

11 DISORDERS OF HIGHER CORTICAL FUNCTION

Overview

Higher cortical functions process raw sensory signals into complex concepts that can be remembered and used to create new ideas that can be formulated into action. It is the part of the brain which, for example, converts a sound (sensation) into a word, then into a sentence. This is then combined with higher-level processes such as semantic memory, which the brain integrates into an idea or thought (conception) that can be remembered, compared with other ideas, and used to create new ideas that in turn can be remembered or acted upon.

The physiology involved in higher cortical function is poorly understood, but definitely involves interaction among many cortical and sub-cortical regions, and often between both hemispheres. The two hemispheres are not equal in function, but the precise differences are not understood. The dominant hemisphere is the one most responsible for language and fine motor control functions such as writing. The left hemisphere is dominant in over 95% of right-handed individuals and in 70% of left-handed individuals.

In simple conceptualization, the cerebral cortex can be divided into 3 regions that deal with sensory information in increasing levels of complex-

ity. Visual, auditory, and somatosensory information goes to the primary sensory cortex. The unimodal association cortex refines single sensory information. The multimodal association cortex receives input from all sensory modalities and handles complex intellectual functions, such as logic, judgment, language, emotion, ambition, and imagination (Figure 11-1). Multimodal association cortices are located in the prefrontal, limbic, and parietal lobes. The prefrontal lobe is responsible for problem solving, self-monitoring, planning, mental tracking, and abstract thinking. The limbic association cortex participates in memory and emotion. The parietal association cortex is the setting for language, space orientation, complex movement, and recognition of self and the world.

Until recently, much of our understanding of higher cortical function has come from the investigation of patients with defined cortical lesions. Based on these studies, we have some understanding of the functions of specific areas. Recent studies of normal individuals using PET, fMRI, and intracortical electrical recordings are providing ideas of the normal functions of cortical areas. To the clinician, recognition of specific higher cortical function syndromes has proven helpful in anatomic cerebral localization. Below are brief descriptions of what is known about the anterior

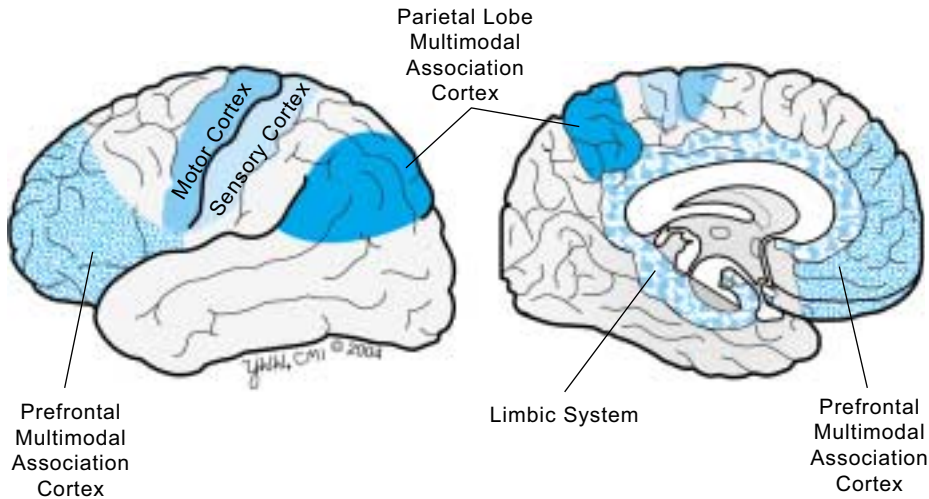


Figure 11-1 Higher cortical function multimodal association cortices.

prefrontal lobe, limbic/temporal lobe, and parietal lobe. In addition, there is a discussion of the clinical deficits patients may experience when lesions occur in a specific multimodal association cortex.

Prefrontal Lobe

The prefrontal association cortex, located anterior to the motor and premotor frontal cortex, is supplied by branches of the anterior and middle cerebral arteries. Table 11-1 lists the recognized functions of the prefrontal 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 neuropsychologic evaluation. In contrast, head trauma causing bilateral prefrontal lobe damage can produce considerable signs and symptoms. This occurs in part because of bilateral damage to fiber pathways that communicate between the frontal cortex and subcortical sites.

Damage to prefrontal cortices 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 cortices. The *grasp reflex* is revealed in the inability to release a grasp when an object, such as the examiner's finger, stimulates the palm. The *snout reflex* is elicited by touching the patient's lips,

causing the mouth to pucker involuntarily. The *suck reflex* is said to be positive when the patient's mouth opens involuntarily in response to an object moving toward it. The *rooting reflex* is positive when lightly stroking the side of the face produces an involuntary head turning toward the stimulation.

Table 11-1 lists the clinical features seen in patients with prefrontal cortical damage. These patients often demonstrate high impulsivity without forethought to the consequences, inability to perform several tasks simultaneously (multitasking), lack of drive to work or complete tasks, and a tendency to appear disheveled or half-dressed.

Limbic System

The limbic system includes the limbic lobe (subcallosal area, cingulate gyrus, parahippocampus, uncus, and hippocampal formation), many nuclei of the nucleus accumbens, the hypothalamus, mamillary bodies, and the amygdala (Figure 11-2). The major arterial supply comes from the anterior and posterior cerebral arteries and anterior choroidal artery. The two major concerns of the limbic system are memory and emotion.

