Dementia syndromes: evaluation and treatment

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As our population ages, diseases affecting memory and daily functioning will affect an increasing number of individuals, their families and the healthcare system. The social, financial and economic impacts will be profound. This article provides an overview of current dementia syndromes to assist clinicians in evaluating, educating and treating these patients.

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Dementia is a progressive disorder of memory loss and impaired cognitive ability. The Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV defines dementia as a decline in memory with impairment of at least one other cognitive function, such as skilled movements (limb apraxia), language (aphasia) or executive function (e.g., planning, attention and abstract reasoning). This decline should represent a change from previous behavior; it should impair social and/or occupational functioning; and cannot be accounted for by other psychiatric conditions such as depression, other mood disorders or psychosis [1,2].

Dementia comes in many forms, with the Alzheimer's and vascular subtypes being most common [3]. Dementia (neurodegenerative) is age related, with prevalence estimated at 20% in individuals older than 85 years [201]. The decline in cognition and memory function not only affects test performance, but often manifests as behavioral and mood changes, as well as the inability to perform activities of daily living (ADLs). With our aging population, the number of patients with dementia will rise and place an increasing burden on families and our healthcare system.

Accurate diagnosis of dementia is important for prognosis and to guide therapy. The number of potentially reversible dementias, perhaps upwards of 11%, is small, but these disorders may improve if identified and treated appropriately [4]. Potentially reversible dementias are more likely to be seen in younger patients (<65 years). Potentially reversible causes may include depression, metabolic, infectious or inflammatory disorders or cognitive dysfunction resulting from structural abnormalities (e.g., tumors). If timely identification occurs, even in subjects with co-occurring Alzheimer's disease (AD) or vascular dementia, treatment may stabilize function and improve patients' quality of life.

Diagnostic approach

General

The first step in evaluating patients with cognitive complaints is defining whether dementia is present. This requires the identification of the cognitive problem, time of onset, progression (if any) and what functional impairment(s) have resulted. This often requires more than one visit before dementia can be confidently diagnosed. Evaluation to identify potentially reversible causes can proceed simultaneously.

Evaluating cognitive dysfunction requires involvement of family or other independent observers (not just the patient). Cognitive abilities should be documented using the Mini-Mental State Examination (MMSE) [5] or other measures, such the Blessed Dementia Rating Scale [6] or the AD Assessment Scale [7]. If there is any clinical doubt, evaluation by a consultant dementia specialist is reasonable.

Patients not meeting criteria for dementia may be diagnosed with mild cognitive impairment (MCI). Please see the 'Syndromic classification' section below.

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Evaluation

An accurate and detailed history is essential to dementia diagnosis (BOX 1). An independent observer (e.g., family member) should be interviewed as well. One attempts to define the type and extent of the cognitive complaint(s), its time course, current and past levels of social and occupational functioning and any safety concerns. Knowing when a patient stopped driving or balancing the checkbook may help in estimating disease onset. One can tailor the history by looking for other factors (e.g., history of mood disorders, trauma, stroke and family history of similar symptoms) that may be contributing to a patient's decline. Assessment of a patient's premorbid function allows one to estimate severity. Questions about a patient's work and educational history may be helpful. Other measures, such as the National Adult Reading Test are available to estimate premorbid intellectual ability in patients approximately 80 years of age [8,202].

Patients with dementia may not complain of cognitive difficulty owing to loss of self-awareness (anosognosia). As a result, concerned family members may initiate the neurological evaluation. By contrast, patients with depression often complain of memory difficulties and seek medical attention of their own initiative. These 'worried well' may benefit from antidepressant therapy and observation rather than dementia care [9,202].

The Folstein MMSE is the most widely used measure of cognitive function. A maximum of 30 points can be awarded based on responses that evaluate orientation, registration, attention, calculation and visuospatial domains [5]. Typically, a score of 24 or less is considered suggestive of dementia, with a sensitivity and specificity of 87 and 82%, respectively. With that said, the MMSE has few pure recall items and is relatively insensitive to early or mild cognitive deficits, particularly in highly educated individuals. It is also insensitive to frontal lobe dysfunction. Age, gender and education-based norms are available [10,11,202].

Another time efficient and clinically useful measure of cognition to consider is the Mini-cog. This test includes assessment of a patient's three-word recall, as well as a clock drawing task. The Mini-cog has similar sensitivity and specificity for dementia as the MMSE [202,12].

In our practice, these assessments are combined with bedside testing of cognitive function, limb praxis (skilled learned limb movements to verbal command) and motivational/organizational functions. Cognitive dysfunction and amnesia must be demonstrated before a patient meets criteria for dementia. Screening a number of cognitive domains is not necessarily time consuming. In our personal experience, we have found that assessing limb praxis with four–eight items (e.g., "show me how you would use a hammer"), assessing picture naming and performing verbal memory screening (which may demonstrate mild amnesia not detected by three-object recall) is quick (<10 mins) and can be helpful in uncovering deficits in early AD.

