signal then exits the spinal cord and travels back up external sympathetic nerves to innervate the pineal gland. Release of norepinephrine via this pathway onto pinealocytes, which occurs during the night, stimulates the synthesis of melatonin. Melatonin is then rapidly discharged into the blood vascular

system and possibly also into the cerebrospinal fluid of the third ventricle and acts on cells in many organs including SCN neurons that contain melatonin receptors MT1 and MT2. Thus, the pineal gland releases melatonin only at night and not in daylight.

Many parts of the brain and systemic organs also have circadian oscillators that are under the control of multisynaptic SCN axons and melatonin. Examples of circadian rhythms are body temperature, potassium excretion, and several pituitary hormones (prolactin, growth hormone, thyroxin, and adrenal corticosteroid secretion).

During wakefulness, neuronal activity from the brainstem ascending reticular activating system sends signals to the thalamus and onto the cerebral cortex. This input results in nonrhythmic cortical activity, stimulating behavioral arousal that is stimulus dependent, and producing a desynchronized EEG with tracings appearing almost random.

The onset of sleep is produced by GABA-ergic neurons located in the basal forebrain, anterior hypothalamus, and medulla that inhibit the ascending reticular activating system and suppress the thalamocortical activity. Hypocretin (or orexin) neurons located in the lateral hypothalamus are important in regulating sleep and wakefulness. Hypocretin neurons project widely to ascending reticular activating system neurons as well as other parts of the CNS. The normal hypocretin system inhibits REM sleep, promotes wakefulness, and stimulates feeding and motor activity.

In summary, normal sleep wake cycles are governed by SCN output and melatonin from the pineal gland producing the sleep circadian rhythm. However, the sleep circadian rhythm can be temporarily influenced by the duration of prior wakefulness. The longer a person is awake, the greater the tendency to sleep. Aging also affects sleep patterns. Babies and children have longer normal sleep times (8–10 h) while older adults tend to sleep less (often 6 h a night) and normally have 3–6 transient nocturnal periods of wakefulness.

General Disturbances of Sleep

Sleep disturbances are common and may be transient or persistent due to a variety of factors. A chronic sleep disorder lasting more than 3 months may be *insomnia* (inability to fall asleep or maintaining sleep the entire night) or *hypersomnia* (excessive daytime sleepiness). Insomnia has many medical and psychological causes. Psychological insomnia is common and often follows a stressful life event that triggers poor sleep that can become chronic. Excessive napping and frequent work shift schedule changes can also provoke insomnia. Medical illnesses associated with sleep disturbances are listed in Table 22.2. Management of transient insomnia is often successful with short time usage (less than 1 month) of hypnotic drugs but chronic insomnia is difficult to manage. Long-term use of hypnotic drugs is generally ineffective. Cognitive behavioral therapy tailored for the type of sleep disturbance has been shown to be more effective.

Hypersomnia is excessive daytime sleepiness and falling asleep inappropriately during the day when not simply tired, fatigued, or lethargic affects about 5% of adults. The most common disease associated with hypersomnia is obstructive sleep apnea and the most common neurologic diseases are restless leg

Table 22.2 Common medical causes of sleep disturbances

Acute or chronic pain from arthritis, low back pain, chronic headaches, fibromyalgia, burning sensory neuropathy
Cardiac and vascular disease such as nocturnal angina, congestive heart failure, and vascular insufficiency producing nocturnal limb pains
Pulmonary disease from chronic obstructive pulmonary disease (COPD), sinusitis, and chronic cough
Gastrointestinal disorders such as gastroesophageal reflux and peptic ulcer pain
Endocrine disease such as menopause symptoms, uncontrolled diabetes, and hypothyroidism
Urinary disorders with incontinence
Neurologic disorders such as Parkinson's disease, post stroke, nocturnal seizures, neuromuscular degenerative disease, and dementia

syndrome and narcolepsy. However, medical conditions listed in table 22.2 can also result in hypersomnia.

Obstructive sleep apnea with chronic headaches

Introduction

Obstructive sleep apnea (OSA) with excessive daytime sleepiness occurs in 4% of men and 2% of women. The prevalence increases with age over 60 years, obesity (body mass index greater than 30), or having a thick neck girth. OSA is an important medical condition that has been associated with hypertension, atherosclerosis, cardiac arrhythmias, atrial fibrillation, diabetes, nocturia, chronic headaches, and gastrointestinal reflux.

Pathophysiology

Recurrent episodes of partial or complete upper airway collapse produce difficulty in breathing, frequent sleep arousals, and hypoxemia. The intermittent hypoxia from the apnea is recognized to activate proinflammatory cytokines and adhesion molecules contributing to atherosclerosis. The hypoxemia and arousals trigger sympathetic overactivity producing hypertension, cardiac disease, and arrhythmias. The exact mechanism that links OSA and chronic headaches and insulin-resistant diabetes is not yet known.

Major Clinical Features

In this disorder, the patient or spouse gives a history of severe snoring interspersed by long gaps of nonbreathing (apnea). Breathing is restored with a loud gasp—often awakening the individual. Patients awaken from a normal length sleep unrefreshed with a dry mouth and often a headache. It is the chronic headache that leads many patients to seek medical attention. OSA most often develops in overweight males but may occur in either sex who have a narrow palate due to a receding chin, large tongue, or enlarged tonsils that cause a respiratory obstruction.

Major Laboratory Findings

A polysomnogram is the best diagnostic test for detecting OSA. It can be done in an overnight sleep laboratory or at home using a portable diagnostic unit. The polysomnogram typically measures an EEG, electrocardiogram, extraocular eye movements, EMG, airflow oximetry, nasal pressure, esophageal pressure, body position, snoring sounds, and rib/abdominal movements. The number of OSA episodes with and without hypoxemia is recorded. Apnea is considered as a 90% or greater decrease in airflow that lasts more than 10 s despite ongoing respiratory effort. Hyponea is a reduction of airflow of 30% from baseline with a 4% desaturation, or a 50% reduction in airflow with a 3% desaturation, or airflow reduction triggering an arousal. In general 5 or fewer events per hour are normal and more than 15 events per hour is serious OSA.

Principles of Management and Prognosis

Key factors in successful treatment of OSA are weight reduction to optimal weight and use of a continuous positive airway pressure (CPAP) machine with a face mask to sleep at night. CPAP delivers a positive stream of air pressure that essentially stents open the airway. Only occasionally are oral appliances or surgical intervention indicated. Successful management of OSA can reduce hypertension, cardiac disease, strokes, and insulin resistance. Elimination of the chronic headaches due to OSA is difficult with conventional medications unless the patient adheres to the above two methods for OSA management.

Narcolepsy

Introduction

Narcolepsy comes from the Greek "narco" meaning numbness or stupor and "lepsy" meaning fit or seizure. Narcolepsy is a chronic neurologic sleep disorder without a known cure that is characterized by excessive daytime sleepiness, disturbed nocturnal sleep, cataplexy, and elements of rapid eye movement sleep. It affects 1 in 2,000 individuals with a prevalence close to 0.04%. However, less than 50% of patients are likely to have been diagnosed.

Pathophysiology

Narcolepsy is due to a 90% or greater loss of hypocretin (or orexin) neurons located in the lateral hypothalamus. The loss of these neurons is thought to occur after infancy (since babies and young children do not develop narcolepsy) and maximizes around late teens and early twenties corresponding to the onset of narcolepsy in most patients. The loss of hypocretin neurons is specific without related death of adjacent hypothalamic neuron populations. To date, no inflammatory markers have been identified to explain the cause and no antibodies to hypocretin have been recognized. However, the frequency of human leukocyte antigen (HLA), DQB1*0602, is highly increased (80–90%) of patients with narcolepsy with cataplexy, but the importance is unclear as it can be found in up to 30% of normal individuals. Currently it is hypothesized that this leukocyte antigen does not directly cause narcolepsy but may create a predisposition to other unknown causative factors.

