Relationship Between Delirium and Dementia

Delirium and dementia frequently coexist, with dementia being a leading risk factor for delirium and delirium resulting in worsened cognitive functioning. The contribution of delirium to permanent cognitive impairment or dementia is an area of active research, given the fact that after delirium, some patients never recover to their baseline level of cognitive function. Delirium and dementia may represent two ends along a spectrum of cognitive impairment with "chronic delirium" and "reversible dementia" falling along a continuum. Dementia is the leading risk factor for delirium, and fully two-thirds of cases of delirium occur in patients with dementia. Studies have shown that delirium and dementia are both associated with decreased cerebral metabolism, cholinergic deficiency, inflammation and abnormal glucose metabolism, reflecting their overlapping clinical, metabolic, and cellular mechanisms. Delirium can alter the course of underlying dementia, with dramatic worsening of the trajectory of cognitive decline, resulting in more rapid progression of functional losses and worsened long-term outcomes including hospitalization and mortality. Additionally, postoperative cognitive decline is accelerated among patients with delirium.

PRESENTATION

Cardinal Features

Acute onset and inattention are the central features of delirium. Determining the acuity of onset requires accurate knowledge of the patient's prior cognitive status and often entails obtaining historical information from another close observer, such as a family member, caregiver, or nurse. With delirium, the mental status changes typically occur over hours to days, in contrast to the changes that occur with dementia, which present insidiously over weeks to months. Another key feature is the fluctuating course of delirium; symptoms tend to wax and wane in severity over a 24-hour period. Lucid intervals are characteristic, and the reversibility of symptoms within a short time can deceive even an experienced clinician. Inattention is manifested as difficulty focusing, maintaining, and shifting attention or concentration. With simple cognitive assessment, patients may display difficulty with straightforward repetition tasks, digit spans, or recitation of the months of the year backward. Delirious patients appear easily distracted, experience difficulty with multistep commands, cannot follow the flow of a

conversation, and often perseverate with an answer to a previous question. Additional major features include a disorganization of thought and altered level of consciousness. Disorganized thoughts are a manifestation of underlying cognitive or perceptual disturbances and can be recognized by disjointed and incoherent speech or an unclear or illogical flow of ideas. Clouding of consciousness is typically manifested by lethargy, with a reduced awareness of the environment that may show diurnal variation. Although not cardinal elements, other frequently associated features include disorientation (more commonly to time and place than to self), cognitive impairments (eg, memory and problem-solving deficits, dysnomia), psychomotor agitation or retardation, perceptual disturbances (eg, hallucinations, misperceptions, illusions), paranoid delusions, emotional lability, and sleep-wake cycle disruption.

Classification of Delirium

The clinical presentation of delirium can take three main forms: hypoactive, hyperactive, or mixed. The hypoactive form of delirium is characterized by lethargy and reduced psychomotor functioning and is the more common form in older patients. Hypoactive delirium often goes unrecognized and carries an overall poorer prognosis. The reduced level of patient activity associated with hypoactive delirium, often attributed to low mood or fatigue, may contribute to its misdiagnosis or underrecognition. By contrast, the hyperactive form of delirium presents with symptoms of agitation, increased vigilance, and often concomitant hallucinations; its presentation rarely remains unnoticed by caregivers or clinicians. Patients can fluctuate between the hypoactive and hyperactive forms—the mixed type of delirium—presenting a challenge in distinguishing the presentation from other psychotic or mood disorders. Recognition of partial or subsyndromal forms of delirium has brought attention to the persistence of symptoms among older patients, particularly during the resolution stages of delirium. Partial forms of delirium also adversely influence long-term clinical outcomes.

Prognosis

Delirium is an important independent determinant of prolonged length of hospital stay, increased mortality, increased rates of nursing home placement, and functional and cognitive decline. Delirium has long been thought to be a reversible, transient condition; however, accumulating evidence brings this

into question. Delirium symptoms generally persist for a month or more; as few as 20% of patients attain complete symptom resolution at 6-month follow-up. Cognitive function is impacted for up to a year following delirium, and patients who develop delirium are at increased risk for development of dementia. The chronic detrimental effects are likely related to the duration, severity, and underlying cause(s) of the delirium in addition to the baseline vulnerability of the patient.

EVALUATION

There are numerous instruments for the identification of delirium. Each delirium instrument has strengths and limitations, and the choice among them depends on the goals for use. The most widely used is the CAM, of which the four-item short form has been applied in over 10,000 studies to date and translated into over 19 languages. The CAM has been adapted for use in other settings, including the intensive care unit (CAM-ICU), nursing home (NH-CAM), and emergency department (CAM-ED and B-CAM). The CAM-S derived from the CAM can be used to rate delirium severity and has demonstrated predictive validity for relevant clinical outcomes. Designed for clinicians with minimal training, several brief screening tools have been validated in postsurgical, medical, emergency department, and postacute care settings. For example, the Ultra-Brief CAM (UB-CAM) requires just 1 minute to complete and can identify delirium with high sensitivity and specificity. Selected screening tools are presented in **Table 58-3**. These can be used as an initial step in delirium detection and should be followed by a comprehensive assessment. Additionally, family-informed tools can be completed by health care professionals and/or families, yielding sensitivities ranging from 67% to 90% and specificities ranging from 56% to 90% in diverse populations.

TABLE 58-3 ■ SELECTED DELIRIUM SCREENING TESTS

BRIEF SCREENING TEST	BRIEF DESCRIPTION
Confusion Assessment Method (CAM) Short Form	Widely adopted 5-min instrument to score 4-item algorithm based on 9 operationalized DSM-IIIR criteria for delirium; involves cognitive assessment; interviewer training recommended for optimal use
Ultra-Brief CAM (UB-CAM)	2-step protocol: The UB-2 (below) is performed first and, when positive, followed by a short interview (3D-CAM) and rating of the CAM diagnostic algorithm. Ultra-Brief 2-Item Screener (UB-2): 2 items. Question 1: "*Please tell me the day of the week.*" Question 2: "*Please tell me the months of the year backwards, say December as your first month.*" Positive screen if one or both is incorrect, followed by a more thorough diagnostic interview such as the 3D-CAM. 3-Minute Diagnostic Confusion Assessment Method (3D-CAM): 3-min version of CAM requiring minimal training; algorithm probes 4 cardinal features of delirium, with 2 essential features and at least 1 of 2 secondary features indicating delirium. Skip patterns can shorten administration.
Confusion Assessment Method—ICU version (CAM-ICU)	Modification of CAM 4-feature algorithm with nonverbal tasks that can be used in the ICU setting
Delirium Triage Screen (DTS), combined with Brief Confusion Assessment Method (bCAM)	DTS: 2 items. Assesses 2 features of delirium: altered level of consciousness (feature 1); attention (feature 2). Attention is assessed using the "LUNCH" backwards spelling test. Validated among emergency department patients. If positive, follow with bCAM. bCAM: 7 items. Like the CAM algorithm, a score is considered positive for delirium if 3 out of 4 features are present (features 1 and 2, and either 3 or 4). Validated in emergency department and palliative care settings.
Nursing Delirium Screening Scale (Nu-DESC)	5-item, 1-min screening scale designed for use by nurses and used during routine care on the hospital floor, scores range from 0 to 10 with higher scores indicating delirium
Recognizing Acute Delirium as part of Routine (RADAR)	3 observational items. Assesses 3 features of delirium: consciousness; attention/hyperactivity; psychomotor retardation. Validated in nursing home and emergency department patients.
4AT	2-min instrument for general practice includes 4 items; scores range from 0 to 12, with a score ≥ 4 suggesting possible delirium.

