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tricyclics, such as amitriptyline, or anticonvulsants, such as topira mate or valproate, are most often tried. This phenotype can be seen in combination with migraine and the TACs, in which cases treatment of the primary headache disorder is often effective for the nummular headache as well. Hypnic Headache This headache syndrome typically begins a few hours after sleep onset. The headaches last from 15–30 min and are typically moderately severe and generalized, although they may be unilateral and can be throbbing. Patients may report falling back to sleep only to be awakened by a further attack a few hours later; up to three repetitions of this pattern occur through the night. Daytime naps can also precipitate head pain. Most patients are female, and the onset is usually after age 60 years. Headaches are typically bilateral but may be unilateral. Photophobia, phonophobia, and nausea are usually absent. The major secondary consideration in this headache type is poorly controlled hypertension; 24-h blood pressure monitoring is recommended to detect this treatable condition. TREATMENT Hypnic Headache Patients with hypnic headache generally respond to a bedtime dose of lithium carbonate (200–600 mg). One to two cups of coffee, or caffeine 60 mg orally, at bedtime may be effective in approximately one-third of patients. Reports suggest that verapamil, 160 mg; flu narizine, 5 mg nightly; or indomethacin, 25–75 mg nightly, can be effective. New Daily Persistent Headache Primary new daily persistent headache (NDPH) occurs in both men and women. It can be of the migrainous type, with features of migraine, or it can be featureless, appearing as new-onset TTH. Those with migrainous features are the most common form and include unilateral headache and throbbing pain; each feature is present in about one-third of patients. Nausea, photophobia, and/or phonophobia occur in about half of patients. Some patients have a previous history of migraine. NDPH may be more common in adolescents. Treatment of migrainous-type primary NDPH consists of using the preventive therapies effective in migraine (see above). Featureless NDPH is one of the primary headache disor ders most refractory to treatment. Standard preventive therapies can be offered but are often ineffective. The secondary NDPHs are discussed elsewhere (Chap. 17). ■ ■FURTHER READING Buse DC et al: Demographics, headache features, and comorbidity profiles in relation to headache frequency in people with migraine: Results of the American Migraine Prevalence and Prevention (AMPP) Study. Headache 60:2340, 2020. Charles A, Pozo-Rosich P: Targeting calcitonin gene-related pep tide: A new era in migraine therapy. Lancet 394:1765, 2019. Cittadini E, Goadsby PJ: Hemicrania continua: A clinical study of 39 patients with diagnostic implications. Brain 133:1973, 2010. Cittadini E et al: Paroxysmal hemicrania: A prospective clinical study of thirty-one cases. Brain 131:1142, 2008. de Boer I et al: Advance in genetics of migraine. Curr Opin Neurol 32:413, 2019. Ferrari MD et al: Migraine. Nat Prim 8:2, 2022. Goadsby PJ et al: Pathophysiology of migraine: A disorder of sensory processing. Physiol Rev 97:553, 2017. Schankin CJ et al: “Visual snow”: A disorder distinct from persistent migraine aura. Brain 137:1419, 2014. Wei DY, Goadsby PJ: Cluster headache pathophysiology: Insights from current and emerging

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Gil D. Rabinovici, Peter A. Ljubenkov,

William W. Seeley, Bruce L. Miller

Alzheimer’s Disease ALZHEIMER’S DISEASE Approximately 55 million people across the world are living with dementia. Alzheimer’s disease (AD) is the most common cause of dementia, contributing to an estimated 60–70% of all cases. Total U.S. health care costs related to dementia care are estimated at $360 billion in 2024, translating into an average of ~$25,000 per patient. Further more, the emotional toll for family members and caregivers is immea surable. AD can manifest as early as the third decade of life, but it is the most common neuropathology contributing to dementia in the elderly. Patients most often present with an insidious loss of episodic memory followed by a slowly progressive dementia. In typical amnestic AD, brain atrophy begins in the medial temporal lobes before spreading to inferior temporal, lateral and medial parietal, and dorsolateral frontal cortices. Microscopically, there are widespread neuritic plaques con taining amyloid beta (Aβ), neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau filaments, and Aβ accumulation in blood vessel walls in cortex and leptomeninges (see “Pathology,” below). The identification of causative mutations and susceptibility genes for AD has provided a foundation for rapid progress in understanding the biological basis of the disorder. The major genetic risk factor for AD is the ε4 allele of the apolipoprotein E (ApoE) gene. Carrying one ε4 allele increases the risk for AD by two- to threefold in women, whereas car rying two alleles increases the risk 10- to 15-fold in both sexes. Rapid progress in the development of imaging, cerebrospinal fluid (CSF), and plasma biomarkers of Aβ and phosphorylated tau has enabled detec tion of AD pathologic hallmarks in living people, opening the door to early detection and intervention with biologically specific therapies. CHAPTER 442 Alzheimer’s Disease ■ ■CLINICAL MANIFESTATIONS The cognitive changes of AD tend to follow a characteristic pattern, beginning with memory impairment and progressing to deficits in executive, language, and visuospatial functions. Yet, ~20% of patients with AD present with nonmemory complaints such as word-finding, organizational, or navigational difficulty. In other patients, visual processing dysfunction (referred to as posterior cortical atrophy syn drome) or a progressive “logopenic” aphasia characterized by difficul ties with naming and repetition is the primary manifestation of AD for years before progressing to involve memory and other cognitive domains. Still other patients may present with an asymmetric akineticrigid-dystonic (“corticobasal”) syndrome or a dysexecutive/behavioral (i.e., “frontal” variant of AD). Depression, social withdrawal, and anxi ety occur in early disease stages and may represent a prodrome before cognitive symptoms are apparent. In early stages of typical amnestic AD, the memory loss may go unrecognized or be ascribed to benign forgetfulness of aging. The term subjective cognitive decline refers to self-perceived worsening in mem ory or other cognitive abilities that may not be noticeable to others or apparent on formal neuropsychological testing. Once the memory loss becomes noticeable to the patient and spouse and is confirmed on standardized memory tests, the term mild cognitive impairment (MCI) is often used. This construct provides useful prognostic information because ~50% of patients with MCI (roughly 12% per year) will prog ress to the dementia stage over 4 years. Increasingly, the MCI construct is being replaced by the notion of “early symptomatic AD” to signify that AD is considered the underlying disease (based on clinical or bio marker evidence) in a

patient who remains functionally compensated. Even earlier in the course, “preclinical AD” refers to a person with bio marker evidence of amyloid pathology (with or without tau pathology) in the absence of symptoms. It is estimated that preclinical biomarker changes may precede clinical symptoms by 20 years or more, creating a window of opportunity for early-stage treatment and prevention

trials. Emerging evidence suggests that partial and sometimes general ized seizures herald AD and can occur even prior to dementia onset, especially in younger patients and those with autosomal dominant AD-causing mutations.

Eventually with AD, the cognitive problems begin to interfere with daily activities, such as keeping track of finances, following instructions on the job, driving, shopping, and housekeeping. Some patients are unaware of these difficulties (anosognosia), but most remain acutely attuned to their deficits in early disease stages. Changes in environment (travel, relocation, hospitalization) tend to destabilize the patient. Over time, patients become lost on walks or while driving. Social graces, routine behavior, and superficial conversation may be surprisingly intact, even into the later stages of the illness. In the middle stages of AD, the patient is unable to work, is easily lost and confused, and requires daily supervision. Language becomes impaired—first naming, then comprehension, and finally fluency. Word-finding difficulties and circumlocution can be evident in the early stages, even when formal testing demonstrates intact naming and fluency. Apraxia emerges, manifesting as trouble performing learned sequential motor tasks such as using utensils or appliances. Visuospa tial deficits begin to interfere with dressing, eating, or even walking, and patients fail to solve simple puzzles or copy geometric figures. Simple calculations and clock reading become difficult in parallel. PART 13 Neurologic Disorders In the late stages, some persons remain ambulatory, wandering aimlessly. Loss of judgment and reasoning is inevitable. Delusions are prevalent and usually simple, with common themes of theft, infidelity, or misidentification. Disinhibition and uncharacteristic belligerence may occur and alternate with passivity and withdrawal. Sleep-wake patterns are disrupted, and nighttime wandering becomes disturbing to the household. Some patients develop a shuffling gait with generalized muscle rigidity associated with slowness and awkwardness of move ment. Patients often look parkinsonian (Chap. 446) but rarely have a high-amplitude, low-frequency tremor at rest. There is a strong overlap between dementia with Lewy bodies (DLB) (Chap. 445) and AD, and some AD patients develop more classical parkinsonian features. In the end stages, patients with AD become rigid, mute, incontinent, and bedridden, and need help with eating, dressing, and toileting. Hyperactive tendon reflexes and myoclonic jerks (sudden brief con tractions of various muscles or the whole body) may occur spontane ously or in response to physical or auditory stimulation. Often death results from malnutrition, secondary infections, pulmonary emboli, heart disease, or, most commonly, aspiration. The typical duration of symptomatic AD is 8–10 years, but the course ranges from 1 to 25 years. For unknown reasons, some patients with AD show a steady decline in function while others have prolonged plateaus without major deterioration. An increased risk for seizures is also increasingly recognized as a feature of AD; different seizure types (both generalized and focal onset) have been reported, and these occur more frequently as the disease progresses. ■ ■DIAGNOSIS See also “Other Causes of Dementia,” below, and the general discus sion of dementia presented in Chap. 31. Early in the disease course, other etiologies of dementia should be excluded (see Tables 31-1, 31-3, and 31-4). Slowly progressive decline in memory and orientation, normal results on systemic laboratory tests, and a magnetic resonance imaging (MRI) or computed