Hypocretin neurons project densely within the hypothalamus and widely to different regions of the cortex, basal forebrain, brainstem, and spinal cord. The neurotransmitter hypocretin mediates the state of arousal and wakefulness as described above and may mediate other functions such as the body's homeostatic need for food intake and the regulation of obesity. Hypocretin neurons fire maximally during active waking and are involved in maintaining skeletal muscle tone. Loss of these neurons results in disregulated wakefulness and excessive daytime sleep producing narcolepsy, and altered suppression of REM sleep behavior during wakefulness, resulting in cataplexy.

Major Clinical Features

There are four major clinical features of narcolepsy with cataplexy: (1) Narcolepsy, (2) cataplexy, (3) sleep paralysis, and (4) hypnagogic hallucinations. Seventy percent of patients have narcolepsy with cataplexy and only a few patients develop narcolepsy without cataplexy. Symptoms usually begin in the late teens and early twenties with excessive daytime sleepiness that may develop rapidly or slowly progress over months. *Narcolepsy* occurs when patients have irresistible urges to sleep even during physical or mentally demanding tasks. The sleep episodes typically occur 3–5 times a day and last a few minutes to an hour. Patients awaken refreshed and can continue their normal activities for several hours before another sleep attack develops. Patients often develop fragmented and disturbed nocturnal sleep.

Cataplexy is the transient (seconds to 2 min), abrupt, and bilateral loss of voluntary muscle tone without loss of eye movements or diaphragm movement. Current evidence suggests that REM sleep components intrude into the awake state due to absence of hypocretin. During cataplexy, the patient remains conscious. Most cataplexy attacks are partial loss of motor tone with the jaw sagging, head drooping, garbled speech, and the dropping of objects held in the hands. Severe attacks result in total loss of limb motor tone with the patient falling to the ground unable to speak. Attacks are commonly triggered by a sudden emotion—most commonly laughter. Other triggers can include anger, embarrassment, surprise, and stress. Cataplexy usually develops within months to 5 years of the onset of narcolepsy.

Sleep paralysis is often associated with *hypnagogic hallucinations*. On falling asleep or upon awakening, patients find themselves paralyzed and usually have a terrifying experience with

visual and often auditory hallucinations occurring on falling asleep or awakening when they find themselves paralyzed and unable to move or speak. The episodes usually end spontaneously within 1–10 min but may terminate when someone touches them.

A clinical diagnosis of narcolepsy is established by a clear history of excessive daytime sleepiness without other causes for at least 3 months duration and a definite history of cataplexy. Diagnostic testing can be pursued for patients who do not meet the clinical criteria.

Major Laboratory Findings

The polysomnogram can rule out other causes of disrupted nocturnal sleep and a multiple sleep latency test confirms narcolepsy by showing a sleep onset latency of less than 8 min and at least two episodes of rapid onset of REM sleep.

A CSF analysis demonstrating a hypocretin-1 level of less than 110 pg/mL also confirms the diagnosis in patients with narcolepsy and cataplexy.

A blood test showing that the patient has the HLA-DQB1*0602 haplotype can be done. While sensitive for narcolepsy, it is not that specific. Thus, its absence should make the clinician consider alternative diagnoses but a positive test does not establish narcolepsy.

Principles of Management and Prognosis

Patients should develop good nocturnal sleep patterns to minimize their daytime sleepiness. Ideally they should try to find time for 3–4 short 15-min daytime naps that will minimize the sudden sleep urges. Exercise does not prevent the sleep urges. Medication to lessen the daytime sleepiness traditionally requires stimulants such as methylphenidate or dextroamphetamine. Recently, modafinil or armodafinil (which is the dextro-enantiomer component of modafinil but a longer half-life) have become the first line drugs. Modafinil, however, has no benefit for cataplexy while the other stimulants do. Sodium oxybate, the sodium salt of gamma-hydroxy-butyrate, has been shown to be quite beneficial for both narcolepsy and cataplexy. Since this drug has been used as a street drug and labeled the "date-rape" drug, special precautions in prescribing are necessary.

Cataplexy attacks can be lessened with selective serotonin reuptake inhibitors like venlafaxine, and tricyclic antidepressants such as imipramine and clomipramine.

Restless Legs Syndrome

Introduction

Restless legs syndrome (RLS) is considered as a sleep disorder because of its circadian day–night oscillations. Clinically, it is defined as an individual with uncomfortable dysesthesias and paresthesias in the legs mainly in the evening and temporarily alleviated by movement. The diagnosis is established clinically as there are no diagnostic laboratory or neuroimaging findings. The prevalence ranges from 5 to 10 % in adults of both sexes and its characteristic dysesthesias and frequent leg movements overlap with many other medical conditions.

RLS patients are divided into two categories: Primary or idiopathic RLS and secondary RLS. Primary RLS is subdivided into early onset before age 45 years and later onset usually after 45 years of age. Early onset RLS occurs more in women and tends to cluster in families. Late-onset RLS has an equal sex distribution and a more rapid symptom progression. Secondary RLS is often associated with renal failure and uremia, iron deficiency, peripheral neuropathy, myelopathy, pregnancy, and neurologic diseases such as Parkinson’s disease and amyotrophic lateral sclerosis.

Pathophysiology

About half of patients have someone else in their family with similar symptoms and a genetic association has been identified for 10 loci in different

chromosomes but their significance is yet to be established. No genetic animal models of RLS exist at this time. Currently, the brain dysfunction triggering RLS is thought to be present in several brain locations with the basal ganglia and substantia nigra as the most likely primary sites. Low iron levels in the brain likely plays a role as individuals with iron deficiency and low serum or CSF ferritin have an increased risk of RLS. Low brain iron has been found by neuroimaging and at autopsy in the basal ganglia. Iron replacement in iron deficient individuals often cures or lessens the symptoms. Patients with a myelopathy often have RLS suggesting the spinal cord may participate in the syndrome and patients with a peripheral neuropathy often develop RLS. However, it is the dopamine pathways that appear most critical since dopaminergic agents are the main treatment and are thought to act mainly via D_2 and D_3 receptors.

Table 22.3 Restless legs syndrome diagnostic criteria

Essential criteria[a]
Undesirable dysesthesias in the legs that occur before sleep onset
Irresistible urge to move the legs when dysesthesias develop but the unpleasant sensation may not always be present
Partial or complete limb movement urges and dysesthesias are temporarily relieved by leg movements such as walking or stretching but soon return after cessation of leg movements
Urge to move and dysesthesias are worse in the evening or night and much less in the morning after sleep
No other diagnosis can account for the symptoms
Supportive criteria
Positive therapeutic response to administration of levodopa or dopamine agonist
Family history of similar clinical syndrome
Disturbed sleep pattern from the syndrome

[a] Modified from the International Restless Legs Syndrome Study group criteria

Major Clinical Features

Patients with RLS describe their abnormal leg sensations as creeping, tugging, burning, itching, tingling, aching, pulling, or like insects crawling on the leg. A key feature of RLS is that the abnormal sensation is temporarily relieved by moving the leg. The dysesthesias are bilateral but may not be symmetrical or develop simultaneously. The symptoms of RLS have a strong circadian rhythm being worse in the evening and night with significant relief in the morning. However, some younger primary RLS patients will have symptoms all day long.