A complete listing of information about delirium tools, along with critical performance characteristics, can be found online from the Network for Investigation of Delirium: Unifying Scientists at https://deliriumnetwork.org/measurement/adult-delirium-info-cards/.

The acute evaluation of suspected or confirmed delirium centers on three main tasks that occur simultaneously: (1) establishing the diagnosis of delirium; (2) determining the potential cause(s) and ruling out life-threatening contributors; and (3) managing the symptoms while assuring patient safety. Delirium is a clinical diagnosis, relying on astute observation at the bedside, careful cognitive assessment, and history-taking from a knowledgeable informant to establish a change from the patient's baseline functioning. Identifying the potentially multifactorial contributors to the delirium is of paramount importance. Many of these factors are treatable, and if left untreated, may result in substantial morbidity and mortality. Because the potential contributors are myriad, the search requires a thorough medical evaluation guided by clinical judgment. The challenge is enhanced by the frequently nonspecific or atypical presentation of the underlying illness in older persons. In fact, delirium is often the *only* sign of life-threatening illness, such as sepsis, pneumonia, or myocardial infarction in older persons.

History and Physical Examination

A thorough history and physical examination constitute the foundation of the medical evaluation of suspected delirium. The first step in evaluation should be to establish the diagnosis of delirium through careful cognitive assessment and to determine the acuity of change from the patient's baseline cognitive state. Because cognitive impairment may easily be missed during routine conversation, brief cognitive screening tests, such as the Mini-Cog test or the UB-CAM assessment, should be used to rate the CAM. The degree of attention should be further assessed with simple tests such as a digit span (inattention indicated by an inability to repeat five digits forward or three digits backward) or recitation of the months of the year backward. A targeted history, focusing on baseline cognitive status and chronology of recent mental status changes, should be elicited from a reliable informant. Historical data including intercurrent illnesses, recent adjustments in medications, the possibility of withdrawal from alcohol, other substances, or medications, and pertinent environmental changes may elucidate precipitating factors of delirium.

The physical examination should comprise detailed review focusing on potential etiologic clues to an underlying or inciting disease process. Vital sign assessment is important to identify fever, tachycardia, or decreased oxygen saturation, each of which may point to specific disease processes. Auscultatory examination may suggest pneumonia or pulmonary effusion. A new cardiac murmur or dysrhythmia may suggest ischemia or congestive heart failure. Gastrointestinal examination should focus on evidence of an acute abdominal process, such as occult bleeding, perforated viscus, or infection. Patients with delirium may also demonstrate nonspecific focal findings on neurologic examination, such as asterixis or tremor. New focal neurologic deficits should raise suspicion of an acute cerebrovascular event or subdural hematoma. In many older patients and especially those with cognitive impairment, delirium may be the initial manifestation of a serious new disease process. Attention to early localizing signs on serial physical examinations is paramount.

A complete medication review, including over-the-counter medications, is critical. Any medications with known psychoactive effects should be discontinued or minimized whenever possible. Medications with potential for withdrawal should be tapered carefully. Because of pharmacodynamic and pharmacokinetic changes in aging adults, these medications may cause

deleterious psychoactive effects even when prescribed at customary doses and with serum drug levels that are within the "therapeutic range."

Laboratory Tests and Imaging

Laboratory evaluation should be guided by clinical judgment and take into account specific patient characteristics and historical data. A thorough history and physical examination, medication review, focused laboratory testing (eg, complete blood count, chemistries, glucose, renal and liver function tests, urinalysis), and search for occult infection should help to identify the majority of potential contributors to the delirium. Additional laboratory testing such as thyroid function tests, B_{12} level, cortisol level, drug levels or toxicology screen, syphilis serologies, and ammonia level should be based on the specific clinical presentation. Further diagnostic work-up with an electrocardiogram, chest radiograph, and/or arterial blood gas test may be appropriate for patients with pulmonary or cardiac conditions. The indications for cerebrospinal fluid examination, brain imaging, or EEG remain controversial. Their overall diagnostic yield is low, and these procedures are probably indicated in fewer than 5% to 10% of delirium cases. Lumbar puncture with cerebrospinal fluid examination is indicated for the febrile delirious patient when meningitis or encephalitis is suspected. Brain imaging (such as CT or MRI) should be reserved for cases with new focal neurologic signs, with history or signs of head trauma, or without another identifiable cause of the delirium. Of note, some neurologic symptoms are associated with delirium, including tremor and asterixis. EEG, which has a false-negative rate of 17% and a false-positive rate of 22% for distinguishing between delirious and nondelirious patients, plays a limited role and is most commonly employed to detect subclinical seizure disorders and to differentiate delirium from nonorganic psychiatric conditions.

Differential Diagnosis

Distinguishing a long-standing confusional state (dementia) from delirium alone, or from delirium superimposed on dementia, is an important, but often difficult, diagnostic step. These two conditions can be differentiated by the acute onset of symptoms in delirium, with dementia presenting much more insidiously and by the impaired attention and altered level of consciousness associated with delirium.

The differential diagnosis of delirium can be extensive and includes other psychiatric conditions such as depression and nonorganic psychiatric disorders (**Table 58-4**). Although perceptual disturbances, such as illusions and hallucinations, can occur with delirium in about 15% of cases, recognition of the key features of acute onset, inattention, altered level of consciousness, and global cognitive impairment will enhance the identification of delirium. Differentiating among diagnoses is critical because delirium carries a more serious prognosis without proper evaluation and management. Treatment for certain conditions such as depression or affective disorders may involve use of drugs with anticholinergic activity, which could exacerbate an unrecognized case of delirium. At times, working through the differential diagnosis can be challenging, and the diagnosis of delirium may remain uncertain. Because of the potentially life-threatening nature of delirium, however, it is prudent to manage the patient as having delirium and search for underlying precipitants until further information can be obtained.