tomography (CT) scan showing only distributed or posteriorly predominant cortical and hippocampal atrophy (see below) are suggestive of AD. A clinical diagnosis of AD reached after careful evaluation is confirmed at autopsy ~70–80% of the time, with misdi agnosed cases usually resulting from limbic-predominant age-related TDP-43 encephalopathy (LATE) with or without hippocampal sclero sis, primary age-related tauopathy (PART), Lewy body disease (LBD), vascular pathology, or frontotemporal lobar degeneration (FTLD; Chap. 443). Simple clinical clues are useful in the differential diagnosis. Early prominent gait disturbance with only mild memory loss suggests vascular dementia or, rarely, normal pressure hydrocephalus (NPH),

discussed later. Resting tremor with stooped posture, bradykinesia, and masked facies suggest PD (Chap. 446) or DLB (Chap. 445). When dementia occurs after a well-established diagnosis of PD, PD dementia (PDD) is usually the correct diagnosis, but many patients with this diagnosis will show a mixture of AD and LBD at autopsy. The early appearance of parkinsonian features in association with fluctuating alertness, visual hallucinations, or delusional misidentification sug gests DLB. Chronic alcoholism should prompt the search for vitamin deficiency. Loss of joint position and vibration sensibility accompanied by Babinski signs suggests vitamin B12 deficiency, especially in a patient with a history of autoimmune disease, small bowel resection or irradia tion, or veganism (Chap. 104). Early onset of a focal seizure suggests a metastatic or primary brain neoplasm (Chap. 95). Previous or ongoing depression raises suspicion for depression-related cognitive impair ment, although significant cognitive changes with depression is com mon and AD and DLB can feature a prodrome of depression or anxiety. A history of treatment for insomnia, anxiety, psychiatric disturbance, or epilepsy suggests chronic drug intoxication. Rapid progression over a few weeks or months associated with rigidity and myoclonus suggests Creutzfeldt-Jakob disease (CJD) (Chap. 449). Prominent behavioral changes with intact navigation and focal anterior-predominant atro phy on brain imaging are typical of FTD. A positive family history of dementia suggests either one of the familial forms of AD or one of the other genetic disorders associated with dementia, such as FTD (Chap. 443), Huntington’s disease (HD) (Chap. 447), prion disease (Chap. 449), or rare hereditary ataxias (Chap. 450). Electroencephalogram (EEG) is usually normal or shows nonspe cific slowing; prolonged EEG can be used to seek out intermittent nonconvulsive seizures. Structural neuroimaging studies (CT and MRI) do not show a single specific pattern with AD and may be normal early in the disease. As AD progresses, more distributed but usually posterior-predominant cortical atrophy becomes apparent, along with atrophy of the medial temporal memory structures (see Fig. 31-1). The main purpose of structural imaging is to exclude other disorders, such as primary and secondary neoplasms, vascular dementia, diffuse white matter disease, and normal-pressure hydrocephalus (NPH). Imaging also helps to dis tinguish AD from other degenerative disorders, such as frontotemporal dementia (FTD) (Chap. 443) or the prion disorder CJD (Chap. 449), which feature imaging patterns that are different from AD. Functional imaging studies, such as fluorodeoxyglucose (FDG) positron emission tomography (PET), reveal hypometabolism in the posterior temporalparietal cortex in AD (see Fig. 31-1). Amyloid PET imaging (e.g., with radiotracers [11C]PIB, [18F]flo rbetapir, [18F]florbetaben, or [18F]flutemetamol) confirms the pres ence of neuritic and diffuse Aβ plaques throughout the neocortex (Fig. 442-1). [18F]florbetapir, [18F]florbetaben, and [18F]flutemetamol are approved for clinical use in the United States and other countries. Although amyloid PET binding is detected in AD, ~25% of cognitively unimpaired older individuals also have positive scans, thought to rep resent preclinical disease and an increase in the risk of converting to clinical AD. Similarly, dementia due to a non-AD disorder can be the underlying etiology in a patient who tests positively on amyloid PET due to

comorbid AD pathology. Amyloid PET ligands also bind to vas cular Aβ deposits in cerebral amyloid angiopathy (CAA) (Chap. 439). Therefore, clinical use of amyloid PET should be restricted to specific scenarios in which knowledge of amyloid status is expected to impact diagnosis and change management. For example, a negative amyloid PET scan in a patient with dementia makes an AD diagnosis unlikely. Conversely, a positive PET scan can be used to establish eligibility for novel amyloid-lowering therapies in a patient who meets the clinical criteria for treatment (see below). Tau PET radiotracers (e.g., [18F]flortaucipir, [18F]MK-6240, [18F] PI-2620) bind to the paired helical filaments that form neurofibril lary tangles and are primarily available in the research setting. [18F] Flortaucipir is also approved for clinical use in the United States "to estimate the density and distribution of aggregated tau neurofibrillary tangles in adult patients with cognitive impairment who are being evaluated for AD." The pattern of binding is largely consistent with

FIGURE 442-1 Molecular imaging of Alzheimer's disease pathophysiology in an 81-year-old with mild Alzheimer's disease. A. Aβ positron emission tomography (PET) with [11C]PIB reveals extensive radiotracer retention in neocortex, consistent with the known distribution of amyloid plaques. B. Tau PET with [18F]FTP shows asymmetric uptake predominantly in the left temporal cortex, consistent with intermediate-stage neurofibrillary tangles. Tracer uptake in midbrain and basal ganglia represents "off-target" (non-tau-related) tracer retention. C. Fluorodeoxyglucose (FDG)-PET reveals reduced tracer uptake in left greater than right temporal and parietal cortex, indicative of decreased synaptic activity. The pattern of hypometabolism corresponds more closely to the pattern of tau than amyloid deposition. A–C. Axial brain slices are shown in neurologic orientation. L, left; R, right; SUVR, standardized uptake value ratio, a quantitative measure of PET radiotracer retention. Braak neuropathologic staging of neurofibrillary tangles, with early retention in medial temporal regions, followed by spread into tempo roparietal and cingulate cortices, dorsolateral prefrontal regions, and ultimately, primary sensory and motor areas. However, tau PET signal lags behind neuropathologic staging of tangles due to limited sensitiv ity, and completely negative tau PET does not rule out early neurofi brillary pathology (Braak stages I–III). Notably, tau PET radiotracers developed to detect AD-related tau aggregation have limited utility in detecting aggregated tau in non-AD tauopathies (e.g., progressive supranuclear palsy [PSP], cortical basal degeneration [CBD], chronic traumatic encephalopathy [CTE]). Routine spinal fluid examination is generally normal, but CSF reductions in Aβ42 levels and the Aβ42/Aβ40 ratio correlate with amy loid deposition, and increases in phosphorylated tau (at residue 181 or 217; p-Tau181 or p-Tau217) detect AD-related changes in tau phosphorylation and secretion. On the other hand, increases in total tau levels represent a nonspecific finding seen in AD but also in other causes of neurodegeneration. Several CSF AD biomarker assays are now approved for clinical use in the United States and other countries. Decreases in the Aβ42/Aβ40 ratio or increases in the p-Tau181/Aβ42 ratio show higher agreement with amyloid PET results or AD neuropathol ogy than any single CSF analyte. Increase in the microtubule-binding region (MTBR) of tau containing the residue 243 (MTBR-tau243) is an experimental biomarker (not yet available in clinical practice) that bet ter correlates with neurofibrillary tangles and tau PET binding. In recent years, there has been significant progress in the develop ment of plasma measurements of Aβ and phosphorylated tau with ultra-sensitive immunoassays or mass spectrometry. These bloodbased AD biomarkers are entering the clinical arena and will undoubt edly improve access, scalability, and cost-effectiveness of AD biomarker testing in diverse practice settings. Similar to CSF, decreases in the plasma Aβ42/Aβ40 ratio and increases in plasma p-Tau181, p-Tau217, or p-Tau231 show high concordance with positive amyloid PET scans and AD neuropathology at autopsy. In conjunction with a clinical