Consolidation of long-term memories from immediate memory (lasting seconds) and short-term memory (lasting minutes) is the basic function of the hippocampal formation. Long-term memory can be recalled days to years later. While

Table 11-1 Major Higher Cortical Brain Areas, Normal Functions, and Syndromes

Cortical Area	Major Functions	Clinical Syndromes Seen When Area Damaged
Prefrontal Lobe	Judgment Insight Foresight Ambition Sense of purpose	High distractibility Lack of foresight or insight Inability to switch from one task to another Lack of ambition Lack of sense of personal responsibility Lack of social propriety and self-monitoring
Limbic System	Short-term memory Consolidation of long-term memory Emotional response	Amnesia Akinetic mutism Flat emotional affect
Parietal Lobe	Perception of somatosensory input Integration of all sensory data Awareness of body and its relationship to external space Language	Cortical sensory deficits Astereognosis Agraphesthesia Poor double simultaneous sensory stimulation Visual neglect and Anton's syndrome Apraxias Construction apraxia Ideomotor apraxia Ideational apraxia Aphasias Global aphasia Broca's aphasia Wernicke's aphasia

the hippocampal formation is responsible for establishing long-term memories, no single brain location appears responsible for the repository of long-term memories, although it is likely cortical. Thus no single brain lesion can eradicate well-formed long-term memories. However, extensive damage to the brain in dementia patients can be associated with impaired long-term as well as short-term memory.

Lesions that cause memory impairment are usually bilateral and may involve the hippocampal formations, dorsomedial nuclei of the thalami, or mamillary bodies. However, damage to the left temporal lobe can produce verbal memory deficits, while damage to the right temporal lobe can produce nonverbal memory deficits. The most common diseases that produce devastating memory loss are Wernicke–Korsakoff syndrome, bilateral temporal lobe contusions from head trauma, anoxia due to cardiac arrest, and advanced Alzheimer's disease.

The limbic system also participates in emotional responses. Electrical stimulation of various sites in the limbic system may produce fear or sorrow (aversion centers) or pleasure (gratification centers). Damage to the limbic system can produce varied emotional changes. Large limbic lesions often produce a flattening of emotions, presumably due to loss of both aversion and gratification centers. Bilateral damage to the anterior cingulate gyri or supplementary motor area may dramatically diminish emotional responses and produce an awake-appearing patient who is immobile, mute, and unresponsive to his or her environment (akinetic mutism).

Parietal Lobe

The parietal lobe begins behind the central sulcus and extends backward and inferiorly to merge with the occipital and temporal lobes at poorly defined

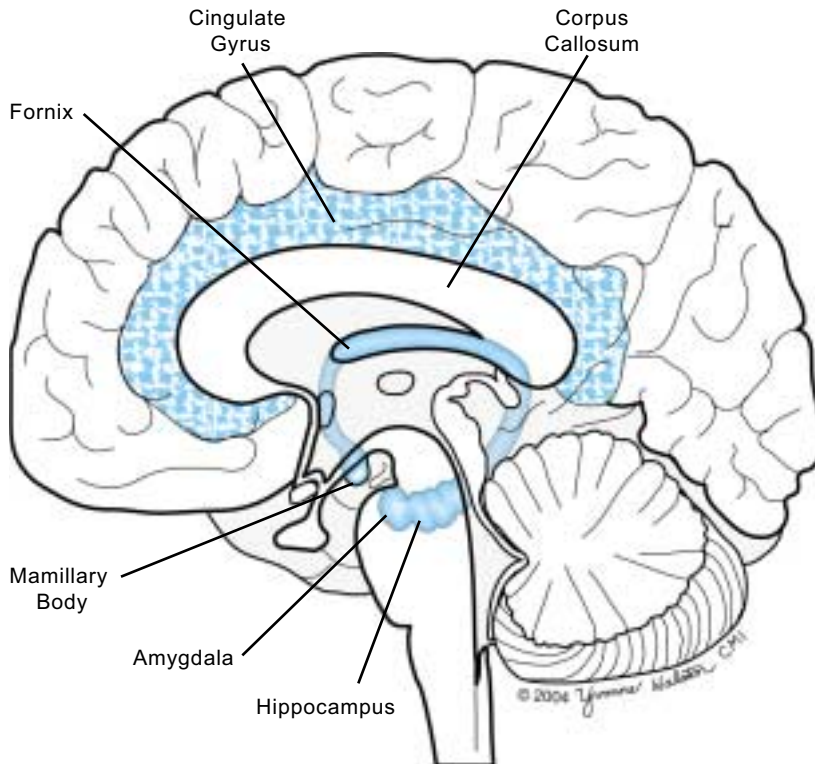


Figure 11-2 Limbic system anatomy.

boundaries. The inferior division of the middle cerebral artery principally supplies blood to the parietal lobe. The parietal lobe is a higher-order integration center whose functions are listed in Table 11-1. Electrical stimulation of most parietal lobe neurons does not evoke specific sensory or motor effects, but lesions do produce specific clinical deficits.