TABLE 58-4 ■ DIFFERENTIAL DIAGNOSIS OF ALTERED MENTAL STATUS

CHARACTERISTIC	DELIRIUM	DEMENTIA	DEPRESSION	ACUTE PSYCHOSIS
Onset	Acute (hours to days)	Progressive, insidious (weeks to months)	Either acute or insidious	Acute
Course over time	Waxing and waning	Unrelenting	Variable	Episodic
Attention	Impaired, a hallmark of delirium	Usually intact, until end-stage disease	Decreased concentration and attention to detail	Variable
Level of consciousness	Altered, from lethargic to hyperalert	Normal, until end-stage disease	Normal	Normal
Memory	Impaired commonly	Prominent short- and/or long-term memory impairment	Normal, some short-term forgetfulness	Usually normal
Orientation	Disoriented	Normal, until end-stage disease	Usually normal	Usually normal
Speech	Disorganized, incoherent, illogical	Notable for parsimony, aphasia, anomia	Normal, but often slowing of speech (psychomotor retardation)	Variable, often disorganized
Delusions	Common	Common	Uncommon	Common, often complex
Hallucinations	Usually visual	Sometimes	Rare	Usually auditory and more complex
Organic etiology	Yes	Yes	No	No

Algorithm for the Evaluation of Altered Mental Status

Figure 58-2 presents an algorithm for the evaluation of altered mental status in the older patient. The initial steps center on establishing the patient's baseline cognitive functioning and the onset and timing of any cognitive changes. Chronic impairments, representing changes that occur over months to years, are most likely attributable to dementia, which should be evaluated accordingly (see Chapter 59). Acute alterations, representing abrupt deteriorations in mental status, occur over hours to weeks and may be superimposed on underlying dementia. They should be further evaluated with cognitive testing to establish the presence of delirium. In the absence of notable delirium features (see "Presentation" earlier in this chapter), subsequent evaluation should focus on the possibility of major depression, acute psychotic disorder, or other psychiatric disorders (see Chapters 65, 60, and 66).

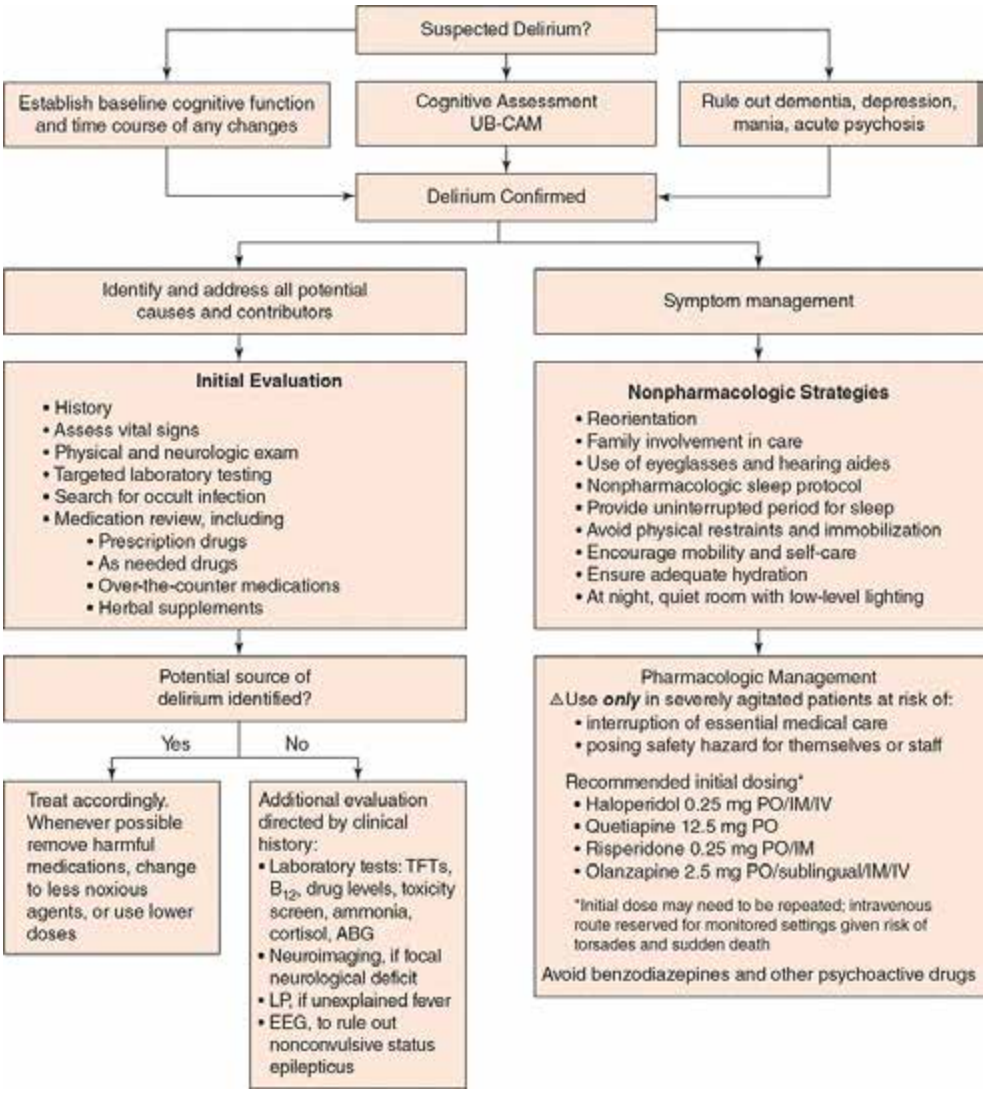

FIGURE 58-2. Flowchart for evaluation of suspected delirium in an older person. ABG, arterial blood gas; B_{12}, cyanocobalamin or vitamin B_{12} level; EEG, electroencephalography; IM, intramuscular; LP, lumbar puncture; PO, by mouth; TFTs, thyroid function tests (eg, T4, thyroid index, thyroid-stimulating hormone); UB-CAM, Ultra Brief Confusion Assessment Method.