evaluation, plasma assays may be sufficient to establish the diagnosis

CHAPTER 442 Alzheimer’s Disease of AD for certain use cases, with the highest-performing assays show ing comparable diagnostic performance to CSF biomarkers in detect ing AD neuropathology. It is important to note that concentrations of Aβ and p-Tau in blood can be impacted by medical comorbidities (e.g., reduced creatinine clearance, elevated body mass index), which may lead to false-positive or false-negative results, particularly if values are near the test’s threshold. While positive AD imaging or fluid biomarkers are highly predic tive of underlying AD neuropathology, the question of whether AD represents a primary or contributing cause to an individual patient’s clinical presentation is not always straightforward. For example, in a patient who presents at a relatively young age with classical AD symptoms, compatible MRI changes, and positive CSF or amyloid PET, it is highly likely that AD neuropathology is the primary cause of cognitive decline. In an elderly patient with the same clinical profile, however, AD is still likely to be contributing to impairment, although a contribution of other non-AD co-pathologies is also likely. In the case of a patient who presents with classical FTD and positive AD biomarkers, FTLD pathology may be the primary cause of impairment, with the positive AD biomarkers indicating incidental preclinical AD. Conversely, a patient who presents with a clinical syndrome suggest ing AD but with negative AD biomarkers is likely to have a non-AD neuropathology as the primary cause of impairment. In older patients, age-related conditions that selectively target the medial temporal lobes, such as LATE or PART, can mimic AD clinically, and these should be high on the list of diagnostic possibilities in biomarker-negative indi viduals presenting with a progressive amnestic dementia. The proliferation of AD biomarkers has led to a movement to rede fine AD on purely biological grounds, based solely on positivity of AD biomarkers and independent of the clinical syndrome. In the Revised Criteria for Diagnosis and Staging of AD proposed by the Alzheimer’s Association, amyloid PET, CSF/plasma Aβ, and p-Tau measures are considered “core 1 biomarkers” that are necessary and sufficient for the diagnosis of AD, irrespective of clinical symptoms. Tau PET is designated a “core 2” biomarker to be used for biomarker-based disease

PART 13 Neurologic Disorders staging. Clinical staging is performed independent of biomarkers based on the level of functional impairment, spanning the range from asymp tomatic “preclinical” AD to severe dementia. ■ ■EPIDEMIOLOGY The most important risk factors for AD are increasing age and a positive family history. In the United States, ~10% of people over age 65 have AD, including 3% of people age 65–74, 17% of people age 75–84, and 32% of people age 85 and older. A positive family history of demen tia suggests a genetic contribution to AD, which is usually attributable to the apolipoprotein E (ApoE) ε4 risk allele. Autosomal dominant inheritance occurs in only 1–2% of patients and is typically accompa nied by a multigenerational history of early-onset dementia. Female sex is a risk factor independent of the greater longevity of females, and women who carry a single Apo ε4 allele are more susceptible than are male ε4 carriers. A history of mild-to-severe traumatic brain injury increases the risk for AD. AD is more common in groups with low edu cational attainment, but education influences test-taking ability, and it is clear that AD can affect persons of all intellectual levels. One study found that the capacity to express complex written language in early adulthood correlated with a decreased risk for AD. Similarly, illiteracy and low educational attainment are risk factors for dementia. Numer ous environmental factors, including aluminum, mercury, and viruses, have been proposed as causes of AD, but rigorous studies have failed to demonstrate a significant role for any of these exposures. Similarly, several studies suggest that the use of nonsteroidal anti-inflammatory agents is associated with a

decreased risk of AD, but this risk has not been confirmed in large prospective studies. Vascular disease, and stroke in particular, seems to lower the threshold for the clinical expres sion of AD. Also, in many patients with AD, amyloid angiopathy can lead to microhemorrhages, large lobar hemorrhages, ischemic infarc tions most often in the subcortical white matter, or in rare cases an inflammatory leukoencephalopathy. Diabetes increases the risk of AD threefold. Elevated homocysteine and cholesterol levels; hypertension; obesity; hearing loss; tobacco use; diminished serum levels of folic acid; low dietary intake of fruits, vegetables, and red wine; sleep disorders; low levels of exercise; and air pollution exposure are all being explored as potential risk factors for dementia in general and AD in particular. ■ ■PATHOLOGY At autopsy, the earliest and most severe degeneration is usually found in the medial temporal lobe (entorhinal/perirhinal cortex and hippo campus), inferolateral temporal cortex, and nucleus basalis of Meynert. The characteristic microscopic findings are neuritic plaques and NFTs (Fig. 442-2). These lesions accumulate in small numbers during nor mal brain aging but dominate the picture in AD. The overall burden of AD neuropathologic changes can be graded based on the topography of Aβ plaques, the density of neuritic plaques, and the spatial extent of NFTs present. Increasing evidence suggests that soluble amyloid spe cies called oligomers may cause cellular dysfunction and represent the early toxic molecule in AD. Eventually, further amyloid polymerization and fibril formation lead to neuritic plaques, which contain a central core of amyloid, proteoglycans, ApoE, α-antichymotrypsin, and other proteins. Aβ is a protein of 39–42 amino acids that is derived pro teolytically from a larger transmembrane protein, amyloid precursor protein (APP), when APP is cleaved by β and γ secretases (Fig. 442-3). The normal function of the Aβ peptides is uncertain. APP has neuro trophic and neuroprotective properties. The plaque core is surrounded by a halo, which contains dystrophic, tau-immunoreactive neurites and activated microglia. The accumulation of Aβ in cerebral arterioles is termed amyloid angiopathy. NFTs are composed of silver-staining neu ronal cytoplasmic fibrils composed of abnormally phosphorylated tau protein; they appear as paired helical filaments by electron microscopy. Tau binds to and stabilizes microtubules, supporting axonal transport of organelles, glycoproteins, neurotransmitters, and other important cargoes throughout the neuron. Once hyperphosphorylated, tau can no longer bind properly to microtubules and redistributes from the axon to throughout the neuronal cytoplasm and distal dendrites, compromising function. Other theories emphasize that abnormal conformations of tau induce misfolding of native (unfolded) tau into pathologic conformations and that this prion-like templating process is responsible for tau spreading (Chap. 435). Finally, patients with AD often show comorbid LBD, TDP-43, or vascular pathology. Most pre vailing rodent models of AD involve expression of mutant transgenes that leads to Aβ42 accumulation in the absence of tauopathy. Even in these models, diminishing neuronal tau ameliorates cognitive defi cits and nonconvulsive seizures while Aβ42 continues to accumulate, A B FIGURE 442-2 Neuropathology of Alzheimer’s disease. A. Early neurofibrillary degeneration, consisting of neurofibrillary tangles and neuropil threads, preferentially affects the medial temporal lobes, especially the stellate pyramidal neurons that compose the layer 2 islands of entorhinal cortex, as shown using Gallyas silver staining. B. Higher magnification view reveals the fibrillar nature of tangles (arrows) and the complex structure of neuritic plaques (arrowheads), whose major component is Aβ (inset shows immunohistochemistry for Aβ). Scale bars are 500 μM in A, 50 μM in B, and 20 μM in B inset.