Patients with a lesion involving the postcentral gyrus, especially in the hand primary sensory area, usually have relatively intact perception of pain, touch, pressure, temperature, and vibration but often have “cortical” sensory deficits. *Astereognosis* is the inability to distinguish and recognize small objects based on size, shape, and texture when placed in a hand that has normal primary tactile sensory input. *Agraphesthesia* is the inability to recognize numbers or letters written on the palm. Loss of *double simultaneous sensory stimulation* is the inability to detect and localize two identical stimuli applied simultaneously and bilaterally to comparable areas on the face or limbs. For example, if the examiner touches the backs of the patient’s hands and asks him or her to identify

which side was touched, the patient will only report feeling the touch on the ipsilesional side.

Neglect syndromes cause lack of attention to the contralateral side of the body (spatial neglect) or to the contralateral visual space (visual neglect). Patients with hemiparesis due to a lesion of the motor cortex or corticospinal tract and a parietal lobe lesion may be unaware of their arm and leg paralysis (anosognosia). Similarly, bilateral occipital lobe lesions that involve the parietal lobe may produce blindness that is denied by the patient (Anton’s syndrome). Lesions involving only the parietal lobe may produce apraxia on one side of the body in dressing and grooming (dressing apraxia). Lipstick may be applied to only one side of the lips and patients may not be able to put on a shirt or pants.

Lesions of the nondominant superior parietal lobe may give rise to disturbances of perception of two- or three-dimensional space. These patients have difficulty with route finding and reproducing geometric figures, and disturbances in organizing parts of a complex object (constructional apraxia) (Figure 11-3). A good bedside test is to ask a patient

to draw a clock with numbers and the hands showing a specific time. Patients with constructional apraxia often crowd the numbers on one side (visual neglect), may draw numbers incorrectly (6 for 9) or on the wrong side of the clock, and cannot draw the hands correctly (Figure 11-3).

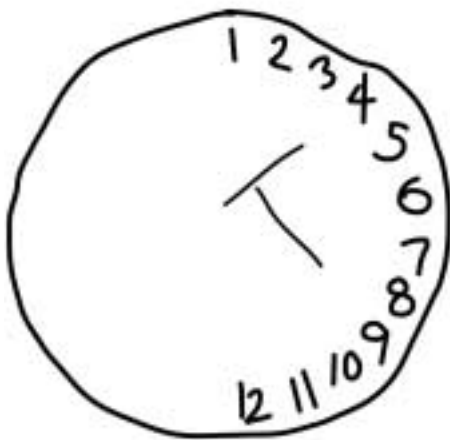
Apraxia is the inability to execute complex and previously learned skills and gestures in a person who is alert and has no weakness or ataxia that prevents the movements. Lesions of bilateral parietal lobes may produce *ideational apraxia* or impaired knowledge of what action is associated with a particular object. Often they use the wrong object for a particular function and display spatial or temporal errors. Lesions of the dominant parietal lobe most frequently produce *ideomotor apraxia* or spatiotemporal deficits imitating movements without objects. For example, the patient might use jerky vertical movement rather than smooth horizontal movements when imitating a carving movement. Apraxias involve both sides of the body, but they are tested in the ipsilesional limb to be sure that they are not due to a motor deficit.

Aphasias

Theories of speech and language continue to evolve as no current hypothesis satisfactorily explains nor-

mal speech. Traditionally, language disorders have been divided into specific categories that originally were thought to be due to damage to focal brain regions, usually different areas of the left hemisphere in right-handed patients. With current neuroimaging, brain regions giving rise to specific types of language disorders have been found to be much larger than previously thought and show considerable overlap (Figure 11-4). Thus fine subdivisions of language currently are of limited clinical usefulness. Nevertheless, dividing language disorders into 3 major categories does have clinical usefulness (Table 11-2).

Global aphasia implies loss of all speech and language function. There is loss of comprehension of verbal and written language plus inability to communicate in speech or writing. These patients do not obey verbal commands, and cannot repeat phrases or produce meaningful speech or writing. However, some patients may express stereotypic utterances such as “OK”, “fine”, “sure”, and “no,” or express simple profanity, none of which are appropriate to the question. Most cases of global aphasia are due to large infarctions involving the central regions surrounding the Sylvian fissure and almost always produce an accompanying hemiparesis, hemisensory loss, and often a homonymous hemianopia. In general, prognosis for recovery is poor.



Contralateral Neglect



Constructional Apraxia

Figure 11-3 Parietal lobe lesions causing neglect and apraxia.