A complete physical examination is recommended to identify comorbid medical illnesses that may be affecting cognition. The value of complete neurological examination is immense. Identification of focal deficits could suggest a vascular or structural etiology. Hypertonia, masked facies and/or slowed movements could suggest parkinsonism. Gait should be closely examined for stability, step size, speed and turning proficiency to identify superimposed pyramidal or extrapyramidal motor deficits.

Laboratory testing should be considered to identify potentially reversible conditions that may mimic dementia. Early identification and aggressive management of such disorders may improve a patient's thinking and daily function. Which laboratory studies to order is controversial. Some clinicians suggest a detailed laboratory evaluation to include complete blood counts (CBC), chemistry panels, erythrocyte sedimentation rate, thyroid function tests (thyroid-stimulating hormone [TSH] and free thyroxine [FT4]), vitamin B12 level, thiamine level and syphilis screening. As tertiary-level neurologists, we tend to agree with this approach for many of our referrals. Others would dispute this assertion from a cost–benefit standpoint, arguing that such evaluations are expensive and usually low yield [13]. The 2001 American Academy of Neurology (AAN) practice parameter recommends evaluating for vitamin B12 deficiency and hypothyroidism in all patients, while tailoring additional testing to the individual patient (e.g., testing for neurosyphilis is not recommended unless there is a strong clinical suspicion) [14,202]. As we have identified cases of neurosyphilis on routine screening (see potentially reversible syndromes), we feel more data are needed on how to triage patients for testing.

Brain imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) is recommended for all patients to identify structural, demyelinating, inflammatory or vascular etiologies. There is no consensus guideline recommending one imaging modality over the other [14]. In our practice, we prefer MRI to CT because of its better resolution for patients with primary attentional or frontal–temporal deficits, history of cancer, if subcortical pathology or stroke is suspected, or if patients have isolated memory deficits, as structural changes may be subtle.

Specialized laboratory studies, such as lumbar puncture, are considered in atypical, primarily attentional or frontal–temporal syndromes to evaluate for infectious, neoplastic or inflammatory causes. Cerebrospinal fluid showing increased levels of tau protein, in combination with decreased levels of amyloid-β 42 protein, may have a positive predictive value of AD approaching 90% [15–17,202]; however, in clinical practice these have not proven useful. An electroencephalogram can help distinguish episodic behavioral symptoms from seizures.

Positron emission tomography (PET) and single photon-emission computed tomography (SPECT) may be useful in difficult to diagnose cases and to improve diagnostic accuracy. For example, in autopsy-proven series, PET has been reported to have 90–95% sensitivity and upwards of 78% specificity [18,19] compared with 85 and 55%, respectively [20] for clinical testing [21]. Furthermore, markers for amyloid and neurofibrillary tangles (NFTs) may allow earlier prediction of

Box 1. Proposed approach for evaluating patients with cognitive dysfunction.

- Step 1: Detailed history
  - Define the cognitive complaint
  - Time of onset and progression (if any)
  - Functional impairment
  - Safety concerns
  - Review medication lists
  - Comorbidities (e.g., stroke, malignancy, metabolic, endocrinopathies)
- Step 2: Physical examination
- Step 3: Neurological examination
- Step 4: Cognitive testing
  - Mini-mental status examination
  - Blessed Dementia Scale
  - Alzheimer's disease assessment
  - National Adult Reading Test
- Step 5: Laboratory testing
  - All individuals
    - Complete blood cell count (differential)
    - Electrolytes
    - Renal, liver and thyroid function tests
    - Vitamin B12 levels
    - Routine relative peak ratio
  - Selected individuals
    - HIV
    - Rheumatologic screening (e.g., erythrocyte sedimentation rate, antinucleolar antibody, rheumatoid factor)
    - Thiamine
    - Methylmalonic acid/homocysteine levels (confirm vitamin B12 deficiency)
    - Fluorescent treponemal antibody absorption, lumbar puncture
- Step 6: Brain imaging
  - Routine: computed tomography or magnetic resonance imaging
  - Selected individuals: single photon-emission computed tomography or positron emission tomography
- Step 7: Specialty consultation
  - Dementia specialist
  - Neuropsychologist
  - Social worker
  - Geriatric psychiatrist

cognitive status and serve as a biomarker for interventional studies [21]. As a result of their expense, we currently only use them when employers or others require 'objective proof' of brain dysfunction.

Syndromic classification

See BOX 2 for types of cognitive and dementia syndromes.

Mild cognitive impairment

In MCI, a demonstrable memory problem for age can be identified; however, patients do not meet the criteria for dementia as they retain normal ADL and social functioning [203]. They may or may not demonstrate other cognitive abnormalities (e.g., impaired naming or skilled learned movement dysfunction), suggesting that MCI may represent a transitional state between normalcy and dementia [22]. Cognitive difficulties in areas other than memory are associated with a significantly increased risk of developing dementia [23]. Cognitive specialists split MCI into various subclasses – the amnestic subtype is most closely linked to incipient AD [24]. A detailed discussion of each subtype is beyond the scope of this article. We believe that MCI patients are important to identify and follow as these individuals may develop AD at a threefold higher rate than those without cognitive dysfunction [25].