Upon examination of a patient with primary RLS, the arms and legs have a normal skin appearance, normal strength and coordination, deep tendon reflexes, and normal sensation including touch, temperature, and position sensations. However, patients with secondary RLS may demonstrate findings of a distal sensory neuropathy, spasticity from their myelopathy, evidence of pregnancy in the last trimester, or clinical signs of Parkinson's disease or amyotrophic lateral sclerosis. Patients with RLS commonly complain of disturbed nocturnal sleep partly because they have difficulty relaxing to fall asleep and partly because they often experience periodic limb movements during sleep. Periodic limb movements of sleep is a movement disorder that develops mainly during sleep and is characterized by periodic repetitive mainly leg movements that are bilateral but may not be symmetrical or occur simultaneously. The muscle contractions are brief (0.5–5.0 s long), may awaken the patient, disturb their bed partner, and affect the quality of their sleep. Presently, the diagnosis of RLS is clinical and patients should satisfy the criteria in table 22.3.

Common mimics of RLS include psychiatric disorders such as major depression, attention deficit hyperactivity disorder, and anxiety and medical disorders such as akathisia, severe burning peripheral neuropathy, radiculopathy with leg pains, and chronic skin infections or rashes. These patients seldom respond to dopaminergic agents.

Primary Laboratory Findings

Routine neuroimaging and laboratory tests are usually normal. However, some patients will have low serum ferritin blood levels indicating that they have iron deficient anemia. Only rarely

is a polysomnogram indicated but it can demonstrate the restless legs occurring before sleep and periodic limb movements during sleep if they are present.

Principles of Management and Prognosis

Caffeine, alcohol, and nicotine should be avoided as they often make RLS worse. Physical activity may ameliorate symptoms in mild cases. If the patient has low blood ferritin levels, replacement with oral iron supplements may improve the patient's symptoms. However, in the absence of iron deficiency, iron supplements are not beneficial.

The most commonly used medications are dopaminergic agents, levodopa, or dopamine agonists such as ropinirole and pramipexole. Patients with primary and secondary RLS respond equally well to these drugs. Direct dopamine agonists are usually prescribed in a modest dose about 1 h before bedtime or when the evening symptoms begin to be troublesome. Over time, the dosage may need to be slowly increased. Young patients with primary RLS and symptoms throughout the day will require the drug several times a day. Occasionally, patients will not tolerate dopaminergic agents and gabapentin or short-acting opioids will be necessary.

Patients usually get a dramatic response to these agents immediately and the drugs can be continued without new adverse effects for years.

Recommended Reading

Squire LR, Bloom FE, Spitzer NC, et al. Fundamental neuroscience, 3rd edn. 2008; Amsterdam: Academic Press. (Comprehensive review of circadian rhythms and sleep wakefulness)

Siegel JM. The neurobiology of sleep. Semin Neurol. 2009;29:277–96. (Comprehensive review of the complexities of sleep)

Pevet P, Challet E. Melatonin: both master clock output and internal time-giver in the circadian clocks network. J Physiol-Paris 2011;105:170–82. (Good review of melatonin and the pineal gland in control of circadian rhythms)

Reading PJ. Sleep disorders in neurology. J Neurol Neurosurg Psychiatr. 2010;10:300–9. (Brief overall review of sleep disorders)

Cao M. Advances in narcolepsy. Med Clin N Am. 2010;94:541–55. (Excellent review of clinical features, pathophysiology, and management of narcolepsy)

Trenkwalder C, Paulus W. Restless legs syndrome: pathophysiology, clinical presentation and management. Nature Rev Neurol. 2010;6:337–46. (Nice review of restless legs syndrome)

Glossary of Common Neurologic Terms

ABCs Term referring to airway, breathing, and circulation management of a patient with impaired consciousness or breathing. Steps include ensuring airway access, delivering oxygen either nasally or via intubation if needed, and establishing intravenous access plus others.

Absence seizure or petit mal seizure Typically begins with arrest of speech and the abrupt onset of loss of awareness without loss of muscle tone or falling followed by seconds of staring without being able to communicate. The individual then becomes alert but does not recall the episode.

Accommodation Sensory nerves having dynamic firing rates that decline with time even though the stimulus is maintained.

Acute disseminated encephalomyelitis (ADEM) Complex monophasic illness, particularly in children, that often follows a recent infection or occasionally vaccination characterized by an abrupt encephalopathy often with obtundation, hemiparesis, ataxia, cranial nerve palsies, visual impairment, and seizures.

Afferent pathway Axons leading to the brain or spinal cord.

Agnosia Implies lack of knowledge and is synonymous with an impairment of recognition. An example is visual agnosia in which patient cannot arrive at the meaning of previously known nonverbal visual stimuli despite normal visual perception and alertness.

Agraphia Inability to recognize numbers/letters written on the palm or fingertips.

Alexia Acquired reading impairment that may be accompanied with writing deficits (alexia with agraphia) or without writing deficits (alexia without agraphia).

Allodynia Nonpainful cutaneous stimuli causing pain.

Amnesia Partial or complete loss of the ability to learn new information or to retrieve previously acquired knowledge.

Amaurosis fugax Transient monocular blindness. This usually comes from an internal carotid artery embolus temporarily occluding the ophthalmic artery.

Amyotrophic lateral sclerosis Progressive neurodegenerative fatal disorder affecting primarily upper and lower motor neurons in the spinal cord and motor cortex.

Amyotrophy Wasting of muscles usually from denervation.

Anal reflex Reflexive contraction of anal sphincter upon perianal sensory stimulation.

Aneurysm Abnormal dilatation or bulging of an intracranial artery wall, usually at bifurcations of the circle of Willis.

Anisocoria Unequal pupil size.

Ankle jerk Deep tendon reflex (Achilles reflex) elicited by striking the Achilles tendon at the ankle resulting in foot plantar flexion.

Anterior horn Gray matter in the ventral spinal cord that contains neurons including anterior horn cells (lower motor neurons).

Anterior root Motor nerves from anterior horn neurons from ventral spinal cord exit to point of joining mixed peripheral nerve at the dorsal root ganglion.

Anton's syndrome Lesions involving the occipital and parietal lobes that produce blindness or a homonymous hemianopia that is denied by the patient.

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Aphasia Disorder of expression or comprehension of spoken language due to dysfunction of language centers in dominant cerebral cortex or thalamus. The most common forms are Broca's aphasia, Wernicke's aphasia, and global aphasia.

Apoptosis Genetically programmed neuronal cell death that may be normal or abnormal.

Apraxia Inability to perform a learned act despite demonstrated ability to perform components of the act usually due to dysfunction of a parietal lobe. The most common forms are limb , constructional, and dressing apraxia.

Arteriovenous malformation (AVM) Abnormal blood vessel complex consisting of arteries, veins, and capillaries located in the brain or spinal cord that often hemorrhage.

Arteritis Inflammation of walls of arteries.

Astereognosis The inability to distinguish and recognize small objects based on size, shape, and texture when placed in the hand that has normal primary tactile sensory input.

Ataxia Incoordination of limb or body movements, particularly gait, often due to impairment of cerebellar function.

Athetosis Involuntary movements characterized by slow, sinuous, twisting changes of arms, legs or body.

Atrophy Wasting of muscle/s from disuse or denervation.

Aura Migraine prodrome that usually is visual with blurred visual and colored flashing lights seen with eyes open or closed that lasts 5–15 min.

Autism Childhood illness affecting language and interpersonal relationships.

Babinski sign Extensor response of the great toe with fanning of the other toes in response to stimulus on sole of foot. The extensor plantar response is normal in infants to about 9 months, thereafter reflects damage to the corticospinal tract (upper motor neuron sign).

Basal ganglia Deep gray matter nuclei of the cerebral hemispheres comprising putamen, caudate, globus pallidus, subthalamic nucleus, substantial nigra, and ? thalamus.

Bell's palsy Abrupt idiopathic peripheral seventh cranial nerve facial palsy of ipsilateral facial muscle weakness plus variable unilateral loss of tearing, taste appreciation, and ability to dampen loud noises. Recovery is usually good.