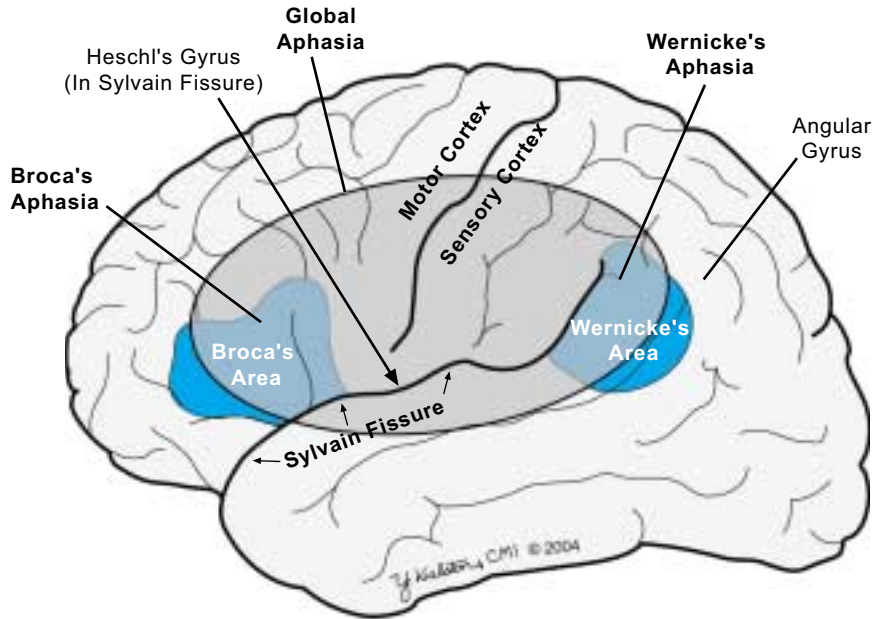


Figure 11-4 Location of brain lesions causing aphasia (left cortex).

Broca's aphasia (expressive/motor/anterior/non-fluent aphasia) implies disproportionate difficulty with formulating sentences and speaking them aloud, compared with comprehending verbal and written communication. Acutely, some patients cannot speak at all. Over time, patients express short telegraphic speech that emphasizes informational nouns and verbs and tends to be devoid of noncritical adjectives and adverbs. The speech melody is distorted, sounds more guttural, and is often explosive. Use of stereotypic utterances may occur but may not be correct responses to the question. Repetition of phrases is impaired. Because patients understand simple spoken language, they may respond appropriately or express their needs

by using nonverbal responses (miming). Lesions that produce Broca's aphasia were originally thought to be from a focal lesion in the inferior frontal area (Broca's area), but it is now recognized that larger lesions in that area can produce Broca's aphasia (Figure 11-4). Patients with Broca's aphasia from a stroke usually have an accompanying hemiparesis. Prognosis depends on the cause (worse for tumors than infarct) and lesion size. For infarction, many patients regain reasonable-to-good functional telegraphic speech over 6 months.

Wernicke's aphasia (receptive/sensory/posterior/fluent aphasia) implies severe impairment in comprehension of verbal and written communications, with the maintenance of fluent speech. Patients are

Table 11-2 Major Aphasia Types and Their Clinical Features

Type	Verbal Expression	Ability to Repeat	Ability to Comprehend
Broca's aphasia	Nonfluent but content, understandable with truncated phrases containing mainly informational words	Impaired	Good for simple one-step commands but impaired for complex commands
Wernicke's aphasia	Fluent but noncomprehensible with excess noninformation words and paraphasias	Impaired	Poor to absent
Global aphasia	Mute or nonfluent	Impaired	Poor to absent

usually unaware of their comprehension difficulties and may appear attentive and cooperative. The speech usually has normal melody or prosody, is pronounced clearly without effort, and is of normal to prolonged length. However, the speech content does not make sense, lacks informational words (nouns), contains excessive adverbs and adjectives, contains nonwords (neologisms), and is mispronounced or has inappropriately substituted words (paraphasias). Semantic paraphasias are errors based on the meanings of words (aunt for uncle) and literal paraphasias are errors based on sounds (hook for took). A patient with psychosis usually has an abnormal frame of reference. Thus in response to the question, “What is your name?” the schizophrenic may answer, “Jesus Christ” (implying he understood the question and answered it relative to his world), while the patient with Wernicke’s aphasia may reply, “It is a lovely, beautiful, warm, rainy day on this weekend (implying he never understood the question).

Wernicke’s aphasia patients cannot repeat phrases. Lesions commonly involve the posterior end of the Sylvian fissure and spread varying distances across the posterior half of the brain (Figure 11-4). Vascular occlusions of the posterior temporal branch and the angular branch of the middle cerebral artery in the dominant hemisphere can cause Wernicke’s aphasia without producing hemiparesis. The prognosis of Wernicke’s aphasia varies. Many recover reasonable verbal comprehension and usable appropriate speech, but the speech may continue to contain paraphasias and word-finding difficulties (dysnomia).

Intelligence

Intelligence is a general mental capability that includes reasoning, planning, solving problems, thinking abstractly, comprehending complex ideas, learning quickly, and learning from experience. Low intelligence does not come from dysfunction of a single brain region but from dysfunction or damage of many bilateral areas of higher cortical function. Although imperfect, intellectual reasoning is usually represented by an intelligence quotient (IQ) obtained from appropriate testing instruments. An IQ score is performance on a standardized test adjusted to the individual’s chronological age. The most com-

monly used tests are the Wechsler Adult Intelligence Scale-III and Wechsler Intelligence Scale for Children-III. In general, mental retardation or dementia can be defined as IQ scores 2 standard deviations or more below the norm. In mental retardation, the patient has never had an IQ score within the norm. In dementia, it is loss of previously acquired intellect. A commonly used rapid office-screening test is called the Folstein Mini Mental Status Exam (MMSE; see Chapter 2, “Neurologic Examination”). Test scores range from 0 to 30 and scores below 24 are an indication of moderate-to-severe dementia, depending on patient age and education level. The test has good sensitivity (90%) but poor specificity (60%) for dementia because it is relatively insensitive to mild cognitive dysfunction, especially in higher-functioning patients.