PREVENTION

Primary prevention—preventing delirium before it develops—is the most effective strategy for reducing delirium and its associated adverse outcomes. **Table 58-5** describes well-documented delirium risk factors and preventive interventions to address each risk factor. A controlled clinical trial demonstrated the effectiveness of a delirium prevention strategy targeted toward these risk factors, which were selected based on their clinical relevance and the degree to which they could be modified by employing

practical and feasible interventions. Compared with standard care, implementation of these preventive interventions resulted in a 40% risk reduction for delirium in hospitalized older patients.

TABLE 58-5 ■ DELIRIUM RISK FACTORS AND TESTED PREVENTATIVE INTERVENTIONS

RISK FACTOR	INTERVENTION PROTOCOL
Cognitive impairment	• Orienting communication, including orientation board • Therapeutic activities program
Immobilization	• Early mobilization (eg, ambulation or bedside exercises) • Minimizing immobilizing equipment (eg, restraints, bladder catheters)
Psychoactive medications	• Restricted use of PRN sleep and psychoactive medications (eg, sedative-hypnotics, narcotics, anticholinergic drugs) • Nonpharmacologic protocols for management of sleep and anxiety
Sleep deprivation	• Noise-reduction strategies • Scheduling of nighttime medications, procedures, and nursing activities to allow uninterrupted period of sleep
Vision impairment	• Provision of vision aids (eg, magnifiers, special lighting) • Provision of adaptive equipment (eg, illuminated phone dials, large-print books)
Hearing impairment	• Provision of amplifying devices; repair hearing aids • Instruct staff in communication methods
Dehydration	• Early recognition and volume repletion

Data from Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1999;340(9):669–676.

The Hospital Elder Life Program (HELP; now AGS CoCare HELP at https://help.agscocare.org/) represents an innovative strategy of hospital care for older patients, designed to incorporate the tested delirium prevention strategies and to improve overall quality of hospital care. Programs such as

HELP underscore the importance of an interdisciplinary team's contributions to the prevention of delirium. For example, trained volunteers and family members can play roles in daily orientation, therapeutic recreation activities, and feeding assistance. Physical rehabilitation experts and nurses can assist with mobilization and the incorporation of daily exercises to prevent functional decline. Dietitians can help to maximize appropriate caloric intake and oral hydration in acutely ill patients. Consultant pharmacists, chaplains, and social workers also may provide specialized expertise to address issues pertinent to individuals at risk for delirium.

At least 14 studies have examined primary prevention with nonpharmacologic multicomponent approaches to delirium in controlled trials with prospective sampling frameworks and validated delirium assessments. These studies applied multifactorial interventions or educational strategies targeted toward health care professionals, staff, and families, and demonstrated significant reductions in delirium rates, in-hospital falls, health care–associated costs, and/or duration of delirium. Proactive geriatric consultation has been demonstrated to reduce the risk of delirium post hip fracture by 40% in a randomized controlled trial. Another trial found that home rehabilitation after acute hospitalization of older adults was associated with lower risk of delirium and greater patient satisfaction, when compared with an institutional setting. In all, trials suggest that up to 50% of cases of delirium may be preventable and that prevention strategies should begin early during hospitalization.

Preventive efforts for delirium will require system-wide changes and large-scale shifts in local and national policies and approaches to care. Recommended changes include routine cognitive and functional assessments on admission of all older patients, beginning in the emergency department setting; monitoring mental status as a "vital sign"; education of physicians and nurses to improve recognition and heighten awareness of the clinical implications; enhanced geriatric physician and nursing expertise; incentives to change practice patterns that lead to delirium (eg, immobilization, use of deliriogenic medications, bladder catheters, and physical restraints); and creation of systems that enhance high-quality geriatric care (eg, geriatric expertise, medication review, family involvement, case management, clinical pathways, and quality monitoring for delirium).

MANAGEMENT

Overview

The recommended management approach for all delirious patients begins with nonpharmacologic strategies, which usually result in successful symptom amelioration. In selected cases, such strategies must be supplemented with a pharmacologic approach, reserved for patients in whom delirium symptoms would result in interruption of needed medical therapies (eg, mechanical ventilation, central lines) or may endanger the safety of the patient or other persons. However, prescribing any drug requires balancing the benefits of delirium management against the potential for adverse medication effects because sedative drugs may prolong delirium and worsen clinical outcomes. The clinical team, family, and caregivers should understand that the choice of almost any medication may further cloud the patient's mental status, prolong delirium symptoms, and obscure efforts to monitor the course of the mental status change. Any drug should be initiated at the lowest starting dose for the shortest time possible.

Nonpharmacologic Management

Nonpharmacologic approaches are the mainstays of prevention and treatment for every delirious patient. These include strategies for reorientation and behavioral intervention, such as ensuring the presence of family members, use of sitters, and transferring a disruptive patient to a private room or closer to the nurse's station for increased supervision. Orienting influences such as calendars, clocks, and the day's schedule should be prominently displayed, along with familiar personal objects from the patient's home environment (eg, photographs and religious artifacts). Personal contact and communication are critical to reinforce patient awareness and encourage patient participation as much as possible. Communication should incorporate repeated reorientation strategies, clear instructions, and frequent eye contact. Correction of sensory impairments (ie, vision and hearing) should be maximized as applicable for individual patients by encouraging the use of eyeglasses and hearing aids during the hospital stay. Mobility and independence should be promoted; physical restraints should be avoided because they lead to decreased mobility, increased agitation, and greater risk of injury and worsening delirium. Patient involvement in self-care and decision making should also be encouraged. Other environmental interventions include limiting room and staff changes and providing a quiet patient care setting with low-level lighting at night. An environment with

decreased noise allowing for an uninterrupted period for sleep at night is of crucial importance in the management of delirium. This may require unit-wide changes in the coordination of nursing and medical procedures, including medication dispensing, vital sign recording, and administration of intravenous medications and other treatments. Hospital-wide changes may be needed to ensure a low level of noise at night, including minimizing hallway noise, overhead paging, and staff conversations. Family involvement in nonpharmacologic management of delirium is critical and has been shown to reduce length of stay and ameliorate anxiety in family members.

Nonpharmacologic Sleep Protocol

Nonpharmacologic approaches for relaxation and sleep can be effective for management of agitation in delirious patients and for prevention of delirium through minimization of psychoactive medications. The nonpharmacologic sleep protocol includes three components: (1) a glass of warm milk or herbal tea, (2) relaxation music or tapes, and (3) back massage. This protocol was demonstrated to be feasible and effective, reducing use of sleeping medications from 54% to 31% in a hospital environment.