Step 1: Cleavage by either α or β secretase APP β α Cell membrane γ β Secretase product α Secretase product Step 2: Cleavage by γ secretase P3 Aβ40 Aβ42 Nontoxic Nontoxic Toxic Amyloidogenic FIGURE 442-3 Amyloid precursor protein (APP) is catabolized by α, β, and γ

secretases. A key initial step is the digestion by either β secretase (BASE) or α secretase (ADAM10 or ADAM17 [TACE]), producing smaller nontoxic products. Cleavage of the β secretase product by γ secretase (Step 2) results in either the toxic Aβ42 or the nontoxic Aβ40 peptide; cleavage of the α secretase product by γ secretase produces the nontoxic P3 peptide. Excess production of Aβ42 is a key initiator of cellular damage in Alzheimer's disease (AD). Therapeutics for AD have focused on attempts to reduce accumulation of Aβ42 by antagonizing β or γ secretases, promoting α secretase, or clearing Aβ42 that has already formed by use of specific antibodies. raising hope for tau-lowering therapies in humans. Biochemically, AD is associated with a decrease in the cortical levels of several proteins and neurotransmitters, especially acetylcholine, its synthetic enzyme choline acetyltransferase, and nicotinic cholinergic receptors. Reduc tion of acetylcholine reflects degeneration of cholinergic neurons in the nucleus basalis of Meynert, located just below the thalamus and adja cent to the third ventricle, that project throughout the cortex. There is also noradrenergic and serotonergic depletion due to degeneration of upper brainstem nuclei such as the locus coeruleus (norepinephrine) and dorsal raphe (serotonin), where tau-immunoreactive neuronal cytoplasmic inclusions can be identified in early adult life, even in individuals lacking entorhinal cortex NFTs. ■ ■GENETIC CONSIDERATIONS Several genes play an important role in the pathogenesis of AD. One is the APP gene on chromosome 21. Adults with trisomy 21 (Down's syndrome) consistently develop the typical neuropatho logic hallmarks of AD if they survive beyond age 40 years, and many develop a progressive dementia superimposed on their baseline defi cits. The extra dose of the APP gene on chromosome 21 is the initiating cause of AD in adult Down's syndrome and results in excess cerebral amyloid production. Supporting this hypothesis, some families with early-age-of-onset familial AD (FAD) have point mutations in APP. Although very rare, these families were the first examples of singlegene autosomal dominant transmission of AD. Investigation of large families with multigenerational FAD led to the discovery of two additional AD-causing genes, the presenilins. Presenilin-1 (PSEN-1) is on chromosome 14 and encodes presenilin-1 protein (also known as S182). Mutations in this gene cause an earlyage-of-onset AD, with onset typically before age 60 and often before age 50, transmitted in an autosomal dominant, highly penetrant fashion. More than 100 different mutations have been found in the PSEN-1 gene in families from a wide range of ethnic backgrounds. Pre senilin-2 (PSEN-2) is on chromosome 1 and encodes the presenilin-2 protein (also known as STM2). A mutation in the PSEN-2 gene was first found in a group of American families with Volga German eth nic background. Mutations in PSEN-1 are much more common than those in PSEN-2. The presenilins are highly homologous and encode similar proteins that at first appeared to have seven transmembrane domains (hence the designation STM), but subsequent studies have suggested eight such domains, with a ninth submembrane region. Both presenilins are cytoplasmic neuronal proteins that are widely

expressed throughout the nervous system. They are homologous to a cell-trafficking protein, sel 12, found in the nematode Caenorhabditis elegans. Prior to symptom onset, patients with mutations in the prese nilin genes have elevated CSF levels of Aβ42, and in cell culture, PSEN-1 mutations produce increased Aβ42. PSEN-1 is involved in the cleavage of APP at the γ secretase site, and mutations in either gene (PSEN-1 or APP) may disturb γ secretase cleavage. Mutations in PSEN-1 are the most common cause of early-age-of-onset FAD, representing 40–70% of all cases. Mutations in PSEN-1 tend to produce AD with an earlier age of onset (mean onset 45 years) and a shorter, more rapidly progres sive course (mean duration 6–7 years) than mutations in PSEN-2 (mean onset 53 years; duration 11 years). Although some carriers of PSEN-2 mutations have had onset of dementia after the age of 70, mutations in the presenilins rarely lead to late-age-of-onset

AD. Clinical genetic testing for these uncommon mutations is available but likely to be revealing only in early-age-of-onset FAD and should be performed in association with formal genetic counseling.

CHAPTER 442 The Apoε gene on chromosome 19 is involved in the pathogenesis of AD. The protein product, ApoE, participates in cholesterol transport (Chap. 419), and the gene has three alleles: ε2, ε3, and ε4. The Apo ε4 allele confers increased risk of AD in the general population, including sporadic and late-age-of-onset familial forms. Approximately 24–30% of the nondemented white population has at least one ε4 allele (12–15% allele frequency), and ~2% are ε4/ε4 homozygotes. Among patients with AD, 40–65% have at least one ε4 allele, a highly significant eleva tion compared with controls. The increased risk of AD associated with a single ε4 allele is approximately three times higher than in ε4 noncar riers (and higher in female than male heterozygotes), while the risk in ε4 homozygotes is 10–15 times higher than in ε4 noncarriers. The risk of AD in Apo ε4 carriers also varies by racial and ethnic background, with increased risk in East Asians and decreased risk in African Americans and Hispanics compared to whites. Additionally, many patients with AD have no ε4 allele, and ε4 carriers may never develop AD. Therefore, ε4 is neither necessary nor sufficient to cause AD. Nev ertheless, the Apo ε4 allele represents the most important genetic risk factor for sporadic AD and acts as a dose-dependent disease modifier, with each Apo ε4 allele associated with an approximately 10-year ear lier age of onset. The association between Apo ε4 and AD is strongest in patients between the ages of 60 and 85 and is weaker in younger patients and in the very old. The precise mechanisms through which Apo ε4 confers AD risk or hastens onset remain unclear, but ε4 leads to less efficient amyloid clearance and production of toxic fragments from cleavage of the molecule. Apo ε can be identified in neuritic plaques and may also be involved in neurofibrillary tangle formation, because it binds to tau protein. Interestingly, carriers of a point muta tion in Apo ε3, termed the Christchurch mutation, may be protective against tau aggregation and dementia despite having amyloid plaques. Apo ε4 decreases neurite outgrowth in dorsal root ganglion neuronal cultures, perhaps indicating a deleterious role in the brain’s response to injury. Increasing evidence suggests that the ε2 allele may reduce AD risk. The ε4 allele is also associated with increased risk for CAA, DLB, and vascular dementia, while its association with FTD is uncertain. Some evidence suggests that ε4 may worsen the expression of non-AD neurodegenerative disorders, as well as following head trauma and other brain injuries. Use of Apo ε4 testing in AD diagnosis remains controversial because its predictive value remains unclear and many individuals with the ε4 allele will never develop dementia. However, clinical Apo ε4 testing is recommended for patients who are being evaluated for treatment with anti-Aβ monoclonal antibodies in order to determine their risk of adverse effects (see below). ApoE genotyping is available in some straight-to-consumer genetic testing platforms. Alzheimer’s Disease Additional genes are also likely to be involved in AD, especially as minor risk alleles for sporadic forms of the disease. Genome-wide asso ciation studies have identified >40 additional common genetic variants that, individually, have small (i.e., odds ratios ~1.1–1.2 or 0.8–0.9) impact on the risk of AD. Implicated genes converge in biological path ways related to innate immunity, lipid metabolism, and synaptic func tion. Examples include the clusterin (CLU), phosphatidylinositol-binding clathrin assembly protein (PICALM), and complement component

(3b/4b) receptor 1 (CR1) genes, among others. CLU may play a role in synapse turnover, PICALM participates in clathrin-mediated endocytosis, and CR1 may be involved in amyloid clearance or synapse loss through the complement pathway. TREM2 is a gene involved with inflammation that

increases the likelihood of dementia. Homozygous mutation carriers develop a frontal dementia with bone cysts (Nasu-Hakola disease), whereas heterozygotes are predisposed to the development of AD. TREM2 risk alleles are rare but have strong effects, with odds ratios estimated at 3–4 for developing clinical AD. Polygenic hazard scores that integrate the presence of multiple risk and protective alleles may be useful in predicting an individual's lifetime risk of developing AD. The vast majority of AD genetic studies have focused on white populations of European descent, and much less is known about the genetics of AD in nonwhite populations.