Neurologic Changes of Normal Aging

Introduction

In order to understand dementia that usually occurs in the elderly, one must first understand the changes that occur with normal aging. In the past decade, studies have identified neurologic changes that occur in normal aging separate from those that develop from disease. Overall, there is a slow loss of many neurologic functions with normal aging, but the loss is subtle, allowing the individual to continue to function normally past age 100 years.

COGNITION

There is an age-related decline in the (1) speed of central processing, (2) performance on timed tasks, (3) recent memory retrieval, and (4) learning. However, verbal intelligence remains well preserved at least through age 80 years. The elderly require more time to process a question centrally, although the answer usually is correct. Memory studies find that, compared with young adults, the elderly have a 10% decline in the time of their immediate recall from working memory. In “benign senescent forgetfulness,” the elderly often describe increased forgetfulness and vague recollections, but studies suggest that this is more from decreased new learning than actual forgetfulness. New learning in the elderly continues throughout life, but the period of time the elderly can concen-

trate diminishes. Some aspects of cognition remain quite stable in the elderly, such as recognition memory and tasks involving well-learned knowledge. While the actual IQ score does not decrease with age because it is corrected for age, the raw score necessary to obtain an IQ of 100 decreases for performance IQ, but not verbal IQ.

VISION AND HEARING

The cranial nerves most affected by aging are those for vision and hearing. Visual loss diminishes due to (1) the pupils becoming progressively smaller and less reactive to light and accommodation, (2) increasing opacity of the lens and vitreous, and (3) subtle retinal changes. Thus presbyopia occurs, with the admittance of less light that is poorly focused on an impaired retina. The range of vertical eye movements diminishes with advanced aging.

Presbycusis is a progressive elevation of the auditory threshold, especially for higher frequencies. Changes of aging, more prominent in men than women, often include loss of cochlear hair cells, degeneration of spiral ganglion neurons, and atrophy of the cochlear stria vascularis. The normal speech range is from 500 to 3000 Hz. When cochlear damage progresses to impair these frequencies, functional hearing loss develops.

STRENGTH, GAIT, AND COORDINATION

With normal aging there is a progressive decline in muscle bulk and strength, speed, and coordination of movement. Muscle wasting is most noticeable in intrinsic hand muscle. Grip strength declines in 85% of normal individuals over age 60, which is out of proportion to loss of muscle bulk. Activities of daily living require 1/3 more time in the elderly, and there is less precise coordination. However, finger-to-nose testing remains normal. Changes of gait in advancing age include a wider-based walking stance, shorter steps, mild loss of accompanying arm swing, and slightly stooped posture.

SENSATION

The elderly have a mild progressive loss of vibration and position sense, mainly in the feet, from a progressive loss of distal peripheral nerve sensory nerve axons. The result is poorer balance, especially with the eyes closed. There is an accompanying diminishment of the ankle jerk, but not loss of it.

Pathologic reflexes, such as clonus, Babinski signs, or grasp reflexes, are not normal aging phenomena.

Dementia

Dementia is an acquired loss of intellect (IQ) that is sufficient to impair the individual's reasoning, planning, and problem-solving skills, as well as the ability to think abstractly, comprehend complex ideas, learn quickly, and learn from experience. Dementia is the fourth most-common cause of death in the United States. The exact prevalence is unknown, but 4 million Americans have dementia and another 3 million have mild cognitive impairment. In most patients, the dementia is progressive (as in Alzheimer's disease), but 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 common pathway is loss of neurons in one or more of the multimodal association cortex regions (prefrontal cortex, limbic system, and parietal lobe). The neuronal loss can occur abruptly by (1) loss of cerebral arterial blood flow from cardiac arrest, (2) cerebral arterial occlusion from thrombosis or emboli, (3) loss of critical brain nutrients from hypoxemia or hypoglycemia, (4) neuronal toxins, (5) head trauma, and (6) CNS infections. Progressive neuronal loss results from (1) neurodegenerative disease, (2) chronic exposure to neurotoxins, (3) vitamin deficiencies, (4) CNS infections, (5) accumulation of cerebral infarctions, and (6) chronic systemic or metabolic encephalopathies (Table 11-3).

Not all patients experience similar clinical deficits. Most patients develop loss of IQ along with additional problems of higher cortical function. For example, patients often forget easily, have difficulty learning new information, and express subtle aphasias and apraxias. Table 11-4 lists the major tests that should be obtained in patients with dementia. In the early stages of dementia, objective neuropsychologic testing (especially memory tests) is abnormal. As the dementia progresses, cerebral atrophy especially is commonly seen on neuroimaging. These images may demonstrate additional abnormalities depending on the disease.