Antipsychotics

As a last resort, antipsychotics are the preferred agents for pharmacologic treatment of delirium. Haloperidol is the agent with the longest track record, although its use may be complicated by extrapyramidal side effects and acute dystonias. Many trials examining the efficacy of haloperidol and the atypical antipsychotics (such as quetiapine, risperidone, and olanzapine) have been low quality and/or inconclusive, with no effect on delirium duration, severity, relief of symptoms, length of stay or mortality. A recent placebo-controlled, randomized trial of haloperidol and ziprasidone in the intensive care setting similarly failed to show a benefit for these medications. Comparisons across antipsychotics have not found superior efficacy of any one agent. Additionally, there is evidence that antipsychotic drugs may prolong delirium and result in poor clinical outcomes. Moreover, official warnings have been issued regarding the increased mortality associated with the use of haloperidol and atypical antipsychotics in patients with dementia. Use of antipsychotics should be avoided in patients with Parkinson disease and Lewy body dementia.

If proceeding with antipsychotic administration, the intravenous route should be reserved for monitored settings due to the risk of torsades and sudden death. Parenteral administration is required in cases where rapid onset of action is required with short duration of action, whereas oral or intramuscular use is associated with a more optimal duration of action. The recommended starting dose is 0.25 mg of haloperidol orally or parenterally. The dose may be repeated every 30 minutes after vital signs have been rechecked. The clinical end point should be an awake but manageable patient, a goal that can be achieved by following the geriatric prescribing principle, "start low and go slow." Most older patients naïve to prior treatment with an antipsychotic should require a total loading dose of no more than 2.5 mg of haloperidol. A subsequent maintenance dose consisting of one-half of the loading dose should be administered in divided doses over the next 24 hours, with doses tapered over the ensuing 48 hours as the agitation resolves. Alternatively, an atypical antipsychotic may be considered at a low starting dose: quetiapine (starting dose, 12.5 mg; 24-h maximum, 25 mg), olanzapine (starting dose, 2.5 mg; 24-h maximum, 10 mg), or risperidone (0.25–0.5 mg; 24-h maximum, 1.5 mg). Patients should be reevaluated continually to assess for ongoing need and tapered off as soon as possible.

Other Pharmacologic Approaches

Benzodiazepines (eg, lorazepam) are not recommended as first-line agents in the treatment of delirium because of their propensity to cause oversedation and to exacerbate acute mental status changes. However, they remain the treatment of choice for delirium caused by seizures and alcohol- and medication-related withdrawal syndromes. While other drugs have been advocated for use in treatment of delirium, evaluation of their use has resulted in discrepant findings, and there is no consensus recommendation for their general use. Trials of the sedative dexmedetomidine in ventilated ICU patients found a reduction in delirium duration and length of ICU stay as well as better effectiveness and safety in haloperidol-resistant patients. Clonidine, an α2-agonist, has been shown to be safe, though no effect was detected on delirium. In randomized trials of melatonin and the melatonin receptor agonist ramelteon, the results have been mixed to date. Overall, data does not support the use of pharmacologic management of delirium, although the consensus in the field is for a limited role of medications for the treatment of

intractable distress and agitation in which nonpharmacologic strategies have failed.

SPECIAL ISSUES

COVID-19

The arrival of the SARS-CoV-2 virus and associated COVID-19 in early 2020 has culminated in a global health crisis. Although COVID-19 typically manifests as an influenza-like respiratory illness, early reports of neurologic symptoms included altered mental status. In one study of older adults presenting to the emergency department with COVID-19, delirium was the sixth most common presenting symptom, and in some cases occurred without the typical symptoms of COVID-19. Rates of delirium during hospitalization with COVID-19 range from 25% to 84%. Delirium may be more severe or prolonged due to social isolation and use of personal protective equipment, resulting in poor communication, reduced social interactions, limited reorienting of patients, and prolonged need for mechanical ventilation, with increased immobilization, depth of sedation, or use of second-line medications due to drug shortages. Nonpharmacologic interventions for delirium prevention have been adapted for COVID-19 and are available online at https://help.agscocare.org/chapter-abstract/chapter/H00107/H00107_PART001_002.

Patient Preference and Decision Making

Given acute fluctuations in attention and decision-making capacity, delirium presents formidable challenges to the ethical care of affected patients (see Chapters 7 and 26). Cognitive assessments in patients with suspected delirium help to ensure that patients can be involved in decision making whenever possible and that appropriate surrogate decision makers are involved in representing a patient's wishes and understanding the risks and benefits of procedures and treatments. Because the patient may exhibit periods of lucidity in delirium, there may be times during which the decision-making and informed consent process can and must involve the patient. The clinician should be cognizant of ongoing subclinical manifestations of delirium, which may be important for both the long-term management and decision-making capacity of the patient.

Nursing Home Setting

For the postacute population receiving short-term rehabilitative care, persistent delirium after an acute hospitalization is a major concern. Prior studies demonstrated that 16% of admissions to postacute care met full CAM criteria for delirium, while another 50% demonstrated signs of subsyndromal delirium. Patients with delirium on admission to postacute care experience more complications such as falls, higher rehospitalization rates, and higher mortality. Of those admitted to postacute care with delirium, over 50% are still delirious 1 month later. Persistence of delirium prevents functional recovery in the postacute setting; only those patients whose delirium cleared within 2 weeks of admission recovered to their prehospitalization functional status. Persistent delirium is also associated with higher mortality.

The long-term care population represents a high-risk group for delirium, with a high prevalence of dementia and functional impairments. Incident delirium is common in this population, frequently heralding the onset of an acute illness that results in hospitalization and/or death. Nursing staffing ratios, high turnover, competing concerns, and the high prevalence of dementia make identification and prevention of delirium challenging in this setting. Nonetheless, these patients represent among the most vulnerable of older adults, and further attention to delirium in this setting is warranted. Research in long-term care settings is challenging, and results are mixed in this area. A recent trial involving nonpharmacologic delirium prevention strategies in the nursing home setting did not prevent delirium or reduce delirium symptoms, with greater than expected improvement in both intervention and usual care groups. This finding underscores the need for further research into effective delirium prevention strategies in this setting.