Benign paroxysmal positional vertigo Brief vertigo when rotating ones head upward or downward without accompanying nausea or hearing loss that develops from abnormal endolymphatic fluid movement in a posterior semicircular canal usually due to the presence of otoconia that broke loose from the macula of the utricle.

Biceps reflex Deep tendon reflex elicited by hitting the biceps tendon resulting in brief contraction of the biceps muscle.

Blood-brain barrier Separation of circulating *blood* from brain *extracellular fluid* due to tight junctions around all brain capillaries that do not exist in normal circulation.

Botulinum toxin Potent neurotoxin produced by Clostridium botulinum causing botulism with prolonged muscle paralysis. The enzymatic toxin inactivates proteins in the posterior synaptic side of the neuromuscular junction preventing normal release of acetylcholine.

Brachioradialis reflex Deep tendon reflex elicited by hitting the distal radius resulting in brief contraction of the triceps muscle.

Bradykinesia or akinesia Difficulty in moving despite intact motor nerves and normal muscles as seen in Parkinson's disease.

Brain abscess Localized intracerebral infection that begins as a focal area of cerebritis, developing into a collection of pus surrounded by a capsule, that is usually due to a bacteria but occasionally from a fungus or protozoa.

Broca's aphasia Motor speech disorder (expressive aphasia, nonfluent or anterior aphasia) due to dysfunction located in the dominant frontal lobe and characterized by effortful, sparse, agrammatic, halting, truncated speech with loss of normal language melody.

Bruit Sound due to turbulence of blood passing a narrow artery segment, often heard from the internal carotid artery in the neck.

Bulbar Refers to the medulla and pons of the lower brainstem.

Calcarine cortex Primary visual cortex located in the medial occipital lobe.

Caloric test Placement of warm or cool water in the external canal to evaluate eye movements from stimulation of the vestibulo-ocular reflex.

Carpal tunnel syndrome Compression mononeuropathy of the median nerve at the carpal canal of the wrist characterized by pain, tingling, and numbness involving mainly the palmar aspect of the thumb, index finger, and middle finger plus variable weakness of median nerve innervated thenar hand muscles.

Charcot-Marie-Tooth disease or Hereditary Motor and Sensory Neuropathy 1 Dominant autosomal genetic disease affecting distal myelinated axons of limbs, especially legs producing distally symmetrical polyneuropathy.

Cauda equina Lumbosacral nerve roots in the lumbar and sacral vertebral canal before the exit via neural foramina.

Caudal Lower in the neural axis as in brainstem is caudal to the basal ganglia.

Central pontine myelinolysis Demyelinating condition affecting the pons or outside of the pons (known as extrapontine myelinolysis) occurring at times of severe osmotic disruption, such as during rapid correction of serum hyponatremia.

Cerebral amyloid angiopathy Intracranial hemorrhage occurring in older adults from deposition of β-amyloid protein into the tunica media and adventitia of cortical arterioles causing the vessel walls to spontaneously rupture.

Cerebral death State of coma in which recovery of consciousness is no longer possible. Cerebral death implies death of all critical brainstem neurons for which normal life depends. It is often embedded in law allowing a physician to turn off a ventilator and individuals to donate organs.

Cerebral edema An excess accumulation of fluid in the intracellular or extracellular spaces of the *brain*. Vasogenic edema is due to breakdown of the tight endothelial junctions which make up the *blood–brain barrier* (BBB) allowing intravascular proteins and fluid to penetrate into the brain extracellular space. Cytotoxic edema has an intact BBB and is due to disruption of cellular *metabolism* leading to glial cell swelling from impairment of the sodium and potassium pump. Interstitial edema in obstructive hydrocephalus is due to disruption of the CSF-brain barrier resulting in trans-ependymal flow of CSF into the brain into the extracellular spaces and the white matter.

Cerebral Palsy Refers to a group of disorders that affect motor, cognitive, communication, and behavioral systems. It is the most common cause of disability in childhood and is due to a permanent, non-progressive brain injury.

Channelopathies Group of diseases with abnormal ion channels (pores) in cell membranes resulting from genetic disorders most often affecting muscle or brain.

Cheyne-Stokes respirations Regular cyclic oscillations of breathing between hyperpnea or over breathing and apnea.

Chorea Abnormal involuntary movements characterized by rapid flicks or jerks of limb, face or trunk muscles.

Chromatolysis Dissolution of *Nissl bodies* in a neuron cell body usually triggered by *axotomy*, *ischemia*, cell toxicity, cell exhaustion, or *virus infection*.

Circadian rhythms Physiological and behavioral processes controlled by circadian clocks that have photoreceptors and visual pathways that transduce photic entraining information, pacemakers that generate a circadian signal, and output pathways that couple the pacemaker to effector systems.

CNS Central nervous system

Cogwheel rigidity Ratchet-like increased resistance to passive movement (hypertonia)

usually found at the wrists of patients with Parkinson's disease.

Cobalamin or cyanocobalamine or (vitamin B_{12}) Water-soluble vitamin with a key role in the normal functioning of the central and peripheral nervous system (PNS) and the formation of red blood cells.

Coma Unconscious pathologic state with inability to arouse from any stimuli to produce appropriate responses.

Complex partial seizures Alteration of consciousness from bilateral cerebral hemisphere involvement often preceded by an aura or simple partial seizure with a feeling of déjà vu, fear, euphoria, or visual disturbances without loss of consciousness. Once consciousness is impaired, the person may display automatisms such as lip smacking, chewing or swallowing followed by amnesia surrounding the seizure event.

Computerized tomography (CT) Neuroimaging technique based on computer processing of data from differential attenuation of x-ray beam passing through tissue (often the skull & brain) that produces a series of slices through the tissue.

Constructional apraxia Disturbances in organizing parts of a complex object.

Continuous positive airway pressure (CPAP) machine Delivers a positive stream of air pressure via a face mask that stents open the airway preventing obstructive sleep apnea.

Corticobulbar tract Descending cortical motor tract traveling to a brainstem motor nucleus.

Corticospinal tract Descending cortical motor tract primarily from motor cortex that descends down the spinal cord to synapse at anterior horn cells or adjacent interneurons.

Countercoup Injury to brain on opposite side as head trauma

Coup Injury occurring to brain on same side as head trauma

Cowdry type A inclusion body Intranuclear collection of virus particles belonging to herpes simplex, varicella-zoster, or Epstein-Barr viruses.

Creatine kinase (CK) Also known as creatine phosphokinase (CPK), is an enzyme commonly found in muscle (especially skeletal or cardiac muscle) that leaks from the muscle into blood following muscle damage such as trauma or diseases which cause necrosis of muscle fibers.

CVA Cerebral vascular accident or stroke

Decerebrate posture Both arms and legs are extended, especially when painful stimuli are administered usually due to a lesion that separates upper from lower brainstem.

Decorticate posture Flexion of one or both arms and extension of ipsilateral or both legs due to lesion that isolates brainstem from contralateral or bilateral cortical influences.

Deep tendon reflexes (DTR) Term used to describe a monosynaptic stretch reflex elicited by tapping a tendon with resulting muscle contraction.

Delirium Conscious state characterized by confusion with agitation and restlessness, sudden movements and rapid, fragmented slurred speech.

Dementia Decline in cognitive abilities in two or more areas of cognition confirmed by mental status exam that reduces normal daily functioning which cannot be explained by delirium or psychiatric disorder deficits. Dementia may be static (i.e., from anoxia episode) or progressive (i.e., from Alzheimer's disease).

Demyelination Primarily loss of the axon nerve sheath in the peripheral or CNS with relative sparing of the underlying axon. Segmental demyelination implies that the myelin loss is patchy along the nerve leaving part of the axon with intact myelin.