TREATMENT Alzheimer's Disease PART 13 Neurologic Disorders The management of AD requires a multidomain approach that includes neurotransmitter-based therapies to manage symptoms, emerging molecular therapies that target AD pathophysiology with the goal of slowing disease progression and clinical decline, and ongoing patient and caregiver education. NEUROTRANSMITTER-BASED THERAPIES Donepezil (target dose, 10 mg daily), rivastigmine (target dose, 6 mg twice daily or 9.5-mg patch daily), galantamine (target dose, 24 mg daily, extended-release), and memantine (target dose, 10 mg twice daily) are approved by the U.S. Food and Drug Administration (FDA) for the treatment of AD. Dose escalations for each of these medications must be carried out over 4–6 weeks to minimize side effects. The pharmacologic action of donepezil, rivastigmine, and galantamine is inhibition of the cholinesterases, primarily acetylcholinesterase, with a resulting increase in cerebral acetylcholine levels. Memantine appears to act by blocking overexcited N-methyl-d-aspartate (NMDA) glutamate receptors. Double-blind, placebo-controlled, crossover studies with cholinesterase inhibitors (in mild-to-severe AD dementia) and memantine (in moderateto-severe AD dementia) have shown them to be associated with modestly improved caregiver ratings of patients' functioning and with an apparent decreased rate of decline in cognitive test scores over periods of up to 3 years. The average patient on an anticholinesterase inhibitor maintains their mini-mental state examination (MMSE) score for close to a year, whereas a placebo-treated patient declines 2–3 points over the same time period. Memantine, used in conjunction with cholinesterase inhibitors or by itself, slows cognitive deterioration and decreases caregiver burden for patients with moderate to severe AD, but is not approved for mild AD. Neither cholinesterase inhibitors nor memantine have proven efficacious in patients with MCI, though the clinical trials lacked biomarkers at the time, and in retrospect likely included a mix of patients with AD and non-AD-related memory impairment. Cholinesterase inhibitors are easy to administer, and their major side effects are gastrointestinal symptoms (nausea, diarrhea, cramps), altered sleep with unpleasant or vivid dreams, bradycardia (usually benign), and muscle cramps. Potential side effects associated with memantine include constipation, dizziness, headache, and somnolence. A common approach to AD drug therapy is to initiate a cholinesterase inhibitor for a patient diagnosed with mild AD dementia and to add memantine when patients enter the moderate stage of disease. Cholinesterase inhibitors may also be effective in treating delusions and hallucinations, while memantine can reduce agitation. THERAPIES TARGETING AMYLOID-b A novel class of antiamyloid monoclonal antibodies has recently been approved for treatment of early clinical stages of AD. These drugs promote clearance of target Aβ epitopes, substantially lower amyloid plaque burden on amyloid PET, and comprise the first class of disease-modifying therapies to receive FDA approval for

treatment of AD. Lecanemab (which targets Aβ protofibrils) and donanemab (which targets a pyroglutamate form of Aβ in plaques) are fully FDA approved for clinical use in early-stage AD based on evidence of clinical efficacy in phase 3, double-blinded, randomized, placebo-controlled

clinical trials. Lecanemab is delivered as an intravenous infusion every 2 weeks, while donanemab is administered intravenously monthly. A third antibody, aducanumab, was the first to receive accelerated FDA approval based on reduction of amyloid PET signal, but evidence of clinical efficacy was ambiguous, and ultimately this drug has been removed from clinical use. All three of these antibodies lead to robust reductions in amyloid burden as measured by PET. Interestingly, drug trials of Aβ-targeting antibodies that showed less robust amyloid lowering on PET (e.g., solanezumab, crenezumab, gantenerumab) did not find a clinical benefit. Antiamyloid antibody therapy is currently restricted to patients with MCI or mild dementia and biomarker confirmation of Aβ pathology by PET or CSF. Clinical trials are underway for cognitively unimpaired individuals with biomarker evidence of Aβ pathology (i.e., preclinical AD). Patients with clinical features suggestive of non-AD causes of cognitive decline were excluded from the pivotal clinical trials and should not be treated, regardless of biomarker status. In Clarity-AD, a phase 3, randomized, placebo-controlled trial of lecanemab in patients with early symptomatic AD, patients who received lecanemab for 18 months experienced an average 27% slowing in their rate of clinical decline compared to placebo, as measured by change in the Clinical Dementia Rating Scale sum of boxes score (CDR-SB), a clinical scale that measures cognition and function and was the study's primary outcome. Similar slowing of decline was reported on all secondary cognitive and functional outcomes. In TRAILBLAZER-ALZ2, a phase 3, randomized, placebocontrolled trial of donanemab in early symptomatic AD, patients on active treatment showed 22% slowing on the integrated Alzheimer Disease Rating Scale (iADRS; primary outcome) and 28% slowing on the CDR-SB (secondary outcome) over 76 weeks compared to placebo, with similar effects on all other secondary clinical endpoints. Patients in TRAILBLAZER-ALZ2 were stratified by tau PET at baseline, with patients with low-medium tau PET at trial entry showing the greatest clinical benefit (35% slowing on iADRS, 36% slowing on CDR-SB), suggesting that amyloid lowering may particularly benefit patients in earlier stages of tau spread. The duration of treatment was titrated based on amyloid PET response, with patients switched from donanemab to placebo when complete amyloid clearance was seen on PET. These findings suggest that limited-duration treatment until PET clearance may be sufficient to derive a robust clinical response. Given these results, future clinical practice may leverage baseline biomarkers of tau burden to identify patients more likely to benefit from antiamyloid therapy, whereas longitudinal biomarkers of Aβ burden may help to define the necessary duration of therapy. Antiamyloid antibodies are associated with significant potential side effects, including infusion reactions and a form of secondary brain inflammation and hemorrhage, collectively referred to as amyloid-related imaging abnormalities (ARIA) (Fig. 442-4). Rates of infusion reactions in the active treatment arms of the phase 3 trials were 26% for lecanemab and 9% for donanemab. ARIA-E manifests as focal areas of edema or sulcal effusions, detected by T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities on MRI. ARIA-H typically manifests as microbleeds or superficial siderosis detected by gradient echo (GRE) or susceptibility-weighted imaging (SWI) MRI sequences, although lobar hemorrhages can rarely occur. Both ARIA-E and ARIA-H are thought to be related to CAA. Spontaneous ARIA-H occurs frequently in AD, but spontaneous ARIA-E (also known as inflammatory CAA) occurs very rarely in lieu of antiamyloid therapies. In the phase 3 trials, overall rates of ARIA-E were 13% for lecanemab and 24% for donanemab, whereas ARIA-H rates were 17% for lecanemab and 31% for donanemab. Approximately 75% of ARIA cases were asymptomatic and detected on safety MRI scans conducted throughout the study. When present,

Radiographic Staging of ARIA-H Radiographic Staging of ARIA-E (Right) (Left) Mild ARIA-E FLAIR hyperintensity confined to sulcus and/or cortex/subcortex white matter in one location <5 cm A B Moderate ARIA-E FLAIR hyperintensity 5 to 10 cm in single greatest dimension, or more than 1 site of involvement, each measuring <10 cm FLAIR SWI C Severe ARIA-E FLAIR hyperintensity measuring >10 cm with associated gyral swelling and sulcal effacement. One or more separate/independent sites of involvement may be noted. FLAIR T2* FIGURE 442-4 Radiographic staging of amyloid-related imaging abnormalities (ARIAs). A. Axial fluid-attenuated inversion recovery (FLAIR) image depicting radiographically mild ARIA-E in an asymptomatic patient receiving lecanemab treatment. Cortical edema and adjacent sulcal effacement are present in a right superior frontal region with <5 cm of involvement. B. Axial susceptibility-weighted imaging (SWI) depicting radiographically mild ARIA-H (including right anterior cingulate and right parietal lobar microhemorrhages) in an asymptomatic patient receiving lecanemab. C–D. Axial FLAIR and T2* sequence images depicting radiographically severe ARIA-E and radiographically severe ARIA-H, respectively, in a patient presenting with focal neurologic symptoms localized to the left occipital lobe during aducanumab treatment. FLAIR imaging reveals multiple regions of cortical edema, with adjacent subcortical edema and sulcal effacement. T2* reveals multiple regions of cortical siderosis, including in bilateral frontal and posterior regions of concomitant ARIA-E, as well as numerous lobar microhemorrhages. ARIA symptoms are typically mild and nonspecific (e.g., headache, dizziness, greater confusion). However, severe symptoms, including seizures, stroke-like episodes, malignant hypertension, and (very rarely) death can occur. The risk of ARIA increases with each copy of the Apo ε4 allele and is highest in Apo ε4 homozygotes. Apo ε4 homozygotes are also at increased risk of symptomatic, severe, and recurrent ARIA, leading the FDA to issue a box warning for ε4 homozygotes in the prescribing information for both lecanemab and donanemab. Clinical Apo ε genotyping is recommended prior to initiating anti-Aβ antibody therapy to adequately inform shared decision-making about treatment risks and benefits. In a clinical setting, uncontrolled hypertension, radiographic evidence of extensive CAA (>4 brain microhemorrhages or ≥1 region of cortical siderosis), and other factors that may increase ARIA risk are regarded as contraindications for antiamyloid anti bodies. Limited data are available about the safety of anticoagulants in the context of anti-Aβ therapy, with the concern that anticoagu lation may increase the risk of ARIA-H. Expert recommendations suggest excluding patients on anticoagulants from treatment until more safety data are available. Patients treated with a single anti platelet agent do not appear to be at higher risk for ARIA. Patients treated with lecanemab or donanemab should be moni tored for ARIA with multiple surveillance MRIs during the first 6–12 months of treatment, following the schedule recommended by the FDA in the prescribing information. T2/FLAIR and GRE/ SWI sequences should be performed, and patients should ideally be imaged longitudinally on the same MRI scanner and sequences to allow optimal comparisons between time points. An urgent MRI should be performed whenever ARIA is clinically suspected based on symptoms. The severity of ARIA is graded based on radiographic criteria, as well as the presence and severity of clinical