Table 11-3 Major Causes of Dementia in the United States

Neurodegenerative and Neurogenetic Diseases*
<p>Alzheimer's disease (60%)</p> <p>Alzheimer's disease plus other causes (especially multiinfarct dementia) (15%)</p> <p>Dementia with Lewy bodies (10%)</p> <p>Down's syndrome</p> <p>Tauopathies (such as progressive supranuclear palsy and corticobasal degeneration)</p> <p>Huntington's disease</p> <p><i>Hepatolenticular degeneration (Wilson's disease)†</i></p>
Cerebrovascular Disease
<p>Multiinfarct dementia</p> <p>Subacute arteriosclerotic encephalopathy (Binswanger's disease)</p> <p><i>Central nervous system vasculitis</i></p>
Infectious Disease
<p>Creutzfeldt–Jakob disease</p> <p>Sequelae of viral encephalitis (such as herpes simplex encephalitis)</p> <p><i>Neurosyphilis</i></p> <p><i>Human immunodeficiency virus infection (acquired immunodeficiency syndrome dementia)</i></p>
Systemic Metabolic Encephalopathies
<p><i>Hypothyroidism</i></p> <p><i>Hepatic encephalopathy</i></p> <p><i>Vitamin deficiencies (B₁ and B₁₂)</i></p> <p><i>Hypoxic disorders</i> (such as cardiac arrest and chronic obstructive pulmonary disease)</p>
Toxic Encephalopathies
<p><i>Heavy metals</i> (such as lead, arsenic, and mercury)</p> <p>Alcoholism</p> <p>Carbon monoxide</p>
Immune Disorders
<p><i>Systemic lupus erythematosus</i></p> <p>Paraneoplastic syndromes</p>
Psychiatric disorders
<p><i>Depression</i></p>

* **Bold** type represents common causes, with “()” being their approximate incidence.

† Type in italics represents causes that may be reversible.

Mild cognitive impairment (MCI) is the term used to describe the earliest signs and symptoms of a dementia. This is the transitional zone between normal aging and dementia. These individuals complain of memory impairment but still lead relatively independent lives. MCI is defined as occurring in patients who have adequate general cognitive functioning and perform normally in activities of daily living but show subjective memory impairment that is corroborated by a spouse or friend and have objective memory impairment on standardized memory tests that is at least 1.5 SD below the normal for age and education status. Long-term studies of individuals with MCI find 12% per year develop frank dementia compared with 1% for age-matched controls. Limited autopsy studies find that 90% of patients who progress to dementia have Alzheimer's disease.

Alzheimer's Disease

Introduction

Alzheimer's disease (AD) accounts for 60% of dementia in the elderly. Of the elderly, 4 million currently suffer from this disease, and the prevalence is expected to climb to 14 million by 2050. About 1,000 elderly adults are diagnosed daily with AD. The prevalence rate is 1% for individuals ages 60 to 64 years and doubles every 5 years to reach 40% by the age of 85 years.

Pathophysiology

The hallmark pathology of AD is an excess of neuritic plaques and neurofibrillary tangles in the cerebral cortex compared with healthy age-matched controls. Neuritic plaques consist of a central core of β -amyloid protein surrounded by a ring of astrocytes, microglia, and dystrophic neurites. The dystrophic neurites 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. Neuritic plaques and neurofibrillary tangles are maximally seen in the hippocampus, limbic system, and frontal lobes (Figure 11-5).

Table 11-4 Laboratory Workup of Patient with Dementia

Blood Tests
<ul style="list-style-type: none"> Hemogram Electrolytes Glucose Calcium Creatinine Liver function studies Thyroid-stimulating hormone Syphilis serology (rapid plasma reagin) [RPR] test and fluorescent treponemal antibody absorption test (FTA-ABS) if RPR is positive Vitamin B₁₂ level Special tests (such as ceruloplasm level for suspected Wilson's disease)
Neuroimaging
<ul style="list-style-type: none"> Magnetic resonance imaging to evaluate for central nervous system (CNS) masses, hydrocephalus, multiple infarctions, and infection) Computed tomography if patient is poorly cooperative
Neuropsychologic Tests
<p>These tests provide a precise quantitation of various cognitive functions. Tests are available to evaluate IQ, memory, apraxias, aphasias, and behavior. They are indicated for (1) diagnosing whether dementia is present, (2) characterizing the cognitive deficits of an atypical dementia, (3) determining whether the dementia is static or progressive, and (4) following response to treatment.</p>
Lumbar Puncture with Cerebrospinal Fluid (CSF) Exam
<ul style="list-style-type: none"> CSF exam is indicated for patients with cancer, CNS infection, systemic infection, reactive syphilis serology, immunosuppression, vasculitis, rapidly progressive course, atypical course, or age younger than 60 years. Cell count Glucose level Total protein and immunoglobulin G levels Oligoclonal bands Bacterial and fungal cultures Venereal Disease Research Laboratory slide test-CSF (CSF-VDRL)
Optional tests based on clinical presentation and family history
<ul style="list-style-type: none"> Genetic tests (such as for Huntington's disease) Urinary heavy metals (such as for lead, mercury, or arsenic) Toxicology screen (for recreational drugs and medications containing anticholinergics, bromine, sedatives, barbiturates, or tranquilizers) Serological tests (such as for human immunodeficiency virus) Antinuclear antibodies Electroencephalogram Single photon/positron emission computed tomography imaging studies

Additional histological features of AD include the 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 histologic changes are incompletely understood. Current evidence points to the accumulation of an abnormal amyloid protein as being central to the cerebral damage. The β -amyloid gene encodes a large protein, amyloid precursor protein, which is normally inserted into neuronal membranes with a β -amyloid fragment of 40 to 42 amino acids located outside the cell. In AD the β -amyloid fragment is abnormally cleaved, producing a β -amyloid peptide that is poorly catabolized, accumulates locally, and is toxic to neurons.