Dizziness General term to describe sensation of light headedness or feeling off balance.

Doll's eyes maneuver Vestibulo-ocular reflex that is performed usually in comatose patient where the head is rotated laterally but the eyes remain stationary and do not move with head.

Dominance Term that refers to cerebral hemisphere that controls language and principle limb involved in writing, eating, and throwing.

Dorsal column nuclei Nucleus gracilis and cuneatus in the caudal medulla that contain 2nd order neuronal cell bodies for the dorsal columns in the spinal cord and usually conduct position sense and some pain and touch sensations.

Dorsal horn Dorsal (posterior) aspect of the spinal cord gray matter that contains neurons associated with peripheral afferent sensory fibers.

Dorsal root Part of the peripheral afferent sensory nerve between the dorsal root ganglia and the dorsal horn of the spinal cord.

Dorsal root ganglia Cluster of 1st order peripheral afferent sensory neuron cell bodies located at each segmental level near vertebral bodies.

Dressing apraxia Lesions only involving the non-dominant parietal lobe that produce neglect on one side of the body in dressing and grooming.

Duret hemorrhages Small areas of bleeding in the upper *midbrain* and *pons* secondary to raised *intracranial pressure* above the tentorium producing displacement of the *brainstem* downward that stretches and lacerates pontine perforating branches of the *basilar artery*.

"Dying-back" neuropathy Distal peripheral neuropathy characterized by dysfunction of the longest sensory and motor axons such as seen in a diabetic neuropathy.

Dysarthria Impaired articulation of speech that sounds like "speaking with rocks in your mouth."

Dysequilibrium Sensation of being off balance that is mainly experienced when standing. The imbalance or unsteadiness usually develops from diminished sensory input from the proprioceptive, visual or vestibular systems or abnormal input from key motor centers, such as the basal ganglia and cerebellum.

Dysesthesias Abnormal skin sensations such as creeping, tugging, burning, itching, tingling, aching, or like insects crawling on the skin.

Dysexecutive syndrome or frontal lobe syndrome Damage to the lateral prefrontal cortex produces deficits in higher level cognitive processing, such as flexible problem solving, organization and planning, mental manipulation of information, and word retrieval. Patients may lack spontaneity and often lack awareness of their deficits.

Dyskinesia Several involuntary movements of limbs or face that include chorea, athetosis, tics, and dystonia.

Dysmetria Limb ataxia in directed movement that misses the target.

Dysphagia Impairment, but not total loss, of speech expression or comprehension.

Dysphonia Difficulty in speaking, often with a low speech volume.

Dystonia Strong, sustained and slow contractions of muscle groups that cause twisting or writhing of a limb or the entire body. The contractions are often painful and may appear disfiguring. The dystonia lasts seconds to minutes and occasionally hours producing a dystonic posture.

Efferent pathway Axons leading away from the brain or spinal cord.

Electroencephalograph Instrument for recording minute electrical currents developed in the brain by means of electrodes attached to the scalp.

Electromyography (EMG) Technique for evaluating and recording the electrical activity produced by skeletal muscles during movement or nerve stimulation. EMG is performed using an electromyograph, to produce a record called an electromyogram.

Electronystagmograpy (ENG) or videonystagmography (VNG) Technique for recording electrical signals generated by eye movements or nystagmus during tests to evaluate patients with vertigo.

Encephalitis A diffuse infection of the brain parenchyma usually due to a virus but occasionally from bacteria or protozoa.

Epilepsy Illness resulting from repetitive seizures due to abnormal brain electrical activity that is often subdivided into specific seizure types.

Epley maneuver or otoconia repositioning maneuver In patients with benign paroxysmal positional vertigo, a variation of the

Hallpike maneuver is performed to roll loose otoconia around the posterior semicircular canal eliminating the recurrent brief vertigo spells.

Extraocular movements Eye movements due to contraction of extraocular eye muscles rather than muscles that govern the iris and lens.

Falx cerebri Rigid dural fold in midsagittal plane that separates the two hemispheres.

Fasciculation Contraction of fascicle (group) of muscle fibers innervated by single nerve from one anterior horn neuron that produces visible intermittent spontaneous twitching of part of a muscle but does not move the body part.

Fetal alcohol syndrome Develops in infants born to mothers who consumed alcohol during the pregnancy. The most characteristic abnormalities involve growth and mental retardation, craniofacial structure abnormalities, neurodevelopment abnormalities, and behavior problems.

Fibrillation Spontaneous contraction (invisible to the eye but detected by EMG) of individual denervated muscle fibers no longer under the control of a motor nerve.

Flaccid Limp muscle that lacks normal muscle tone.

Foramen magnum Large opening at base of skull where spinal cord and brainstem join.

Fovea Central part of macula of retina related to sharpest vision for reading.

Frenzel glasses Strong positive lenses used to detect nystagmus that inhibit patients from seeing clearly enough to fixate but allow the examiner to see the eye.

Gadolinium Rare earth compound given intravenously before magnetic resonance imaging (MRI) to detect brain areas that have a broken blood-brain barrier (such as tumors).

Ganglia Clusters of neurons all having similar function, such as dorsal root ganglia.

Generalized seizure or grand mal seizure Loss of consciousness and widespread bilateral abnormal muscle contractions Typically in a tonic and clonic fashion usually lasting one to several minutes.

Gerstmann's syndrome The inability to designate or name the different fingers of the two hands, confusion of the right and left sides of the body and inability to calculate or to write.

Glasgow coma scale Simple scoring system of unconscious patients based on eye opening, motor response and verbal response that is useful for prognosis.

Glia Term for supporting cells of CNS that includes astrocytes and oligodendroglia.

Glioma Term used for CNS tumors of astrocyte or oligodendrocyte lineage.

Glioblastoma multiforme Most common and most aggressive malignant primary *brain tumor* involving *glial cells* that is also called stage 4 glioma.

Global aphasia Acquired loss of ability to comprehend or produce verbal messages.

Gower's maneuver Seen in muscular dystrophy where an individual with weak proximal leg muscles place their hands on the knees and climbing up their thighs to stand.

Gram stain Method of differentiating bacterial species into two large groups (Gram positive and Gram negative) based on staining properties of their cell walls.

Grasp reflex Involuntary grasping of the hand when the palm is stimulated. This is normal in babies but abnormal in older children and adults, and is often associated with diffuse frontal lobe damage.

Gray matter Term that refers to gray color of part of CNS that contains neurons rather than white matter which contains mainly white myelin sheaths covering axons.

Guillain-Barré Syndrome Acute monophasic autoimmune disease involving only myelinated nerves in the PNS.Hallpike maneuver or Dix Hallpike maneuver A test to detect positional nystagmus performed by laying a patient down with their head hanging below the table.

Hammer toes Cocking up of toes like gun hammers often due to a distal sensorimotor polyneuropathy causing atrophy and weakness of intrinsic flexor toe muscles with overriding pull of more proximal extensor toe muscles.

Hemianopia Refers to loss of vision in ½ visual field in the vertical plane. If both eyes are equally involved, it is called homonymous hemianopia.

Hemiparesis Incomplete weakness involving one side of body.

Horner's syndrome Miosis, ptosis, and diminished sweating on the ipsilateral face due to lesion in the three neuron pathway starting in hypothalamus and traveling to the brainstem, thoracic spinal cord, cervical sympathetic ganglion, and sympathetic nerves along the carotid and ophthalmic arteries.

Hydrocephalus Abnormal enlargement of one or more ventricles of the brain. Obstructive hydrocephalus is when there is obstruction of CSF flow in ventricular system or subarachnoid space. Hydrocephalus ex vacuo refers to passive ventricular enlargement from loss of surrounding white matter and neurons. Communicating hydrocephalus refers to non-obstructed pathway from spinal subarachnoid space to lateral ventricles.