The efficacy of treating MCI patients with cholinesterase inhibitors is unclear and deserves further study. A recent Cochrane review suggests that MCI patients should not be treated with the cholinesterase inhibitor donepezil [26]. Donepezil treatment has been associated with a lower rate of progression to AD during the first year of treatment but has not been proven to impact the rate of progression at 3 years [27]. A randomized study of 270 patients also found no significant treatment effect after 24 weeks of donepezil [28]. Vitamin E supplementation was not demonstrated to be beneficial for MCI [27]. In studies of the effects of galantamine on MCI, treatment was associated with increased mortality [29].

In our practice, we approach MCI patients in the same manner described earlier. We attempt to define and quantify the cognitive impairment, identify any potentially reversible conditions and address comorbidities, such as vascular risk factors in hopes of preventing progression. Much of our effort is oriented towards education of patients and their families.

Alzheimer's disease

AD is by far the most common type of dementia, accounting for between 60 and 80% of cases [3]. Over 4 million individuals in the USA were diagnosed with AD in 2000 and approximately 13 million sufferers are projected by 2050 [3]. Patients present with some combination of insidious memory loss and focal cognitive dysfunction. AD is characterized by progressive deterioration of cortical functions such as language, visuospatial tasks, abstract reasoning, calculating, left–right disorientation and/or limb praxis. Motor skills, such as walking, are relatively preserved. Onset typically occurs after 45 years of age but is more common after 65 years or age. Supportive findings of AD include altered behavior and inability to perform ADLs [3,5,6]. Although progressive, plateaus in the course may be observed. Symptoms, such as depression, insomnia and hallucinations, may occur. Incontinence (if not functional) may occur late in the course of the disease.

Box 2. Cognitive and dementia syndromes.

- Neurodegenerative
  - Mild cognitive impairment
  - Alzheimer's type
  - Dementia with Lewy bodies
  - Parkinson's disease dementia
  - Parkinson's plus syndromes
- Mixed dementia
- Vascular dementia
- Potentially reversible syndromes
  - Depression
  - Medication induced
  - Metabolic derangements
    - Vitamin B12 deficiency
    - Thyroid disorders
    - Thiamine deficiency
    - Chronic disease (e.g., renal failure, hepatic failure, malignancy)
  - Gastrointestinal disorders
    - Whipple's disease
    - Vitamin E deficiency
    - Pellagra
  - Structural brain lesions
    - Tumor
    - Subdural hematoma
    - Normal pressure hydrocephalus
  - Infectious
    - Neurosyphilis
    - HIV/AIDS

Pathologically, AD is associated with the accumulation of neuritic plaques (NPs) and NFTs in the brain. What triggers these events is unclear. NPs are probably the result of abnormal metabolism of amyloid-β 40 and amyloid-β 42 leading to its accumulation, while NFTs are formed from hyperphosphorylated tau protein [30]. The severity of cognitive decline in AD is more closely related to NFT burden than with amyloid deposition [31]. The presence of hyperphosphorylated tau helps distinguish this disorder from synucleinopathies, such as dementia with Lewy Bodies (DLB) and Parkinson's disease (PD).

AD remains a clinical diagnosis, as there is no definitive laboratory test except autopsy to confirm. AD diagnosis by experienced clinicians is accurate in approximately 90% of cases [32]. As mentioned earlier, DSM-IV criteria require that patients demonstrate deficits in memory and in at least one other cognitive area, which is not attributable to disturbances in consciousness (i.e., delirium) or comorbid illness. The DSM-IV AD criteria has a sensitivity of 76% and a specificity of 80% [33].

Dementia syndromes associated with parkinsonism

Dementia with Lewy Bodies

Lewy body disease is second only to AD in prevalence. DLB may be more prevalent in men [204]. The presentation of DLB is varied and it is often useful to think of these disorders as a continuum with varying degrees of dementia and parkinsonism. Prominent features of DLB include: deficits in attention and concentration, reduced fluency, difficulty performing visuospatial tasks and psychomotor slowing. These patients are often very sensitive to neuroleptic medications. The presence of fluctuating levels of alertness, visual hallucinations and parkinsonism are considered necessary for the diagnosis of probable DLB [4,34,35]. Insoluble α-synuclein aggregations are a major component of Lewy bodies (LBs) – the key pathological feature of DLB. LBs are identified as round, eosinophilic inclusions that are surrounded by white halos on microscopic examination. LBs are seen in cortical and subcortical regions of affected individuals [204]. The likelihood of DLB is graded as low, intermediate or high, depending on LB density (low, intermediate or high) and the distribution of LBs (brainstem predominant, limbic-transitional or diffuse neocortical involvement) [35,204].