Mild ARIA-H Includes one or more of the following: • ≤4 new incident microhemorrhages • 1 new focal area of superficial siderosis Moderate ARIA-H Includes one or more of the following: • 5 to 9 new incident microhemorrhage • 12 focal areas of superficial siderosis CHAPTER 442 D Severe ARIA-H Alzheimer’s Disease Includes one or more of the following: • 10 or more microhemorrhages • >2 focal areas of superficial siderosis • ≥1 macrohemorrhage(s) (≥10 cm) symptoms. Patients can be treated safely through asymptomatic and radiographically mild ARIA, provided MRI scans

are performed monthly to monitor evolution. Symptomatic or radiographically moderate to severe ARIA should lead to temporary suspension of treatment until ARIA-E resolves and ARIA-H stabilizes. Permanent cessation of treatment is recommended if symptoms are severe, ARIA has recurred more than twice, ARIA-H has led to macrohe morrhage or >10 additional microhemorrhages since treatment ini tiation, or more than one area of superficial siderosis has emerged. Cases of catastrophic, multifocal brain hemorrhages due to severe ARIA-E and ARIA-H leading to death have been reported in patients receiving antiamyloid antibody therapy while being treated with thrombolytic medications (e.g., tissue plasminogen activa tor) for acute stroke. When presenting with stroke-like symptoms, patients receiving anti-Aβ monoclonal antibodies should receive an immediate MRI to differentiate acute stroke from ARIA. Until more data are available, treatment with lecanemab or donanemab should therefore be considered a contraindication to peripheral thrombolysis. It is current practice at our institution to restrict use of antiamy loid monoclonal antibodies to patients with biomarker-confirmed Aβ pathology and early symptomatic disease, including MCI or mild AD dementia, who are not expected to require anticoagulant therapy. We corroborate interpretation of Aβ biomarkers and scru tinize baseline brain MRI for disqualifying lesions that may increase risk of ARIA and intracerebral hemorrhage, such as radiographic evidence of extensive CAA. All patients must know their ApoE allele status and understand their associated ARIA risk before start ing treatment. Apo ε4 homozygous patients may elect to pursue therapy at our institution after careful consideration of their ARIA risk, although several institutions do prohibit or carefully restrict

use in Apo ε4 homozygous patients. Finally, and consistent with consensus clinical practice, all patients who receive therapy must undergo regular MRI safety screening to rule out ARIA.

PATIENT AND CAREGIVER EDUCATION Building rapport with the patient, family members, and other care givers is essential. In the early stages of AD, memory aids such as notebooks and posted daily reminders can be helpful. Family mem bers should emphasize activities that are pleasant while curtailing those that increase stress on the patient. Kitchens, bathrooms, stair ways, and bedrooms need to be made safe, and eventually, patients will need to stop driving. Patients can be encouraged to engage in lifestyle modifications that may be protective against aging and neurodegeneration, such as physical, cognitive, and social activity; vascular risk factor modification; healthy sleep habits; and dietary modifications (e.g., Mediterranean or Dietary Approaches to Stop Hypertension diets). Loss of independence and change of environ ment may worsen confusion, agitation, and anger. Communication and repeated calm reassurance are necessary. Caregiver “burnout” is common, often resulting in nursing home placement of the patient or new health problems for the caregiver. Respite breaks for the caregiver help to maintain a successful long-term thera peutic milieu. Use of adult day care centers can be helpful. Local and national support groups, such as the Alzheimer’s Association and the Family Caregiver Alliance, are valuable resources. Internet access to these resources has become available to clinicians and families in recent years. PART 13 Neurologic Disorders ADDITIONAL THERAPIES Mild to moderate depression is common in the early stages of AD and may respond to antidepressants or cholinesterase inhibitors. Selective serotonin reuptake inhibitors (SSRIs) are commonly used due to their low anticholinergic side effects (e.g., escitalopram, tar get dose, 5–10 mg daily). Seizures can be treated with levetiracetam unless the patient had a different regimen that was effective prior to the onset of AD. Agitation, insomnia, hallucinations, and bel ligerence are especially troublesome characteristics of some AD patients, and these behaviors can lead to nursing home placement. The

newer generation of atypical antipsychotics, such as risperi done, quetiapine, and olanzapine, are being used in low doses to treat these neuropsychiatric symptoms. Brexpiprazole, an atypical antipsychotic that acts on noradrenergic, serotonergic, and dopa minergic neurotransmitter systems, is the only drug to receive FDA approval for treatment of agitation in AD, based on a 12-week, double-blinded, randomized, placebo-controlled trial. The few con trolled studies comparing drugs against behavioral intervention in the treatment of agitation suggest mild efficacy with significant side effects related to sleep, gait, and cardiovascular complications, including an increased risk of death. Antipsychotics carry a black box FDA warning for use in elderly patients with dementia and thus should be prescribed only with caution; however, careful, daily, non pharmacologic behavior management is often not available, ren dering medications necessary for some patients. Medications with strong anticholinergic effects should be vigilantly avoided, includ ing prescription and over-the-counter sleep aids (e.g., diphenhydr amine) or incontinence therapies (e.g., oxybutynin). Several commonly used medications and supplements, includ ing estrogen hormone replacement therapy, statins, vitamin E, and ginkgo biloba, appeared to be associated with a decreased risk of AD in epidemiologic or observational studies but did not show efficacy in prospective, randomized, double-blinded, placebo-con trolled trials. Many vitamins and dietary supplements are marketed directly to consumers as “memory enhancing” or protective against AD without clinical evidence. Patients and families may come across anecdotal reports of “miraculous” responses to aggressive treatments such as anti-interferon intrathecal infusions, intrave nous immunoglobulin, antibiotics (purportedly to treat Lyme dis ease or another questionable infection), metal chelation, and stem cell therapies, but there is no scientific evidence to support use of

any of these approaches to treating AD and significant concern for harm. EXPERIMENTAL THERAPIES The design of AD clinical trials has been transformed by the avail ability of PET, CSF, and more recently blood-based biomarkers of Aβ and tau. Many trials now require biomarker evidence of AD for trial inclusion. Biomarkers help assess target engagement (e.g., changes in Aβ biomarkers in an antiamyloid trial) or modifica tion of downstream disease pathophysiology (e.g., changes in tau biomarkers in an antiamyloid trial), with the pivotal trials leading to approval of lecanemab and donanemab being emblematic of this novel approach. Increasingly, many trials have shifted toward enrolling patients in the asymptomatic (preclinical) or very early symptomatic stages of AD, using positive biomarkers as the primary inclusion criterion. Primary (biomarker negative) and secondary (biomarker positive but no symptoms) prevention trials are under way in autosomal dominant mutation carriers, Apo ε4 homozy gotes, and even in the normally aging population. Active vaccination against Aβ is another approach that aims to promote immune-mediated clearance of amyloid pathology. The first Aβ42 vaccine trial in humans was aborted after a minority of patients developed meningoencephalitis, but subsequent trials with less immunogenic formulations have shown more favorable safety profiles. Oral drugs that inhibit β and γ secretase reduce the cleavage of APP to Aβ42 and showed promise in ameliorating pathology and behavioral changes in AD transgenic mice. Unfortunately, placebo-controlled trials failed to show clinical efficacy, and trials of β secretase inhibitors, in particular, found significant worsening of cognition in treated patients versus placebo, although fortu nately, this effect proved transient after discontinuing the drug. It is unclear whether toxicity of β and γ secretase inhibitors was directly related to changes in Aβ metabolism or to “off-target” drug effects. Monoclonal antibodies directed against phosphorylated tau are in earlier stages of development. These antibodies aim to prevent the transsynaptic spread of tau and have proven effective in tau transgenic mice. Safety profiles in human studies have proven favorable thus far, but clinical results have been lacking. Lower ing of