Hypertonia Increased muscle tone or resistance produced by passive movement of a limb on a joint.

Hypotonia Decreased muscle tone or resistance produced by passive movement of a limb on a joint.

Hypsarrhythmia Random, high voltage slow waves and spikes seen on electroencephalogram (EEG) that vary from in time and location.

Ice water caloric Test used in comatose patients to determine whether the pathway from the vestibular inner ear to the 3rd and 6th cranial nerves is intact. When pathway is intact, ice water irrigated in one ear produces bilateral eye movement to the ipsilateral side.

Infantile spasms Brief, symmetric contractions of neck, trunk and limb muscles seen in infants (also called salaam seizures).

Ischemic penumbra Area of brain around an acute stroke that has insufficient blood flow to enable normal neuronal function but sufficient flow to prevent cell death.

Insomnia Chronic inability to fall asleep or maintain sleep the entire night.

Intracerebral hemorrhage Bleeding into the brain parenchyma that may extend into the ventricles and into the subarachnoid space due to rupture of cerebral blood vessels.

Jaw jerk Corticobulbar reflex produced by tapping downward on the chin with resulting contraction of masseter muscles and upward jaw movement. When unusually brisk, the jaw jerk implies an upper motor neuron abnormality in corticobulbar tract to fifth cranial nerve nuclei.

Kernicterus Deposition of bile pigment in deep brain nuclei with neuronal degeneration from neonatal jaundice.

Knee jerk (KJ) The patellar reflex is a deep tendon reflex in which the patellar tendon is tapped causing a brief extension of the leg.

Korsakoff's syndrome or psychosis Loss of the ability to learn new memories with a tendency to fabricate answers. It is usually part of the Wernicke-Korsakoff encephalopathy from alcoholism.

Lacune or lacunar stroke Small infarction primarily located in the basal ganglia, thalamus, brainstem, internal capsule, and centrum semiovale.

Lateral geniculate body (nucleus) Thalamic nucleus that receives input from optic nerves and sends outward optic radiations to the occipital cortex and upper brainstem.

Lateral medullary syndrome Infarction of dorsolateral medulla and inferior cerebellum due to occlusion of posterior inferior cerebellar artery, a branch of the vertebral artery.

Lenticular (lentiform) nucleus Combination of the putamen and the globus pallidus.

Leukomalacia Abnormal softening of white matter areas

Lhermitte's sign Electrical sensation that runs down the back from the neck into the limbs that is often elicited by bending the head forward.

Limbic encephalitis A form of inflammation of the brain caused by an autoimmune disease that is often associated with a cancer outside the brain. Brain damage is due to a host immune response against various areas of their own brain.

Limbic system Part of the brain involved in emotion and memory which includes the limbic lobe (subcallosal area, cingulate gyrus, parahippocampus, uncus, and hippocampal formation), many nuclei of the nucleus accumbens, the hypothalamus, mammillary bodies, the amygdala, and the cingulate gyrus.

Lordosis Curvature of the spinal column with a forward convexity.

Lower motor neuron Motor neurons in the anterior horn of the spinal cord or brainstem that directly innervate muscles.

Lumbar puncture Placement of a hollow needle with a stylet into the spinal canal in the lower lumbar space to withdraw CSF or instill medications.

MRI Use of changing magnetic fields to create brain images as brain slices in any plane.

Medication overuse headaches frequent, often daily, chronic headaches in a patient with one type of headache who overuses medications such as triptans, butalbital, opioids, and other analgesics.

Melatonin Key molecule in circadian rhythms produced by the pineal gland that releases melatonin into blood and CSF only at night and not in daylight.

Meniere's disease or endolymphatic hydrops abrupt attacks of vertigo lasting hours developing without warning associated with depressed unilateral hearing and loud tinnitus.

Meningioma Tumors arising from the *meninges*, the membranous layers surrounding the CNS, which are usually slow growing, benign, and rarely metastasize to other areas of the brain or body.

Meningitis Inflammation of the meninges due to viruses, bacteria, fungi, parasites, chemicals, and neoplasms.

Meralgia paresthica Sensory impairment and dysthesias in the skin distribution of the lateral femoral cutaneous nerve of the thigh.

Mesial temporal sclerosis Progressive loss of neurons and gliosis in one hippocampus that often causes complex partial seizures.

Mild Cognitive Impairment Global cognition functioning is near normal but patient has subjective complaints or objective evidence of cognitive deficits that cannot be related to other causes, such as depression or medications.

Miller-Fisher syndrome CNS autoimmune related to Guillain-Barre syndrome and characterized by a monophasic illness with ataxia, absence of DTR, and paralysis of eye movements.

Miosis Abnormal constriction of a pupil.

Muscular dystrophy Muscle diseases that weaken the musculoskeletal system and hamper locomotion that are characterized by progressive skeletal muscle weakness, defects in muscle proteins, and the death of muscle cells and adjacent tissue. Most types are due to a genetic mutation.

Myalgia Muscle aches and pains that are not cramps.

Myasthenia gravis Most common synaptopathy affecting the neuromuscular junction and is due to autoantibodies directed against the post-synaptic acetylcholine receptor interfering with normal neuromuscular transmission and causing ptosis, diplopia, and skeletal muscle weakness.

Myelin Lipid-protein sheath that wraps peripheral nerves that is made by Schwann cells and central nerves that is made by oligodendroglia.

Myelitis Focal or diffuse inflammation within the spinal cord.

Myeloradiculopathy Disease process affecting the spinal cord, adjacent peripheral nerve roots, and nerves.

Myoclonus Rapid, brief muscle jerks involving specific muscles or the entire body that do not blend together and are shorter duration than chorea. Nocturnal myoclonus is the normal abrupt body jerks that occur when an individual is falling asleep. The EEG may or may not have spikes correlating with the myoclonus.

Myopathy General term implying disease of muscle from any cause.

Myotonia Abnormal sustained muscle contractions with slow relaxation that have a characteristic pattern on electromyogram.

Narcolepsy Chronic neurologic sleep disorder characterized by excessive daytime sleepiness, disturbed nocturnal sleep, cataplexy (loss of voluntary muscle tone from emotions such as laughing or anger), and elements of rapid eye movement (REM) sleep. Narcolepsy is due to loss of hypocretin (or orexin) neurons located in the lateral hypothalamus.

Neglect Inability to attend normally to a portion of extrapersonal or intrapersonal space or both that cannot be explained by altered perception. In visual neglect, the patient ignores objects, persons, or movement in the left or right of the environment.

Neuraxis Longitudinal axis of the CNS that runs from the rostral forebrain to the caudal spinal cord.

Neuromyelitis optica or Devic's disease CNS autoimmune disease mainly of optic nerve and spinal cord due to recurring attacks of CNS astrocytes in white matter from circulating IgG1 antibodies against the astrocyte water channel aquaporin 4.

Neuronophagia Destruction of neurons by phagocytic cells.

Neuropathic pain Abnormal peripheral nerve pain that persists, becomes more severe, and can expand from the region of original discomfort to show hypersensitivity to painful triggers and change in character in how the pain is perceived.

Neuropathy Term that describes disorders of peripheral nerves.

Nocioceptive Sensory receptors that respond to painful stimuli.

Non REM sleep Characterized by little body movement, dreaming is rare, and muscles are not paralyzed.

Non-convulsive status epilepticus Complex partial status epilepticus where the patient has constant confusion and impaired awareness but can move their limbs.

Nystagmus Oscillatory eye movements that may be physiologic (following spinning in a circle) or abnormal (from inner ear, brainstem, and cerebellar dysfunction).