PD dementia

PD is common, may disproportionately affect thinking and is thought to share similar pathology to DLB. PD, a disorder that features resting tremor, slowed movement and gait disorder, can manifest cognitive features, such as amnesia, psychomotor slowing and depression. Masked facial expression, soft voice, tiny handwriting (micrographia), cogwheel rigidity of the limbs and gait problems are key features of the physical examination.

PD is associated with an almost sixfold increased risk of developing dementia [36]. The prevalence of dementia in PD may approach 80% [37]. Common features of PD dementia (PDD) include impaired attention, memory, and poor executive function [37]. Interestingly, patients may not be aware of cognitive or motor dysfunction and may be skeptical of the diagnosis. PDD should be diagnosed only in those patients with PD of greater than 1 year duration. However, PD without dementia may occasionally present with forgetfulness as a first clinical complaint, with symptoms resolving after dopaminergic or antidepressant medication is instituted.

PD plus syndromes with dementia

The relatively rare syndromes of progressive supranuclear palsy (prevalence of one in 50,000 persons) and cortical basal ganglionic degeneration (prevalence of 1:100,000 persons) are both 'PD-plus syndromes', in which patients typically have cognitive abnormalities and abnormal voluntary movement but lack tremor [38]. Isolated cognitive abnormalities may be observed early in the disease. As mentioned previously, these syndromes can be looked at as representing a clinical spectrum of disease sharing common features of cognitive dysfunction and parkinsonism.

Fronto–temporal dementia syndromes

Fronto–temporal dementias (FTD) arise from degeneration of the frontal and temporal lobes without evidence of the classic pathology seen in AD (e.g., amyloid plaques and NFTs) [39]. Although the pathophysiology is not fully understood, FTD interestingly shows serotonergic deficits with relative sparing of acetylcholine function [40,201]. Patients with PD are often younger than those with AD (<65 years of age) and may progress faster with their disease. In FTD, personality change and inappropriate social conduct, with early loss of insight and blunted emotional responses, are prominent features [41,201]. Memory and visuospatial skills are often preserved [201,4,41,42].

Vascular dementia

Vascular dementia is considered the second major dementia classification. Its prevalence is second only to AD, accounting for 10–20% of cases. Patients may have comorbid conditions such as diabetes, hypertension and hyperlipidemia. Different criteria for diagnosis have been proposed [43,44]. With that said, most clinicians follow DSM-IV criteria for dementia. In addition, individuals should demonstrate some causal relationship between dementia and cerebrovascular disease such as a recent stroke (generally within 3 months). Vascular dementia can present as an abrupt deterioration in cognitive function or in a fluctuating, stepwise manner. These patients may have focal neurological findings such as hemiparesis, visual field deficits and hemisensory deficits. Suspected cases should have evidence on brain imaging suggesting one or more infarcts, and/or extensive periventricular ischemic white-matter disease. In contrast to AD, vascular dementia may be dominated by subcortical features, such as early gait disturbances with falls, early urinary difficulties, pseudobulbar palsy and other frontal subcortical deficits, such as abulia, mood changes and emotional lability [4].

Mixed dementia

AD and vascular dementia share many features and can be difficult to separate clinically. It is becoming increasingly recognized that a transitional state or 'mixed dementia' in which features of both disorders occurs. Support for this thesis includes studies demonstrating that stroke occurring in the setting of AD is more likely to result in clinical dementia [45]. Analysis of over 1000 autopsies showed that large artery atherosclerosis was associated with increased frequency of NPs [46]. In addition, cerebrovascular risk factors of diabetes, hypertension, coronary artery disease and current smoking have been shown to independently increase the risk of developing AD and vascular dementia, particularly as the number of risk factors increases. Diabetes and smoking appear to be particularly toxic [47]. Autopsy series show that approximately 25% [32,48] and 45% [49] of AD and vascular dementia patients have pathological findings of both entities. A systematic review found that mixed dementia responds similarly to AD when treated with cholinesterase inhibitors and memantine [50].

Potentially reversible syndromes

There are a variety of medical conditions that may result in cognitive changes similar to those observed in demented patients. Identification and early treatment may help improve these patients. While most clinicians feel that screening for common reversible conditions is reasonable for all patients, it is controversial as to the extent of laboratory evaluation needed.

In general, it appears that the frequency of potentially reversible dementia syndromes identified has decreased. The most frequent causes are medications, depression and metabolic diseases [51,52]. Most studies have reported a range somewhere between 0 and 20% of patients who are found to have a potentially reversible etiology. Of those, not all improve with therapy [53,201].

We suggest a basic laboratory screening evaluation (BOX 1) for all patients, limiting exhaustive evaluations to subjects with primary attentional dysfunction, frontal–temporal symptoms and subjects at high risk of other conditions (e.g., previous hospitalizations for depression or subjects with isolated amnesia). Extensive testing in clinically typical AD may not be beneficial to patients or families, expending time and energy needed for other purposes.