tau expression via antisense oligonucleotides (ASOs) or small interfering RNA is a compelling therapeutic strategy that rescues most elements of the AD phenotype in AD transgenic mice. A recent phase 1 trial of the tau-targeting ASO MAPTRX, delivered intrathecally, showed the treatment to be well tolerated, with significant lowering of tau biomarkers in CSF and PET. A phase 2 clinical trial is currently underway. Additional therapeutic approaches targeting tau include active immunization; inhibition of tau phosphorylation, acetylation, and aggregation; and microtubule stabilization. Other druggable pathways represented in the AD drug development pipeline include those targeting neuroinflammation, metabolism/bioenergetics, synaptic plasticity, neuroprotection, and neurotransmitter-based cognitive enhancement or treatment of neuropsychiatric symptoms. A general approach to the symptomatic management of dementia is presented in Chap. 31. OTHER CAUSES OF DEMENTIA FTD (Chap. 443), vascular dementia (Chap. 444), DLB (Chap. 445), and prion diseases (Chap. 449) are covered in dedicated chapters. Prion diseases such as CJD are rare neurodegenerative conditions (prevalence ~1 per million) that produce dementia. CJD is a rapidly progressive disorder associated with dementia, focal cortical signs, rigidity, and myoclonus, causing death <1 year after first symptoms appear. The rapidity of progression seen with CJD is uncommon in AD so that the distinction between the two disorders is usually straightforward, although AD can on occasion present as a rap idly progressive dementia. In general, CBD (Chap. 443) and DLB (Chap. 445), more rapid degenerative dementias with prominent

movement abnormalities, are more likely to be mistaken for CJD. The differential diagnosis for CJD includes other rapidly progres sive dementing conditions such as viral or bacterial encephalitides, Hashimoto’s encephalopathy, central nervous system (CNS) vasculitis, lymphoma, or paraneoplastic/autoimmune syndromes (Chap. 99). The markedly abnormal periodic complexes on EEG and cortical ribboning and basal ganglia hyperintensities on diffusion-weighted imaging or FLAIR MRI are diagnostic features of CJD, although rarely, prolonged focal or generalized seizures can produce a similar imaging appearance. Huntington’s disease (HD) (Chap. 447) is an autosomal dominant degenerative brain disorder. HD clinical hallmarks include chorea, behavioral disturbance, and executive impairment. Symptoms typi cally begin in the fourth or fifth decade, but there is a wide range, from childhood to >70 years. Memory is frequently not impaired until late in the disease, but attention, judgment, self-awareness, and executive functions are often deficient at an early stage. Depression, apathy, social withdrawal, irritability, and intermittent disinhibition are com mon. Delusions and obsessive-compulsive behavior may occur. Disease duration is variable but typically lasts ~15 years. NPH is a relatively uncommon but treatable syndrome. The clinical, physiologic, and neuroimaging characteristics of NPH must be care fully distinguished from those of other dementias associated with gait impairment. Historically, many patients treated for NPH have suffered from other dementias, particularly AD, vascular dementia, DLB, and PSP (Chap. 443). For NPH, the clinical triad includes an abnormal gait (ataxic or apractic), dementia (usually mild to moderate, with an emphasis on executive impairment), and urinary urgency or inconti nence. Neuroimaging reveals enlarged lateral ventricles (hydrocepha lus) with little or no cortical atrophy, although the sylvian fissures may appear propped open (so-called “boxcarring”), which can be mistaken for perisylvian atrophy. Crowding of dorsal frontal-parietal gyri helps distinguish NPH from other movement disorders, such as PSP and CBD, in which dorsal atrophy with sulcal widening is common. NPH is a communicating hydrocephalus with a patent aqueduct of Sylvius (see Fig. 31-3), in contrast to aqueductal stenosis, in which the aqueduct is small. Lumbar puncture opening pressure falls in the high-normal range, and the CSF protein, glucose, and cell counts are normal. NPH may be caused by obstruction to normal CSF flow over the cerebral convexities and delayed

resorption into the venous system. The indo lent nature of the process results in enlarged lateral ventricles with rela tively little increase in CSF pressure. Presumed edema, stretching, and distortion of subfrontal white matter tracts may lead to clinical symp toms, but the precise underlying pathophysiology remains unclear. Some patients provide a history of conditions that produce meningeal scarring (blocking CSF resorption) such as previous meningitis, sub arachnoid hemorrhage, or head trauma. Others with longstanding but asymptomatic congenital hydrocephalus may have adult-onset dete rioration in gait or memory that is confused with NPH. In contrast to AD, the patient with NPH complains of an early and prominent gait disturbance without cortical atrophy on CT or MRI. Numerous attempts to improve NPH diagnosis with various spe cial studies and predict the success of ventricular shunting have been undertaken. These tests include radionuclide cisternography (showing a delay in CSF absorption over the convexity) and various efforts to monitor and alter CSF flow dynamics, including a constant-pressure infusion test. None has proven to be specific or consistently useful. A transient improvement in gait or cognition may follow lumbar punc ture (or serial punctures) with removal of 30–50 mL of CSF, but this finding has also not proved to be consistently predictive of postshunt improvement. Perhaps the most reliable strategy is a period of close inpatient evaluation before, during, and after lumbar CSF drainage. Occasionally, when a patient with AD presents with gait impairment (at times due to comorbid subfrontal vascular injury) and absent or only mild cortical atrophy on CT or MRI, distinguishing NPH from AD can be challenging. Hippocampal atrophy on MRI favors AD, whereas a characteristic “magnetic” gait with external hip rotation, low foot clearance, and short strides, along with prominent truncal sway or instability, favors NPH. The diagnosis of NPH should be avoided when hydrocephalus is not detected on imaging studies, even if the

symptoms otherwise fit. Thirty to fifty percent of patients identified by careful diagnosis as having NPH will improve with ventricular shunting. Gait may improve more than cognition, but many reported failures to improve cognitively may have resulted from comorbid AD. Importantly, the presence of positive CSF AD biomarkers or amyloid PET is associated with lower likelihood of response to shunting. Shortlasting improvement is common. Patients should be carefully selected for shunting, because subdural hematoma, infection, and shunt failure are known complications and can be a cause for early nursing home placement in an elderly patient with previously mild dementia.

Intracranial hypotension, sometimes called sagging brain syndrome, is a disorder caused by low CSF pressure, leading to downward pres sure on the subcortical structures and disruption of cerebral function. It presents in a variable manner with headache, often exacerbated by coughing or a Valsalva maneuver or by moving from lying to stand ing. Other common symptoms include dizziness, vomiting, disruption of sleep-wake cycles, and sometimes a progressive behavioral variant FTD-like syndrome (Chap. 443). Although sometimes idiopathic, this syndrome can be caused by CSF leaks secondary to lumbar puncture, head trauma, or spinal cord arachnoid cysts. Treatment consists of finding and patching the CSF leak. CHAPTER 442 Dementia can accompany chronic alcoholism (Chap. 464) and may result from associated malnutrition, especially of B vitamins, par ticularly thiamine. Other poorly defined aspects of chronic alcohol ism may, however, also produce cerebral damage. A rare idiopathic syndrome of dementia and seizures with degeneration of the corpus callosum has been reported primarily in male Italian red wine drinkers (Marchiafava-Bignami disease). Alzheimer’s Disease Thiamine (vitamin B1) deficiency causes Wernicke’s encephalopa thy (Chap. 318). The clinical presentation is usually a malnourished

patient (frequently but not necessarily alcoholic) with confusion, ataxia, and diplopia resulting from inflammation and necrosis of peri ventricular midline structures, including dorsomedial thalamus, mam millary bodies, midline cerebellum, periaqueductal gray matter, and trochlear and abducens nuclei. Damage to the dorsomedial thalamus correlates most closely with the memory loss. Prompt administration of parenteral thiamine (100 mg intravenously for 3 days followed by daily oral dosage) may reverse the disease if given within the first days of symptom onset. Prolonged untreated thiamine deficiency can result in an irreversible and profound amnestic syndrome (Korsakoff's syndrome) or even death. In Korsakoff's syndrome, the patient is unable to recall new informa tion despite normal immediate memory, attention span, and level of consciousness. Memory for new events is seriously impaired, whereas knowledge acquired prior to the illness remains relatively intact. Patients are easily confused, disoriented, and cannot store information for more than a few minutes. Superficially, they may be conversant, engaging, and able to perform simple tasks and follow immediate com mands. Confabulation is common, although not always present. There is no specific treatment because the previous thiamine deficiency has produced irreversible damage to the medial thalamic nuclei and mam millary bodies. Mammillary body atrophy may be visible on MRI in the chronic phase (see Fig. 318-6). Vitamin B12 deficiency, as can occur in pernicious anemia, causes a megaloblastic anemia and may also damage the nervous system (Chaps. 104 and 453). Neurologically, it most commonly produces a spinal cord syndrome (myelopathy) affecting the posterior columns (loss of vibration and position sense) and corticospinal tracts (hyper active tendon reflexes with Babinski signs); it also damages peripheral nerves (neuropathy), resulting in sensory loss with depressed tendon reflexes. Damage to myelinated axons may also cause dementia. The mechanism of neurologic damage is unclear but may be related to a deficiency of S-adenosyl methionine (required for methylation of myelin phospholipids) due to reduced methionine synthase activity or accumulation of methylmalonate, homocysteine, and propionate, providing abnormal substrates for fatty acid synthesis in myelin. Use of histamine blockers or metformin, vegan diets, autoimmunity against gastric parietal cells, and various causes of malabsorption are the typical causes for vitamin B12 deficiency. The neurologic sequelae of

vitamin B12 deficiency may occur in the absence of hematologic mani festations, making it critical to avoid using the complete blood count (CBC) and blood smear as a substitute for measuring B12 blood levels. Treatment with parenteral vitamin B12 (1000 μg intramuscularly daily for a week, weekly for a month, and monthly for life for pernicious anemia) stops progression of the disease if instituted promptly, but complete reversal of advanced nervous system damage will not occur.