The most potent risk factor for developing AD is the presence of the apolipoprotein (apo) E4 allele. Of the three forms, E2, E3, and E4, only E4 increases the likelihood of AD. The lifetime risk for individuals carrying an E4 allele is 29% compared with 9% for individuals carrying the other alleles. How the E4 protein increases the risk is unclear. Other risk factors for developing AD are increasing age, head trauma, low folate and vitamin B₁₂ 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 amount of “cognitive reserve” the patient can lose before dementia becomes evident.

Major Clinical Features

Table 11-5 lists common early and late clinical features of AD. Patients usually are apathetic and have impairment of recent memory and some preservation of remote recall memory. Patients lose the ability to perform previously learned complex tasks such as balancing a checkbook, handling money, and reading street maps. They also lose the ability to reason, plan activities, hold complex conversations, and play games such as bridge or chess. Except in the very early stage, patients lose insight into their cognitive problems and deny or ignore their presence. Thus patients may get lost driving their car or walking about in their own town. Some patients experience unexpected periods of agitation, anger, and abnormal sexual activity. As the disease progresses, apraxias become more evident with the inability to dress, prepare a meal, or groom. Meals are often forgotten and patients may become malnourished. Surprisingly, language function is maintained until late, so patients often can carry out simple “cocktail party” conversations

Table 11-5 Common Features of Alzheimer’s Disease

Early Disease	Later Disease
Progressive decline in recent memory	Loss of insight
Progressive decline in executive functioning	Loss of judgment
Normal speech and gait	Behavioral changes with marked mood swings and depression
Mild to moderate frontal-temporal brain atrophy on neuroimaging	Global dementia including apraxias and severe memory loss
Normal Cerebrospinal fluid	Terminal apathy and withdrawal from social situations, leading to virtual mutism Marked brain atrophy on neuroimaging with hydrocephalus ex vacuo

yet cannot discuss current events. As the disease progresses, patients lose the ability to recognize close friends, carry out meaningful conversations, and keep track of time and place.

Nearly 10% of AD occurs in association with vascular dementia. Vascular dementia is characterized pathologically by widespread white matter changes presumably from ischemic brain injury, and multiple infarcts. Clinically, vascular dementia is identified by a tendency for a stepwise progression of dementia.

The clinical or presumptive diagnosis of AD is based on an insidiously progressive decline in intellect, especially recent memory and executive functioning, beginning after age 50 years. This progresses over several years to a global dementia, including loss of insight and judgment as well as behavioral changes. No other medical causes of dementia should be present.

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 biopsy or autopsy. Routine blood and CSF tests are normal. Neuroimaging usually demon-

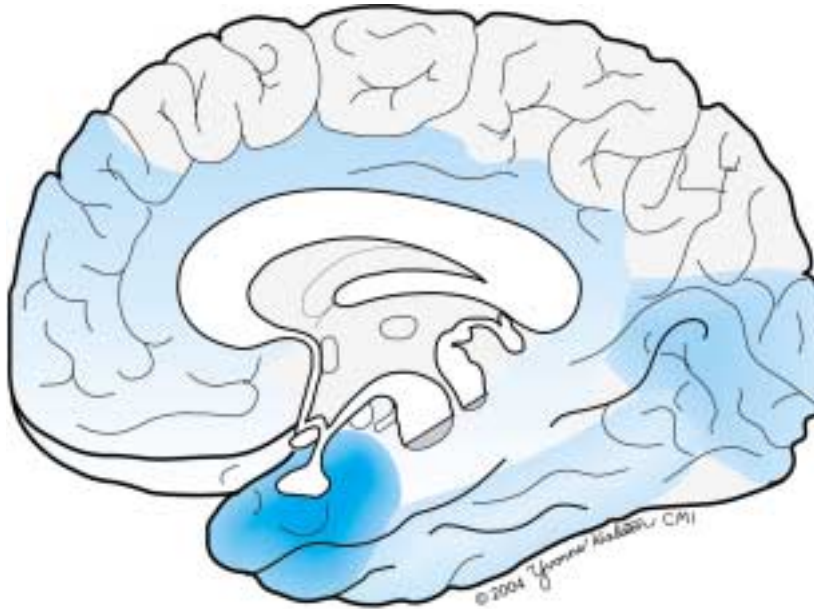


Figure 11-5 Schematic brain of patient with Alzheimer's disease showing locations of neuritic plaques and neurofibrillary tangles.

strates symmetrical brain atrophy that is out of proportion for age, with an accompanying hydrocephalous ex vacuo of the third and lateral ventricles. An EEG shows a diffuse slowing of background activity that is nonspecific. PET/SPECT scans demonstrate hypometabolism and reduced blood flow to the temporal and parietal lobes.