Depression (pseudodementia)

Depression is epidemic in the elderly, affecting at least one in four persons older than 65 years in the USA. It is well documented that depression can lead to memory loss, attention deficits, initiation problems and is commonly termed 'pseudodementia of depression' [54]. Depression can also cause wordfinding difficulty (anomia) that mimics early AD [55].

Some elderly persons are unaware of their mood state (alexithymia) and deny sadness, guilt or other symptoms of dysthymia. This reinforces the need for input from independent observer(s). The clinician who actively looks for signs of sadness or anxiety (e.g., crying during the examination) and pays attention to reported vegetative symptoms and signs (e.g., early-morning awakening, weight loss) may be able to detect nonreported depression.

Is depression in elderly persons separate from early AD? Older people with depression may be at increased risk for dementia [56]. Alternatively, depression may simply be a common early AD presentation. Decreased levels of serotonin that bring on depression may precede low acetylcholine levels associated with memory loss, although both systems function abnormally later. Reactive depression, with enough functional impact to require medication, is also common in early AD. Depression should be treated with therapeutic doses of an antidepressant. Practitioners should ensure that the dose is titrated to an adequate level for 4–8 weeks before deciding that a particular antidepressant is ineffective. Long periods of starting-dose treatment, with only partial symptom relief, should be avoided. If cognitive abnormalities progress after dysthymia is aggressively treated, a diagnosis of both conditions can be considered.

Medication induced

Elderly patients are often hypersensitive to medication side effects. As a result, each patient's medication list should be screened for inciting agents. Common offenders include analgesics (e.g., percocet and tramadol), sedatives and anxiolytics (e.g., benzodiazepines or sleep aids), antipsychotics, such as haloperidol, and anticholinergics, such as diphenhydramine, which can lead to sedation, confusion and agitation in some patients. Eliminating or reducing dosages of certain medications may improve patients' function. Since memory-disordered patients may not be able to adhere to a complex medication schedule, even with help, reducing medications may also improve medication safety and efficacy. In our practice, we closely examine each patient's medication list and attempt to minimize the total number of medications as well as the dosage if possible. This requires patience as we typically eliminate medications by gradually lowering dosages over time.

Metabolic derangements

Vitamin B12 deficiency

The classic dementia work-up includes a vitamin B12 assay. Serum folate should also be measured. An estimated 10–15% of individuals over 60 years of age may be deficient [57]. Hematologic abnormalities may not occur with vitamin B12 deficiency, even with nervous system involvement [58]. In deficient states, vitamin B12 supplementation should improve mentation and prevent the disability associated with progressive myelopathy and peripheral neuropathy. Like depression, vitamin B12 deficiency is more common in AD, although it is unclear why [59]. Physicians need to monitor mental status in patients with vitamin B12 deficiency whose clinical profile is otherwise consistent with AD. If cognitive abnormalities progress even after vitamin B12 levels normalize, a diagnosis of both conditions can be made.

Laboratory testing may show a megaloblastic anemia and low vitamin B12 levels (<200 pg/ml). Serum methylmalonic acid and homocysteine levels can be ordered to confirm vitamin B12 deficiency. If a deficiency is suspected, a variety of additional tests can be ordered to include Schilling's test, as well as measurements of intrinsic factor and parietal cell antibodies. These tests have less than perfect sensitivity and specificity and many clinicians argue that monthly intramuscular supplementation is safe and probably cheaper [4]. We traditionally insist on intramuscular supplementation as superior to oral treatment in our practice. However, a recent open-label study suggests that oral supplementation with doses of 2000 µg per day raises serum vitamin B12 levels and is equally effective in reversing neurological symptoms [60]. Periodic vitamin B12 monitoring may be helpful in either case.

Thyroid disorders

Chronic endocrinopathies, often with few physical findings, can result in cognitive dysfunction that mimics AD. Hypothyroidism is particularly common in elderly persons [61]. However, apathetic hyperthyroidism (i.e., paradoxical presentation of hyperthyroidism with fatigue, psychomotor slowing, depression and weight gain) can also occur. A thorough history, physical examination and testing for TSH and T4 levels are appropriate. Both thyroid function tests should be ordered: a normal TSH level may not exclude central hypothyroidism, which may not be as rare in elderly persons as previously thought [62].

Rarely, elderly persons with autoimmune hypothyroidism have Hashimoto's encephalopathy, with cognitive abnormalities (usually a delirium state but sometimes resembling a stroke) [205]. Patients are screened for Hashimoto's encephalopathy with thyroid autoantibody testing. Thyroid hormones are unlikely to be directly involved in this condition, which may respond to corticosteroid treatment.

Thiamine deficiency

Thiamine deficiency, which is typically associated with alcoholism, may result in a Wernicke–Korsakoff syndrome that may mimic AD. This encephalopathy is characterized by delirium, coinciding with eye-movement abnormalities and ataxia. Vestibular abnormalities, as well as other neurologic symptoms can occur. Elderly persons with poor nutrition may be at risk of developing such a syndrome – even if they do not abuse alcohol. In one series, formal assays showed that 20–40% of geriatric patients had moderate-to-severe thiamine deficiency [63].