Obstructive sleep apnea Excessive daytime sleepiness from recurrent episodes of partial or complete upper airway collapse producing difficulty in breathing, frequent sleep arousals, and hypoxemia.

Obtundation Conscious state characterized by a disorder of alertness associated with confusion and slow reaction times (psychomotor retardation) in which individuals can be aroused by verbal stimuli but respond poorly to questions with a prolonged delay in their verbal or motor responses.

OD Right eye

Oligoclonal bands Homogenous immunoglobulins produced in CSF or blood that have identical molecular configuration allowing them to travel as a specific band together on an electrophoresis gel. CSF oligoclonal bands are common seen following CNS infections or multiple sclerosis.

Oligodendrocyte CNS glial cell that provides support and insulates axons by creating a myelin sheath. Myelin increases axonal conduction velocity via saltatory conduction of action potentials jumping from one node of Ranvier to the next and protects the axon from environmental toxins.

Ophthalmoplegia Paralysis of eye movements.

Opioids Psychoactive chemical often derived from the opium poppy that binds to opioid receptors found principally in the central and PNS and gastrointestinal tract. Opioids are often used to treat pain but have a high addiction potential.

Oriented x 3 Oriented to person, place, and time in mental status testing.

Orthostatic hypotension Fall in blood pressure upon standing causing dizziness or even syncope.

OS Left eye

Otoconia Tiny calcium carbonate crystals embedded in a gelatinous matrix above the macula of the utricle and saccule that move with gravity changes bending attached hair cells allowing detection of gravity.

Otorrhea CSF drainage from nose

Papilledema Swelling of optic nerve disc from elevated intracranial pressure.

Paraphasias Mispronounced or inappropriately substituted words with sematic paraphasias being errors based on meanings of words (aunt for uncle) and literal paraphasias being errors based on sounds (hook for took).

Paresthesias Spontaneous firing of peripheral nerve fibers causing a tingling sensation.

Parkinsonism Neurological syndrome characterized by tremor, hypokinesia, and rigidity, the features of Parkinson's disease, but often due to other causes.

Paroxysmal Sudden event, as in spikes on EEG.

Past pointing Repeated missing a target by going too far or off to one side when using a finger or toe with closed eyes that is due to dysfunction of the vestibular system or cerebellum.

Patellar reflex KJ reflex is a deep tendon reflex in which the patellar tendon is tapped causing a brief extension of the leg.

Peripheral neuropathy Damage to nerves of the PNS caused either by disease or trauma to the nerve or from side effects of systemic illness. The most common form is a symmetrical polyneuropathy, which mainly affects the feet and lower legs.

PNS All neural structures that lie outside the spinal cord and brainstem include motor, sensory and autonomic nerves and their ganglia.

PERRLA Abbreviation for pupils equal, round, and reactive to light and accommodation.

Persistent vegetative state Chronic severe disorder of consciousness in which patients with severe brain damage are alive but in a state of only minimal arousal rather than true awareness. Most patients are unresponsive to external stimuli but a few do respond, in varying degrees, to stimulation.

Phlebitis Inflammation of veins.

Phonophobia Discomfort from noises that normally do not cause discomfort.

Photophobia Abnormal eye pain from bright lights.

Pituitary adenoma T*umors* that occur in the *pituitary gland* which may be tiny or enlarge outside the pituitary gland. They often secrete hormones not under hypothalamus feedback control.

Plaque Demarcated hypocellular area in brain white matter characterized by the loss of myelin, relative preservation of axons, and the formation of astrocytic, glial scars that is common in multiple sclerosis.

Plasmapheresis Process in which whole blood is withdrawn from the person, the liquid portion or plasma is removed from the blood and replaced. This is often done to remove unwanted antibody from the blood in patients with an autoimmune disease.

Polymerase chain reaction Molecular biochemical technology to amplify a single or a few copies of a piece of deoxyribonucleic acid (DNA) across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence that allows identification of specific genes and thus infectious agents or gene mutations.

Polyneuropathy Diffuse and symmetrical distal dysfunction of sensory, motor, and autonomic nerve axons that usually begins in the feet.

Polysomnogram Measures an EEG, electrocardiogram (EKG), extraocular eye movements, EMG, airflow oximetry, nasal pressure, esophageal pressure, body position, snoring sounds, and rib/abdominal movements during a night's sleep to analyze sleep disturbances.

Positron emission tomography (PET) Imaging technique that detects emissions from injected radiolabeled compounds to create a quantifiable image of blood flow, glucose utilization or location of specific ligands that attach to brain receptors, etc.

Postherpetic neuralgia Persistent of severe pain following shingles that lasts more than three months.

Posterior fossa Part of the *intracranial cavity* that is located between the *foramen magnum* and *tentorium cerebelli*. It contains the *brainstem* and *cerebellum*.

Prefrontal lobe Part of brain anterior to the motor and premotor cortex that is a multisensory association cortex.

Presyncope Feeling of light-headedness or of impending faint that may be associated with a feeling of unsteadiness usually resulting from hypoperfusion, or changes in blood chemical composition to the brainstem.

Prion Abnormal protein configuration of a normal host protein that causes transmissible spongiform encephalopathies, like Creutzfeldt-Jakob disease.

Proprioception Sense of position of body part relative to fixed object like a floor that is unconscious and conscious.

Prosopagnosia Inability to recognize familiar faces (facial agnosia).

Pseudobulbar palsy Syndrome that affects speech articulation, phonation, swallowing, and emotional lability due to bilateral dysfunction of corticospinal tracts in upper brainstem or motor cortex.

Psychomotor retardation Abnormal slowing of mental behavior and limb movements that is not due to mental retardation.

Ptosis Abnormal drooping of one or both eyelids.

Putamen Part of basal ganglia and part of the striatum and lentiform nucleus.

Quadrantanopia Loss of vision in one quadrant of vision or ¼ of entire visual field.

Radiculopathy Damage to a nerve root leaving the spinal cord that causes weakness, sensory loss or dysesthesias, and diminished reflex in corresponding myotome and dermatome.

Ramsay Hunt syndrome Acute facial weakness due to herpes-zoster virus reactivation from the geniculate ganglion.

REM sleep Characterized by rapid and random movement of the eyes, dreaming with often vivid dreams, low muscle tone, and a rapid, low-voltage EEG.

REM REM sleep is characterized by rapid and random eye movements, dreaming, low muscle tone and a rapid, low voltage EEG that occupies about 25 % of total normal sleep.

Restless legs syndrome Defined as an individual with uncomfortable dysesthesias and paresthesias in the legs mainly in the evening and temporarily alleviated by movement.

Reticuloendothelial system or mononuclear phagocyte system Class of mononuclear phagocytic cells that are part of the body's defense mechanisms and widely located in lymph nodes, lung, spleen, and brain (microglia). They engulf and destroy bacteria, viruses, other foreign substances, and worn-out or abnormal body cells.

Rigidity Constant resistance to muscle stretching in both flexors and extensors throughout range of motion due to the stretching force inducing some motor units to fire. In Parkinson's disease, rapid flexion and extension of wrist or elbow often elicits a ratchet-like feeling (cogwheel rigidity).

Rinne test Comparison of bone conduction (placing a vibrating tuning fork on the mastoid process) to air conduction. Air conduction normally is heard better.

Rolandic fissure Fissure that separates the motor cortex in the frontal lobe from the sensory cortex in the parietal lobe.

Romberg sign Ability to stand with feet together and eyes open, and the inability to maintain posture with the eyes closed.

Rooting reflex Normal turning of infant's face and lips toward a nipple touching the cheek but abnormal "frontal release reflex" when seen in adults upon touching the cheek.

Rostral Direction or position of neuroaxis toward the forebrain and away from the caudal spinal cord.