Palliative and End-of-Life Care

Because delirium occurs in more than 80% of patients at the end of life, it is considered nearly inevitable in the terminal stages by most hospice care providers and may serve as a marker of approaching death. Establishing goals of care with the patient and family is a crucial step, including discussions about the potential causes of the delirium, intensity of medical evaluations considered appropriate, and the potential trade-off between alertness and adequate control of pain and agitation. Some patients may wish to preserve their ability to communicate as long as possible, while others may focus on comfort perhaps at the expense of alertness. Physicians must be cognizant that even in the terminal phase, many causes of delirium are

potentially reversible, and may be amenable to interventions (eg, medication adjustments, treatment of dehydration, hypoglycemia, or hypoxia) that may improve comfort and quality of life. However, the burdens of evaluation or treatment (eg, reduction in narcotic dose) may not be consistent with the goals for care. In all cases, symptom management should begin immediately, while evaluation is underway. Nonpharmacologic approaches should be instituted in all patients, with pharmacologic approaches for selected cases. Haloperidol remains the first-line therapy for delirium in terminally ill patients, although a recent randomized controlled trial did not support its use. In end-of-life care, sedation may be indicated as an additional therapy for management of severe agitated delirium in the terminally ill patient, which can cause considerable distress for the patient and family. Because sedation poses the risks of decreased meaningful interaction with family, increased confusion, and respiratory depression, this choice should be made in conjunction with the family according to the goals of care. If sedation is indicated, an agent that is short acting and easily titrated to effect is recommended. Lorazepam (starting dose 0.5–1.0 mg PO, IV, or SQ) is the recommended agent of choice.

FURTHER READING

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Chapter 59

Dementia Including Alzheimer Disease

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Alzheimer disease (AD) is the most common neurodegenerative disorder affecting older adults, projected to affect more than 13 million Americans and 115 million individuals worldwide by 2050. Compared to projections in high-income countries, the number of individuals with AD in low- and middle-income nations is increasing at an even greater rate. The disease is characterized by diffuse functional and structural abnormalities in the brain that lead to progressive cognitive and behavioral deficits and functional decline. AD is associated with significant morbidity and mortality and is currently the sixth most common cause of death in the United States. The physical, psychological, functional, and socioeconomic impact of AD substantially affects the well-being and quality of life of patients and their caregivers. Caring for patients with AD places heavy financial burden on patients, families, communities, and the health care system at large. In the United States in 2020, the average lifetime cost of caring for a person with AD exceeded $350,000. The total cost of caring for Americans with AD exceeds $355 billion annually. Evidence is beginning to emerge on the economic impact of dementia care in low- and middle-income countries as most of the costs in these nations are related to informal care.

Recognizing the enormity of the burden of AD, international collaborations between clinicians, researchers, policy makers, patient advocacy groups, the media, and many others have increased public awareness of the global impact of the disease and have laid the foundation for the development of effective preventive and therapeutic strategies as well as improvements in care management for patients with AD. An example of

such a coordinated effort is the 2011 United States National Alzheimer's Project Act (NAPA), a law designed to create and maintain an integrated national plan to address AD. The plan encompasses federal coordination of AD research and services and aims to improve early diagnosis and coordination of care, accelerate development of effective treatments, promote health equity in AD care among ethnic and racial minority populations, and stimulate coordination with international groups to address AD globally. Such national and international collaborations will help accelerate optimal diagnosis and care of patients at risk for AD and related dementias. Another example is the public health prevention effort underway to address 12 recognized modifiable risk factors that contribute to dementia and recommend policy interventions to mitigate these risks. In the United States, this is the focus of the Alzheimer's Association's Centers for Disease Control and Prevention: Building Our Largest Dementia (BOLD) Public Health Center of Excellence on Dementia Risk Reduction supported by the BOLD Infrastructure for Alzheimer's Act—PL115-406.

Learning Objectives

- Describe the current diagnostic criteria for dementia, Alzheimer disease (AD), and mild cognitive impairment (MCI), and how these conditions differ from normal cognitive aging.
- Understand the effects of age and other genetic and nongenetic risk factors on risk of developing AD.
- Identify key neuropathologic features and mechanistic pathways associated with AD.
- Recognize common reversible causes of cognitive dysfunction.
- Describe an effective dementia care management plan across care settings and stages of disease, integrating use of pharmacologic and nonpharmacologic interventions, education, and community resources.

Key Clinical Points

1. **AD is the most common neurodegenerative disorder affecting older adults with prevalence rates increasing with advancing age.**
2. **While aging is the most established risk factor for late-onset AD, various other genetic, lifestyle, and environmental factors also influence dementia risk.**

3. **The diagnostic evaluation for dementia, AD, and MCI depends heavily on a careful assessment of an individual's change in functional status, a structured cognitive assessment, a thorough clinical examination, and exclusion of other competing causes of cognitive decline.**
4. **There are currently no proven preventive or disease-modifying therapies for AD; however, aducanumab is the first FDA-approved medication that reduces amyloid burden in the brain, but without significant improvement in cognition. The current standard-of-care management plans integrate use of pharmacologic therapies to delay symptom progression; nonpharmacologic strategies to optimize function, behavior, and safety; and education and support for patients and their care partners.**
5. **Advanced care planning prior to loss of decisional capacity is of critical importance in developing patient-centered goals of care in persons with cognitive impairment.**

DEFINITION

In defining AD features, it is widely recognized that the clinical cognitive and behavioral signs and symptoms do not always correlate with the degree of AD neuropathologic changes noted in the brain. The discrepancy between the neuropathologic changes and the individual clinical expression of disease is likely related to additional unidentified physiologic, metabolic, or genetic factors that either accelerate or slow cognitive decline. For example, some older adults with normal cognitive function just prior to death have been found to have significant AD neuropathology on autopsy. These individuals may have unrecognized neuroprotective factors that help preserve cognitive function despite notable neuropathologic changes. Thus, in order to disentangle the clinical syndrome from the neuropathologic changes, the current AD core clinical criteria are distinct from the AD neuropathologic guidelines, yet encourage clinicians and researchers to postulate the most likely neuropathology underlying the clinical presentation of disease.

In 2011, the National Institute on Aging and the Alzheimer's Association (NIA-AA) released cosponsored revised clinical diagnostic guidelines for dementia, dementia due to AD, MCI, and a theoretical framework for defining the preclinical stages of AD. Core clinical diagnostic criteria for dementia, AD, and MCI were designed for use in all clinical settings and are summarized in **Tables 59-1** and **59-2**. In 2013, the American Psychiatric Association published the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). Within this edition, the term "dementia" was replaced with "major neurocognitive disorder" and the term "mild cognitive impairment" with "mild neurocognitive disorder." While the DSM-5 and NIA-AA terminologies differ, the diagnostic criteria for major neurocognitive disorder and dementia as well as those for mild neurocognitive disorder and MCI are nearly identical (see **Tables 59-1** and **59-2**) and, thus, in most circumstances are interchangeable. For simplicity, this chapter uses the terms "dementia" and "MCI."