Alcoholism itself can cause amnesia and can go undetected in an estimated 6–16% of elderly persons, particularly those who began heavy drinking in their 40s or 50s (late-onset alcoholic pattern). Patients may be reluctant to quantify their alcohol intake; therefore examiners may need to approach this subject tactfully and indirectly. A number of screening tools are available, or a social worker, nurse practitioner, psychiatrist or psychologist can assist in identifying signs suggestive of alcohol abuse. Elderly persons who abuse alcohol moderately or heavily are also at high risk for depression and suicide [64]. Interestingly, mild alcohol consumption may be protective and is discussed later.

Other metabolic abnormalities associated with dementia

Many elderly patients have little in the way of cognitive 'reserve'. As a result, relatively minor disturbances of electrolytes, such as potassium, sodium, calcium and glucose, can result in cognitive changes in susceptible individuals. These patients, in contrast to those with typical AD, usually have prominent attentional impairment (i.e., delirium). Basic electrolyte screening can identify these individuals and facilitate appropriate intervention.

Anemia is also common in elderly patients, and may be secondary to chronic medical conditions (e.g., renal insufficiency), medications, nutrition or blood loss. Screening with CBC is simple and can guide further evaluation and treatment.

Folate deficiency is most commonly owing to dietary causes in the elderly. A change in higher cortical functions is a common presentation and may mimic dementia, depression or psychosis.

Low serum folate levels suggest a deficient state and supplementation may be indicated [4]; vitamin B12 levels should also be assessed.

Researchers have suggested that hyperhomocysteinemia may be associated with higher risk of dementia [65]. However, since hyperhomocysteinemia may be caused by vitamin B12 deficiency, elevated homocysteine levels may simply provide further evidence of that association [66]. Before assuming that a person with dementia has idiopathic hyperhomocysteinemia, we screen for vitamin B12 deficiency and consider intramuscular supplementation, as described above.

Sequelae of other chronic diseases, such as uremia associated with renal failure, hepatic failure, chronic obstructive pulmonary disorder and severe congestive heart failure, can all manifest with cognitive dysfunction mimicking dementia [4].

Primary gastrointestinal conditions

Several gastrointestinal (GI) disorders, such as Whipple's disease, vitamin E deficiency and niacin deficiency (pellagra), may cause cognitive changes that could be confused with dementia. In general, these conditions cause difficulties with attention and executive functioning, with relative sparing of cognitive functions, such as identifying right–left orientation, limb praxis, naming and visuospatial function. However, in early stages of CNS involvement, primary GI disorders may cause amnesia [206].

The classic presentation of Whipple's disease with CNS involvement resembles progressive supranuclear palsy [38]. It features a frontal lobe subcortical dementia, disordered eye movement and gait and slowed limb movements. A rhythmic movement of the eyes, face and even shoulders and arms (oculomasticatory myorhythmia) may also occur [67]. Patients are usually anemic and may not have prominent GI complaints. Jejunal biopsy may reveal macrophages with periodic acid-Schiff-positive material.

Pellagra is caused by a deficiency in levels of niacin. Patients can present with confusion, depressed mood and impaired cognition. In addition, patients may develop neurological signs of a myelopathy affecting the posterior and lateral columns. Further examination may reveal a scaly dermatitis and diarrhea. Diagnosis is evaluated with serum levels and confirmed with decreased excretion of urinary *N*-methyl-nicotinamide [4].

Vitamin E deficiency can result in a variety of neurological signs and symptoms. Deficiency states can result from long-standing malabsorption and steatorrhea. Vitamin E (α-tocopherol) levels are easily measured. Supplementations with large oral doses (800–3600 IU/day) or semi-weekly injections have been used. Reversal of neurological symptoms with supplementation is variable [4].

Structural brain lesions

The most important reason for brain imaging in dementia evaluations is to detect structural lesions (e.g., tumors, arteriovenous malformations or hemorrhage) warranting intervention. Space-occupying lesions, particularly involving the parietal lobes, may cause clinical symptoms resembling AD. Although other abnormalities (i.e., sensory, behavioral and/or visuospatial deficits) usually occur, patients may be unaware of their deficits (anosognosia) and such findings could be missed on cursory examination.

Structural lesions may respond to neurosurgical intervention and include tumors, subdural hematomas or normal pressure hydrocephalus (NPH). Tumors involving the frontal, temporal or parietal lobes may respond to neurosurgical or radiation therapies. Subdural hematomas may lead to cognitive dysfunction mimicking dementia in some individuals. Surgery may or may not improve cognition; however, it should prevent further progression. The syndrome of NPH is characterized by ataxia, urinary incontinence and dementia. Imaging studies show ventricular enlargement out of proportion to age-related atrophy and neurosurgical evaluation may be helpful. These lesions may be treated with shunting procedures [4,68]. However, this disorder could be misdiagnosed in clinical syndromes that are more consistent with vascular dementia or parkinsonism. Careful consideration of whether treatment for stroke or parkinsonism may be more appropriate than invasive shunting is suggested.