Saccadic eye movement Fast eye movement, voluntary or reflex, usually accomplishing foveal fixation

Saltatory conduction Nerve action potential that moves down a myelinated nerve by jumping from node of Ranvier to node of Ranvier, increasing conduction velocity to as fast as 80 m/s.

Semicircular canals Three canals at right angles to each other located in the temporal bone detect angular acceleration and serve to keep eyes steady during head movement.

Sciatica Term for radiating pain down a leg from damage to one or more lumbosacral nerve roots that form the sciatic nerve.

Schwann cell Principal glia of the PNS and functions to support axons by wrapping around axons of motor and sensory neurons to form a myelin sheath. Myelin increases axonal conduction velocity via saltatory conduction of action potentials jumping from one node of Ranvier to the next. For small diameter axons, the Schwann cell encases naked sensory axons to protect them.

Scoliosis Condition in which a person's spine or vertebral column is curved from side to side and classified as congenital, idiopathic (cause unknown), or secondary to another primary condition.

Seizure Transient signs and symptoms of abnormal excessive neuronal activity in the brain that clinically may be as wild thrashing movements (tonic-clonic seizure) or as a brief loss of awareness (absence seizure).

Shingles or herpes zoster Vesicular rash that follows a dermatomal pattern due to varicella-zoster virus.

Shunt Tubing used to move CSF that is blocked along its pathway (usually a ventricle) to the abdomen or jugular vein where it can be absorbed.

Single photon emission computed tomography (SPECT) Imaging system that is similar to PET that qualitatively determines regional blood flow or brain metabolism relative to other brain areas.

Skew deviation of vision Vertical and slightly horizontal (diagonal) double vision that is the same in all fields of gaze due to a brainstem lesion.

Sleep Occurs in a recumbent posture, has a low level of motor output, raised threshold to respond to sensory stimulation, and dreaming.

Snout reflex Pouting of lips following tapping the lips.

Spasticity Condition resulting from damage to the corticospinal tract in which at rest muscles are in midposition and limbs held in a characteristic flexed posture. Rapid passive limb movement initially produces little resistance but then quickly has increasing muscular resistance to a point when the resistance suddenly disappears ("clasp-knife" phenomena).

Spinocerebellar ataxia Multiple genetic diseases involving the cerebellum characterized by a progressive cerebellar ataxia, unsteady gait, clumsiness, and slurred speech. Depending on the specific genetic abnormality, symptoms of cognitive abnormalities, other movement disorders, and visual disturbances can be present.

Status epilepticus More than 5 min of continuous clinical and/or electrographic seizure activity or recurrent seizures without full recovery to baseline between seizures.

Stenosis Narrowing of lumen of artery or spinal canal.

Strabismus Lack of eye alignment such that the two visual axes assume positions relative to each other different from that required by the physiologic task.

Straight leg raise test Test for lumbar radiculopathy in which passive elevation of a straightened leg produces pain in the lower back.

Striate cortex Primary visual cortex

Striatum Combination of the caudate nucleus and the putamen.

Stroke General term that implies death of cerebral tissue from abnormalities of the blood supply.

Stupor or semi-coma Barely conscious state in which individuals require constant strong verbal or physical stimuli to remain aroused. Their responses are simple and often inaccurate. When the stimulus stops, patients return to unconsciousness.

Subarachnoid hemorrhage Presence of blood in the meninges and CSF most often from head trauma or ruptured saccular aneurysm.

Subdural hematoma Following head trauma blood appears in the subdural space between the dura mater and arachnoid mater of the meninges. Over time the hematoma may

spontaneously contract or expand to become large enough to cause increased intracranial pressure and displace brain medially often producing headache, lethargy, and focal neurologic signs such as hemiparesis.

Subfalcial space Space beneath the falx in which the cingulate gyrus can herniate from increased intracranial pressure.

Suck reflex Normal sucking response of infants when a nipple touches the lips but abnormal "frontal-release" reflex in adults when touching the lips elicits a sucking response.

Sylvian fissure Major horizontal fissure that separates the temporal lobe from adjacent parts of the frontal and parietal lobes.

Synaptopathy Diseases that limit limits neuromuscular transmission preventing muscle contraction and leading to weakness. Synaptopathies occur from chemical or biologic toxins, antibodies directed against synaptic receptor molecules, or genetic mutations in the synaptic receptor or membrane channel.

Tandem gait Walking heel to toe in a straight line.

Tentorium A fold of the dura mater forming a partition between the cerebrum and cerebellum.

Tics Abrupt, transient, repetitive, stereotypical movements of face and limbs or vocalizations that may be briefly voluntarily suppressed but is often then followed by a burst of tics when the suppression is removed.

Tonsillar herniation Downward movement of cerebellar tonsils into the foramen magnum in response to increased intracranial pressure from localized mass in the posterior fossa.

Tonsils Most inferior part of the midline cerebellum.

Transient ischemic attack Focal neurologic signs from transient occlusion of a cerebral artery that usually last less than 20 min but always less than 24 h.

Treponema pallidum The bacterium that causes syphilis

Triceps jerk Deep tendon reflex elicited by tapping the triceps tendon above the back of the elbow.

Triptans Migraine medications that are receptor agonists acting at the serotonin 5-HT_{1B} receptor located on meningeal blood vessels and trigeminal nerve endings to reduce headache pain during an acute attack.

Uncal herniation Movement of the uncal gyrus of the medial temporal lobe under the tentorial notch in response to mass in the temporal-frontal lobes producing increased intracranial pressure.

Upper motor neuron Neurons in the upper brain that synapse with lower motor neurons in the brainstem or spinal cord.

Utricle Part of the inner ear that detects gravity

Valsalva maneuver Increase in intrapulmonic pressure by forcible expiration against a closed glottis that secondarily increases intracranial pressure.

Ventricles Four CSF-filled cavities in the brain (two lateral ventricles, third ventricle and fourth ventricle) along the CSF pathway.

Vermis Midline part of the cerebellum that participates in truncal balance and gait.

Vertigo Illusion of abnormal spinning movement by the individual or his environment.

Vestibular neuritis Abrupt onset of idiopathic severe horizontal vertigo that causes severe ataxia, nausea, and vomiting that lasts a few weeks.

Vestibulo-ocular reflex A *reflex eye movement* that *stabilizes images* on the *retina* during head movement by producing an eye movement in the direction opposite to head movement, thus preserving the image on the center of the visual field.

Wakefulness State characterized by an active and deliberate sensorimotor discourse with the environment.

Wallenberg's syndrome or lateral medullary infarction Unilateral infarction of the lateral medulla from occlusion of the posterior inferior cerebellar artery usually causing acute dizziness, vertigo, nausea, nystagmus, skew deviation of vision, gait ataxia and ipsilateral limb ataxia.

Watershed brain territory Cerebral cortex located between the distal ends of the middle

and posterior cerebral arteries (parietal lobe) and middle and anterior cerebral arteries (anterior frontal lobe) that are damaged when hypoperfusion of the brain occurs.

Wernicke's aphasia Language disorder in which there is loss of ability to comprehend verbal or written communications and ability to speak in fluid sentences with normal melody that make no sense.

Wernicke's encephalopathy An acute condition presenting with triad of oculomotor abnormalities, gait ataxia and confusion that develops in individuals deficient in thiamine (vitamin B_1), especially in alcoholics with low food intake.

West's syndrome Infants develop a triad of epileptic spasms (brief, symmetric contractions of neck, trunk and limb muscles), hypsarrhythmia on EEG, and mental retardation. Also known as infantile spasms or hypsarrhythmia.

White matter Central nervous tissue that contains mainly myelinated (white appearing) nerve fibers, but not their neuronal cell bodies.

Xanthochromia Yellow color of CSF supernatant that comes from lysed RBCs, bilirubin, or very elevated CSF protein concentration.

Index

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