TABLE 59-1 ■ NIA-AA CORE CLINICAL DIAGNOSTIC CRITERIA FOR ALL-CAUSE DEMENTIA AND DEMENTIA DUE TO ALZHEIMER DISEASE

DEMENTIA

The patient has cognitive or behavioral symptoms that:

- Interfere with the ability to function at work or at usual activities
- Represent a decline from previous levels of functioning and performing
- Are not explained by delirium or major psychiatric disorder

Cognitive impairment is detected and diagnosed through a combination of:

- History-taking from the patient and a knowledgeable informant
- An objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing

The cognitive or behavioral impairment involves a minimum of two of the following domains[a]:

- Impaired ability to acquire and remember new information
- Impaired reasoning, judgment, and handling of complex tasks
- Impaired visuospatial abilities
- Impaired language functions
- Changes in personality, behavior, or comportment

PROBABLE DEMENTIA DUE TO ALZHEIMER DISEASE[b]

The patient meets criteria for dementia *and* has the following characteristics:

- Insidious onset over months to years, not sudden over hours or days
- Clear-cut history of worsening cognition by report or observation
- Initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:
  - *Amnestic presentation* (most common presentation)—Deficits should include impairment in learning and recall of recently learned information, plus cognitive dysfunction in at least one other cognitive domain.
  - *Nonamnestic presentations*[c]:
    - *Language presentation*—The most prominent deficits are in word finding, but deficits in other cognitive domains should be present.
    - *Visuospatial presentation*—The most prominent deficits are in spatial cognition, but deficits in other cognitive domains should be present.
    - *Executive dysfunction*—The most prominent deficits are impaired reasoning, judgment, and problem solving, but deficits in other cognitive domains should be present.

The diagnosis of probable AD dementia *should not* be applied when there is evidence of:

- Substantial concomitant cerebrovascular disease (defined by a history of a stroke temporally related to onset or worsening of cognitive impairment or presence of multiple or extensive infarcts or severe white matter hyperintensity burden)
- Core features of dementia with Lewy bodies
- Prominent features of behavioral variant frontotemporal dementia
- Prominent features of primary progressive aphasia
- Active neurologic disease or a medical comorbidity or use of medication that could have a substantial effect on cognition

[a]Diagnostic criteria for DSM-5 "major neurocognitive disorder" require a significant cognitive decline in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition).
[b]The diagnosis of "probable AD dementia with increased level of certainty" is made when there is a documented cognitive decline and/or evidence of a causative genetic mutation (APP, PSEN1, or PSEN2, not APOE4) in addition to the above diagnostic criteria.
[c]Diagnostic criteria for DSM-5 "major neurocognitive disorder due to Alzheimer disease" require that one of the affected cognitive domains be memory and learning.
Data from McKhann GM, Knopman DS, Chertkow H, et al. *The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263–269.*

EPIDEMIOLOGY

AD is the most common cause of dementia in older adults, currently affecting more than 6 million Americans. Worldwide more than 44 million individuals currently have AD or a related dementia. Unless effective preventive strategies are identified, it is anticipated that the prevalence of AD will double every 20 years. The United Nations predicts that the major rate of increase in the prevalence of AD will likely occur in developing countries that may not possess the essential resources, public health support system, or medical expertise to care for patients with AD. There is clear evidence that a

number of risk factors significantly enhance the overall risk for developing AD. These risk factors relate to both genetic and nongenetic markers and are discussed below.

Aging

Age is the single most important and validated risk factor for AD. Epidemiologic studies indicate that the incidence and prevalence of AD both increase with age. Based on data from the 2010 US Census, the prevalence of AD was approximately 3% among adults between the ages of 65 to 74, 17% in persons aged 75 to 84, and 32% in individuals age 85 and older. With the average human lifespan increasing, the prevalence of AD is expected to accelerate at an even greater rate in coming decades. Although not clearly understood, converging research findings provide clues concerning the potential molecular pathway(s) underlying the association between aging and AD. Increases in the pathologic hallmarks of AD, notably amyloid plaques and neurofibrillary tangles, have been noted in the brains of older adults.

Age-related changes in molecular pathways involving insulin-like growth factor 1 receptor (IGF1-R), neurotrophin signaling, β-site amyloid precursor protein cleaving enzyme 1 (BACE1), and amyloid precursor protein (APP) metabolism may account for some of the increase in incidence and prevalence of AD with aging. Additionally, aging and IGF1-R signaling are both associated with cerebrovascular dysfunction, which may play a key role in the development of AD. An increased exposure time to age-dependent vascular risk factors or an interaction between aging and vascular risk factors may in part account for the effects of aging on the pathobiology of AD.

Apolipoprotein E Genotype

Late-onset AD is the most common form of the disorder, accounting for greater than 95% of all AD cases. Although some cases of younger-onset AD have strong links to the genes coding for *APP* and presenilin 1 (*PSEN1*) and 2 (*PSEN2*) proteins, many cases of late-onset AD are seen in individuals without any clear genetic predisposition. A common polymorphism in the apolipoprotein E (*APOE*) gene is the major determinant of risk in families with late-onset AD. Of the three allelic forms (ε2, ε3, and ε4), AD risk is increased fourfold in individuals with at least one ε4 allele and 12-fold in persons with two copies of the ε4 allele. While ε4 genotype modifies an

individual's risk of the disease, by itself it is neither necessary nor sufficient for the development of AD. In the Framingham study, 55% of ε4 homozygote carriers, 27% of ε4 heterozygote carriers, and 9% of noncarriers developed AD by age 85. *APOE* ε4 genotype may contribute to AD by influencing processes related to the development of AD, including altering the rate of production, clearance, or aggregation of amyloid β-peptide and/or influencing cerebral cholesterol metabolism and inflammation.

Vascular Risk Factors

Midlife vascular risk factors, including hypercholesterolemia, hypertension, diabetes mellitus, metabolic syndrome, obesity, and physical inactivity, have all been associated with a greater risk of developing AD in later life. High midlife total cholesterol and blood pressure levels are associated with a two- to nearly threefold increased risk of developing AD decades later and may convey an even greater risk than that caused by *APOE* ε4 allele. Abnormal cholesterol metabolism is related to *APOE* ε4 allele, suggesting that some of the adverse effects of this genotype on AD risk may be partially mediated through lipoprotein dysregulation. In a community-based cohort study, higher glucose levels were associated with an increased risk of dementia in populations both with and without diabetes mellitus. Metabolic syndrome is also associated with increased risk for AD, although this cluster of risk factors is more consistently related to greater risk of vascular dementia. Midlife obesity (RR 1.60, 95% CI 1.34–1.92) and physical inactivity (RR 1.82, 95% CI 1.19–2.78) are interrelated and both independently increase the risk for developing AD in late life. With more than 35% of current US adults meeting criteria for obesity, there is concern that this risk factor could further accelerate projected increases in AD incidence rates over the coming decades.