Cancer

Amnesia, changes in mood or personality, delirium and/or seizures could be remote manifestations of an occult malignancy. In particular, attentional deficits can occur with paraneoplastic limbic encephalitis, a rare remote effect of cancer usually associated with nonsmall-cell lung cancer but also with thymoma, Hodgkin's disease and cancers of the breast, colon, bladder and testicle [16]. Most patients with limbic encephalitis are not known to have cancer until their mental status changes. Anti-Hu or anti-Ta (also called anti-Ma2) antibodies may be detectable in serum and cerebrospinal fluid, although no antibodies may be found. Most commonly, limbic encephalitis occurs rapidly over days to weeks and may be accompanied by other neurologic symptoms (e.g., ataxia, visual changes and/or neuropathy). In one series, treatment of the primary tumor was associated with neurologic improvement in up to 64% of patients [69].

Neurosyphilis

The prevalence of neurosyphilis has decreased substantially since the 1980s. However, treponemal infection remains a risk, particularly in immunocompromised patients (e.g., patients with HIV infection or AIDS) and patients who have direct or indirect exposure to sexually transmitted diseases. Some experts no longer recommend routine relative peak ratio (RPR) or Venereal Disease Research Laboratory (VDRL) Test screening for patients with classic symptoms of AD, as the number of false-positive results (secondary to the patient's age or cross-reactivity owing to comorbid conditions) may outnumber true positive results.

We are concerned about this recommendation. In our opinion, too few physicians consider risk factors associated with syphilitic infection in elderly patients (e.g., HIV risk factors

and individuals or spouses of individuals that may have sexual contact with high-risk people, such as prostitutes). Second, RPR or VDRL test that produces a false-positive result can be easily evaluated with a sensitive fluorescent treponemal antibody absorption (FTA-ABS) test. Third, detection of another disorder that can cause a positive RPR test result (e.g., Lyme disease or lupus) is not trivial. Finally, further complications of tertiary syphilis can be prevented with a relatively benign antibiotic treatment. We recommend routinely considering RPR or VDRL testing in dementia screening and urge clinicians to test for it in the evaluation of any person with relevant social history, frontal–temporal symptoms (especially disinhibition), pupillary abnormalities (e.g., anisocoria, Argyll Robertson pupil, or tonic pupils), other clinical signs (e.g., loss of deep-pain sensation) or any HIV risk factors.

Unfortunately, upward of 57% of patients with neurosyphilis may be nonreactive to VDRL testing. Although many laboratories resist performing FTA-ABS testing without prior VDRL screen, physicians may consider testing FTA-ABS alone if neurosyphilis (i.e., disinhibited frontotemporal dementia) or tabes dorsalis is strongly suspected [3].

Neuroprotection

Currently, there is no US FDA-approved therapy to delay onset or progression of dementia. Theories suggesting causal relationships between free-radical oxidative stress, inflammation, vascular risk factors and hormonal factors have been postulated. A number of other agents have been examined for treatment of dementia but have not been sufficiently proven to recommend routine use. See BOX 3 for agents with neuroprotective characteristics.

Box 3. Agents with possible neuroprotective characteristics.

- Vitamins and dietary supplements
  - Vitamin E
  - Vitamin B6
  - Folate
  - *Ginkgo biloba*
  - Curcumin spice
  - Docosahexaenoic acid
- Hormones
  - Testosterone
  - Estrogen
- Medications
  - Selegiline
  - Nonsteroidal anti-inflammatory drugs
  - Lipid-lowering agents (i.e., statins and fibrates)
- Alcohol
- Vaccines (experimental)

Vitamin E

Vitamin E supplementation, used in doses up to 2000 IU/day, was thought to slow progression to nursing home (NH)-placement or development of severe AD. The 2001 AAN practice parameter suggests that vitamin E may delay clinical worsening; however, objective evidence is not robust [70]. No difference was seen when vitamin E was compared to selegiline alone or in combination [71]. Given the lack of convincing evidence that vitamin E prevents AD, it is not recommended for routine use [207]. With that said, we have been reluctant to abandon vitamin E supplementation altogether. When patients wish to take vitamin E, we recommend much lower doses (200–400 IU/day).

Selegiline

Selegiline has been shown to delay progression to severe AD or NH-placement in some studies but not in others [4]. No significant change in cognitive function has been proven with selegiline treatment of AD patients [72]. It is therefore not recommended at this time.

Vitamin B6

Vitamin B6 may be important in regulation of mood and cognitive function (e.g., depression, seizures and migraines). Vitamin B6 is a cofactor for the remethylation of homocysteine, which itself is considered a risk factor for cerebrovascular disease. A 2003 meta-analysis found no randomized controlled trials of vitamin B6 supplementation in patients with MCI or dementia to support its routine use. In healthy older men and women, vitamin B6 did lower homocysteine levels; however, it had no significant impact on measurements of mood and cognition [73].