Principles of Management and Prognosis

There is no method to stop or reverse the progression of AD. However, cholinesterase inhibitors produce modest transient improvements in memory and 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. Studies are underway to determine if reducing amyloid production and aggregation or enhancing amyloid removal may offer clinical benefit.

The heart of management lies in a quality caregiver. Family caregivers provide most of the daily care, which can be a 24-hour-a-day undertaking since patients require almost constant supervision. Ideally, patients should be able to safely wander without becoming lost, have meals provided and supervised, and have domestic needs done by oth-

ers (shopping, bill paying, and keeping doctor's appointments). Sudden worsening of confusion occurs when the patient is moved to new surroundings such as a hospital or nursing home. The family caregiver is at risk of becoming exhausted, depressed, and feeling guilty as the disease relentlessly worsens. Use of other family members or professional attendants to allow caregivers time for themselves, or even brief respites where the patient is placed in a nursing home setting, may be needed. It is strongly recommended that the spouse have scheduled time away and respite care.

The duration of AD, once diagnosed, is about 3 to 5 years and death usually comes from pneumonia and other systemic illnesses.

Mental Retardation

Mental retardation is a disability characterized by significant limitations both in intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills. The disability usually begins in early life and before age 18. This definition must be considered within the context of community environments typical of the individual's age peers and culture as

Table 11-6 Major Risk Factors for Mental Retardation

Time Period	Biomedical	Social	Behavioral	Educational
Prenatal	Chromosomal disorders Single-gene disorders Metabolic disorders Cerebral dysgenesis Maternal age and illness	Maternal malnutrition No access to prenatal care	Maternal drug use Maternal alcohol use	Parental cognitive disability without supports
Perinatal	Prematurity Birth injury Neonatal disorders	Lack of access to birth care	Parental rejection of child or caretaking	Lack of medical services
Postnatal	Traumatic brain injury Malnutrition Meningitis Degenerative disorders	Impaired child caregiver Lack of infant stimulation Placement in institution	Child abuse Inadequate safety measures Social deprivation	Delay in medical care or diagnosis Inadequate education services Impaired parenting

well as disabilities in communication, sensorimotor function, and behavior. Disability is the expression of limitations in individual function in a social context and represents a substantial disadvantage to the individual.

Limitation in adaptive behavior affects both daily life and the ability to respond to life changes and environmental demands. Examples of conceptual adaptive skills include language, reading, money concepts, and self-direction. Examples of social adaptive skills include interpersonal conduct, responsibility, self-esteem, gullibility, naiveté, and following rules and laws. Examples of practical adaptive skills include activities of daily living (eating, dressing, and toileting), functional aspects of daily life (transportation, housekeeping, money management, and taking medication) and occupational skills.

Mental retardation is often classified with respect to severity. Mental retardation that is mild presents with an IQ between 50 and 70; moderate is between 35 and 49, severe between 20 and 34, and profound below 20.

Mental retardation may occur from a wide variety of biomedical, social, behavioral, and education problems that occur in the prenatal, perinatal, or postnatal periods. Table 11-6 lists risk factors for each time period. Table 11-7 lists the major causes of mental retardation. It is important to understand that some causes of mental retardation are due to progressive degenerative illnesses resulting in steady worsening of the IQ and mental retardation. Other causes are static (such as peri-

natal birth injury) and do not progress as the child grows. However, the manifestations of the mental retardation may evolve as the child fails to gain expected childhood developmental skills. Appro-

Table 11-7 Common Causes of Mental Retardation

Prenatal
Fetal alcohol syndrome Down's syndrome Fragile-X syndrome Cerebral dysgenesis Autism (not all cases)
Perinatal
Birth injury Marked prematurity and very low birth weight, especially with periventricular hemorrhage Infant illnesses such as severe sepsis, bacterial meningitis, and undiagnosed hypothyroidism
Postnatal
Head trauma from child abuse (shaken baby syndrome), sports injury, or automobile accident Severe malnutrition such as marasmus or kwashiorkor Toxic metabolic disorders such as lead intoxication Severe epilepsy Childhood degenerative diseases Infections such as bacterial meningitis, whooping cough, and encephalitis

appropriate treatment of the child with mental retardation requires establishing the etiology and treating the cause, if possible, as well as maximizing the personal support the child requires. Mental retardation is often accompanied by physical disabilities that also require skilled attention. In children with static mental retardation the IQ may not improve over time, but the function in adaptive skills can and this would be significant in the individual's quality of life.

RECOMMENDED READING

Albert ML, Knoefel JE, eds. *Clinical Neurology of Aging*. New York: Oxford University Press; 1994. (Covers many neurologic aspects of normal aging.)

Cummings JL, Cole G. Alzheimer's disease. *JAMA* 2002;287;2335–2338. (Current review of pathophysiology and treatment.)

Luckasson R, Borthwick-Duffy S, Buntinx WHE, et al. *Mental Retardation: Definition, Classification, and Systems of Support*, 10th ed. Washington DC: American Association of Mental Retardation; 2002. (Current overview of mental retardation and available support systems.)

Petersen RC. Aging, mild cognitive impairment, and Alzheimer's disease. *Neurol Clin* 2000;18:789–805. (Nice review of mild cognitive impairment and the workup of patients with suspected dementia.)