Deficiency of nicotinic acid (pellagra) is associated with skin rash over sun-exposed areas, glossitis, and angular stomatitis (Chap. 344). Severe dietary deficiency of nicotinic acid along with other B vitamins such as pyridoxine may result in spastic paraparesis, peripheral neu ropathy, fatigue, irritability, and dementia. This syndrome has been seen in prisoners of war and in concentration camps but should be con sidered in any malnourished individual. Low serum folate levels appear to be a rough index of malnutrition, but isolated folate deficiency has not been proved as a specific cause of dementia. CNS infections usually cause delirium and other acute neurologic syndromes. However, some chronic CNS infections, particularly those associated with chronic meningitis (Chap. 144), may produce a dementing illness. The possibility of chronic infectious menin gitis should be suspected in patients presenting with a dementia or behavioral syndrome, who also have headache, meningismus, cranial neuropathy, and/or radiculopathy. Between 20 and 30% of

patients in the advanced stages of HIV infection become demented (Chap. 208). Cardinal features include psychomotor retardation, apa thy, and impaired memory. This syndrome may result from secondary opportunistic infections but can also be caused by direct infection of CNS neurons with HIV. Neurosyphilis (Chap. 187) was a common cause of dementia in the preantibiotic era; it is now uncommon but can still be encountered in patients with multiple sex partners, particularly among patients with HIV. Characteristic CSF changes consist of pleo cytosis, increased protein, and a positive Venereal Disease Research Laboratory (VDRL) test. The recent SARS-CoV-2 pandemic was associated in some individuals with persistent postrecovery changes in memory, executive, and other cognitive functions; responsible mechanisms might include effects of inflammation, multiorgan system failure, or virus-associated vascular injury. PART 13 Neurologic Disorders Primary and metastatic neoplasms of the CNS (Chap. 95) usually produce focal neurologic findings and seizures rather than dementia, but if tumor growth begins in the frontal or temporal lobes, the initial manifestations may be memory loss or behavioral changes. An auto immune, sometimes paraneoplastic, syndrome of dementia associated with occult carcinoma (often small-cell lung cancer) is termed limbic encephalitis. In this syndrome, confusion, agitation, seizures, poor memory, emotional changes, and frank dementia may occur. Paraneo plastic encephalitis associated with NMDA receptor antibodies presents as a progressive psychiatric disorder with memory loss and seizures; affected patients are often young women with ovarian teratoma. Autoimmune etiologies also include antibodies targeting leucine-rich glioma-inactivated 1 (LGI1; faciobrachial dystonic seizures); contactin-

associated protein-like 2 (Caspr2; insomnia, ataxia, myotonia); and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor (limbic encephalitis with relapses), among others (Chap. 99). A nonconvulsive seizure disorder (Chap. 436) may underlie a syn drome of confusion, clouding of consciousness, and garbled speech. Often, psychiatric disease is suspected, but an EEG demonstrates the epileptic nature of the illness. If recurrent or persistent, the condition may be termed complex partial status epilepticus. The cognitive dis turbance often responds to anticonvulsant therapy. The etiology may be previous small strokes or head trauma; some cases are idiopathic. Nonconvulsive temporal lobe seizures can also emerge early in the course of AD. It is important to recognize systemic diseases that indirectly affect the brain and produce chronic confusion or dementia. Such conditions include hypothyroidism; vasculitis; and hepatic, renal, or pulmonary disease. Hepatic encephalopathy may begin with irritability and confu sion and slowly progress to agitation, lethargy, and coma. Isolated vasculitis of the CNS (CNS granulomatous angiitis) (Chaps. 375 and 438) occasionally causes a chronic encephalopathy

associated with confusion, disorientation, and clouding of conscious ness. Headache is common, and strokes and cranial neuropathies may occur. Brain imaging studies may be normal or nonspecifically abnormal. CSF analysis reveals a mild pleocytosis or protein eleva tion. Cerebral angiography can show multifocal stenoses involving medium-caliber vessels, but some patients have only small-vessel disease that is not revealed on angiography. The angiographic appear ance is not specific and may be mimicked by atherosclerosis, infec tion, or other causes of vascular disease. Brain or meningeal biopsy demonstrates endothelial cell proliferation and mononuclear infil trates within blood vessel walls. The prognosis is often poor, although the disorder may remit spontaneously. Some patients respond to glucocorticoids or chemotherapy. Chronic metal exposure represents a rare cause of dementia. The key to diagnosis is to elicit a history of exposure at work or home. Chronic lead poisoning from inadequately fire-glazed pottery has been

reported. Fatigue, depression, and confusion may be associated with episodic abdominal pain and peripheral neuropathy. Gray lead lines appear in the gums, usually accompanied by an anemia with basophilic stippling of red blood cells. The clinical presentation can resemble that of acute intermittent porphyria (Chap. 428), including elevated levels of urine porphyrins as a result of the inhibition of δ-aminolevulinic acid dehydrase. The treatment is chelation therapy with agents such as ethylenediamine tetraacetic acid (EDTA). Chronic mercury poisoning produces dementia, peripheral neuropathy, ataxia, and tremulousness that may progress to a cerebellar intention tremor or choreoathetosis. The confusion and memory loss of chronic arsenic intoxication is also associated with nausea, weight loss, peripheral neuropathy, pigmenta tion and scaling of the skin, and transverse white lines of the fingernails (Mees' lines). Treatment is chelation therapy with dimercaprol (BAL). Aluminum poisoning is rare but was documented with the dialysis dementia syndrome, in which water used during renal dialysis was contaminated with excessive amounts of aluminum. This poisoning resulted in a progressive encephalopathy associated with confusion, nonfluent aphasia, memory loss, agitation, and, later, lethargy and stupor. Speech arrest and myoclonic jerks were common and associ ated with severe and generalized EEG changes. The condition has been eliminated by the use of deionized water for dialysis. Recurrent head trauma in professional athletes may lead to a dementia previously referred to as "punch-drunk" syndrome or dementia pugilistica but now known as chronic traumatic encepha lopathy (CTE) to signify its relevance to contact sport athletes other than boxers (Chap. 454). The symptoms can be progressive, beginning late in an athlete's career or, more often, after retirement. Early in the course, a personality change occurs, associated with social instability, explosive rage, and sometimes paranoia and delusions. Later, memory loss progresses to full-blown dementia, often associated with parkin sonian signs and ataxia or intention tremor. At autopsy, the cerebral cortex shows tau-immunoreactive NFTs that are more prominent than amyloid plaques (which are usually diffuse or absent rather than neu ritic). NFTs and tau-positive reactive astrocytes are often clustered in the depths of cortical sulci and in a perivascular distribution. TDP-43 inclusions have also been reported, highlighting the overlap with the FTD spectrum (Chap. 443). Loss of neurons in the substantia nigra is a variable feature, and some with TDP-43 inclusions also develop motor neuron disease (MND) (Chap. 448). Chronic subdural hematoma (Chap. 454) is also occasionally associated with dementia, often in the context of underlying cortical atrophy from conditions such as AD or HD. Transient global amnesia (TGA) is characterized by the sudden onset of a severe episodic memory deficit, usually occurring in persons aged

> 50 years. Often the amnesia occurs in the setting of an emotional stimulus or physical exertion. During the attack, the individual is alert and communicative, general cognition seems intact, and there are no other neurologic signs or symptoms. The patient may seem confused and repeatedly ask about their location in place and time. The ability to form new memories returns after a period of hours, and the individual returns to normal with no recall for the period of the attack. Frequently no cause is determined, but cerebrovascular disease, epilepsy (7% in

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