Studies support that vascular factors exert an independent additive effect on AD risk. The presence of multiple cardiovascular risk factors at midlife substantially increases the risk of late-life dementia in a dose-dependent manner. The positive corollary to these findings is that about a third of AD cases worldwide might be attributable to potentially modifiable risk factors, thus, providing a target for preventive strategies. Vascular risk factors exert their adverse effects on AD pathology through a variety of mechanisms, including modulation of β-amyloid (Aβ) metabolism, effects on insulin receptors, blood-brain barrier (BBB) integrity, endothelial dysfunction, and

cerebral blood flow. These vascular-mediated changes subsequently lead to tissue hypoxia, increased oxidative stress, inflammation, and cognitive decline.

Traumatic Brain Injury

There is increasing epidemiologic evidence that moderate or severe traumatic brain injury (TBI) is a risk factor for AD in late life and may precipitate earlier onset of the disease. In longitudinal studies, the magnitude of AD risk increases with TBI severity. Compared to controls, World War II veterans with moderate TBI were twice as likely to develop AD, whereas the risk was fourfold in veterans with severe TBI with loss of consciousness. Neuropathologic examination of brains from patients with a history of head trauma generally reveals changes of diffuse amyloid plaques together with tau pathology, inflammatory response, and loss of cholinergic neurons. These pathologic changes may be related to transient upregulation of BACE1 together with increased generation of Aβ. These features are accompanied by tau hyperphosphorylation and increased caspase-mediated cleavage of APP. Thus, head trauma may lead to AD by triggering accelerated neurodegeneration.

Newer evidence demonstrates that recurrent mild TBI, including both concussive and subconcussive injuries, may also contribute to future risk of cognitive decline. However, it has been difficult to establish risk estimates of the impact of repetitive mild TBI on risk for AD due to a variety of methodologic challenges. The high frequency of concussive and subconcussive injuries, the variability in definitions and measurements of mild TBI, the heterogeneity of injuries among various cohorts (ie, military combat veterans vs contact sport athletes), and selection and recall biases have complicated research of this area. Repetitive concussive injuries may also lead to chronic traumatic encephalopathy (CTE), a condition that is neuropathologically distinct from AD. Symptoms of CTE frequently include headaches and disturbances in attention or concentration and depression—Chapter 64 provides additional details on CTE. Research is underway to clarify the varying types and severity of TBI and the effects of such injuries on risk for posttraumatic neurodegeneration.

Depression

More than 30% of patients with AD develop depression during the course of their illness, and some may present with depressive symptoms as their first clinical manifestation of underlying AD. While depression has long been recognized as a common psychiatric condition in older adults that may mimic dementia, depression is likely also a risk factor for AD. Findings of a meta-analysis involving over 20 population-based prospective studies supported an increased risk of AD in patients with a history of late-life depression (pooled risk OR [95% CI] 1.65 [1.42–1.92]). To date, the precise mechanisms underlying the association between depression and enhanced AD risk are unknown. Several potential mechanisms have been proposed that are common to both AD and depression, including elevated levels of cytokines, increased vascular risk factors, and the potential role of *APOE4* allele. More research is needed to better understand the biological basis of increased risk of AD in patients with a history of depression.

Race and Ethnicity

The assessment of differences in AD prevalence rates across geographic regions worldwide and among various racial and ethnic groups has proven to be challenging. Differences in education, literacy, life expectancy, access to health care, nutrition, social stressors, vascular risk factors, and cultural beliefs in what is considered normal aging can all influence AD prevalence estimates. In the Indianapolis/Ibadan studies, the incidence and prevalence of AD were significantly lower among Africans in Ibadan, Nigeria, than among age-matched African Americans in Indianapolis, suggesting that differences in environmental factors may play a larger role than race in influencing the development of AD. The significant influence of environmental factors on AD risk is also supported by data showing that migrant populations tend to have dementia rates that fall between those seen in their homeland and adopted countries. Standardized approaches to case ascertainment of dementia and statistical comparisons across nations have been implemented to better assess variations in prevalence rates among low-, middle-, and high-income countries. These approaches have produced age-adjusted dementia prevalence estimates of approximately 5% to 9% in people older than age 60 across global regions.

Studies assessing ethnic and racial variations in dementia rates within countries have identified some group differences in AD incidence and prevalence. In a population-based study in the Washington Heights and

Inwood communities of New York City, the cumulative incidence of AD was increased twofold among individuals of African-American and Caribbean Hispanic origin. The group differences in AD incidence did not change following corrections for differences in years of education or history of vascular risk factors. In a study in Houston, Texas, both the incidence and prevalence of AD were higher among older African-American and Hispanic individuals compared to non-Hispanic White adults. In Singapore, ethnic Malays and Indians had higher rates of dementia compared to ethnic Chinese, independent of vascular risk factors. While some research suggests there may be biological or genetic differences driving variations in AD risk, other studies support that these racial and ethnic group differences will not persist after rigorously accounting for important social, cultural, and environmental factors influencing risk of dementia.

Education

Low educational attainment, poor educational quality, and illiteracy have been shown to be associated with increased risk for AD. In a meta-analysis of 13 cohort and six case-control studies, low education had a pooled relative risk (RR) estimate for AD of 1.80 (95% CI 1.45–2.27) compared to high education, although the estimate from cohort studies (RR 1.59 [95% CI 1.35–1.86]) was significantly lower than the estimate based on case-control studies (2.40, [1.32–4.38]). Prospective cohort studies likely provide a more accurate assessment of the association between education and dementia since they allow for documentation of a decline from a previous level of cognitive performance. Some studies have found that education may be a marker of cognitive reserve as it modifies the association between AD neuropathology and level of cognitive function. For the same degree of brain pathology, persons with higher education demonstrate less cognitive impairment. In addition, higher levels of education may help individuals cope more effectively with cognitive changes. Access to higher levels of education may also be a marker of socioeconomic status, coexisting chronic diseases, access to health care resources, and premorbid intellectual abilities. Thus, while low educational attainment is associated with increased AD risk, it is not clear to what extent low education contributes to AD or whether early educational interventions will protect against the development of dementia.

Gender