Folate supplementation

Folate deficiency has been associated with increased levels of homocysteine. If folate is adminstered to people with undiagnosed vitamin B12 deficiency, it will correct the anemia but may delay diagnosis of the vitamin B12 deficiency, which is neurotoxic. No benefit of folate supplementation (750 mg/day) alone in older healthy females, or the combination of 2 mg folate/1 mg vitamin B12 in mild-to-moderate AD showed significant difference in cognition [74].

Nonsteroidal anti-inflammatory drugs

Studies of patients with arthritis, on chronic nonsteroidal anti-inflammatory drug therapy, demonstrated a lower incidence of dementia, suggesting that inhibiting inflammatory pathways may be beneficial [75]. Results since then have been mixed and these medications are not currently recommended for neuroprotection.

Hormone-replacement therapies

Estrogen

Retrospective epidemiological studies suggested that postmenopausal women taking hormone-replacement therapy (HRT) had lower incidence rates of AD [76–79,207]. To study this further, the prospective Women's Health Initiative

Memory Study (WHIMS) was initiated to examine the effects of HRT on the incidence of dementia. Unfortunately, these data have not shown that HRT delays AD. In fact, HRT may actually increase the risk [80–83]. As a result, HRT is not generally remmended for the prevention or treatment of AD [84].

Testosterone

Androgen deficiency results in reduced synaptic density in hippocampi of rodents and nonhuman primates, causes neurotransmitter changes in the prefrontal cortex of rodents and increases plasma amyloid-β levels in humans [85]. Lower testosterone levels in combination with higher estradiol levels are associated with poor performance on tests of cognition [86]. Testosterone supplementation has been reported to improve spatial, working and verbal memory in older men [87]. Other studies have disputed the significance of the correlation between testosterone level, cognition and AD [88]. Further studies are needed before testing serum testosterone levels and supplementation can be routinely recommended.

Antihypertensives

Vascular risk-factor modification should be considered. Hypertension is a known risk factor for stroke and epidemiological studies have consistently suggested a link between cardiovascular risk factors and subsequent dementia [46]. Several observational studies have reported reduced risk of AD with the use of antihypertensives [89]. Common sense would dictate that any modifiable risk factor should be addressed; however, efficacy is uncertain. Meta-analysis of three large trials (> 12,000 patients) was unable to prove that blood pressure reduction prevents the development of dementia [90]. In our practice, we routinely monitor blood pressure and work closely with our patients' primary care physicians to maximize vascular risk-factor management.

Lipid-lowering agents

Large vessel cerebral atherosclerosis probably contributes to the development of AD, as it is associated with an increase in NPs, one of the main pathological manifestations of AD [46]. Studies have shown an association between elevated serum cholesterol levels and development of dementia [91,92]. Furthermore, cholesterol may be a key factor in the synthesis of the amyloid-β protein that accumulates in AD brains [91,93]. Animal data suggest that simvastatin reduces amyloid-β 40 and amyloid-β 42 brain levels [91,94].

With that said, the role of lipid-lowering agents (LLAs) in humans is unclear. For example, a cross-sectional study of 57,000 patients suggested that patients taking statins had upwards of 73% lower incidence of developing AD [95]. Similarly, a French study of 9294 subjects suggested that LLA use is associated with a reduced risk of dementia but only in subjects who had normal lipid levels. No difference was seen between statin versus fibrate use [91]. By contrast, pravastatin use in elderly patients, at high risk for cardiovascular or cerebrovascular disease, did not show significant impact on cognition [91,96]. In summary, there is no consensus recommendation supporting the use of LLAs for the prevention or treatment of dementia.

Ginkgo biloba

Ginkgo biloba has been used in traditional Chinese medicine for over 5000 years [97]. EGb 761 (tanakan), a standard Ginkgo extract, appears safe and may have antioxidative and antiapoptotic effects [97]. EGb 761 may confer protection against amyloid-β peptide-induced toxicity and rescue hippocampal neurons [98,99]. A 1998 meta-analysis of 50 clinical studies reported that treatment with EGb 761, at doses of 20–240 mg/day for 3–6 months, had a small but significant effect [100] that was comparable to donepezil [101]. Two Phase III clinical trials are ongoing in the USA and France. We believe that further research is needed before Ginkgo can be recommended [102].

Curcumin

Curcumin, a yellow curry spice, is known to have anti-inflammatory and antioxidant effects [97]. Its use may be a factor in the 4.4-fold lower prevalence of AD in the Asian–Indian population [103]. Addition of curcumin to the diet of transgenic APPsw mice resulted in reduced inflammation, suppression of oxidative damage, reduced levels of interleukin-1b (a proinflammatory cytokine) and a 43–50% reduction in amyloid plaque burden [97,104]. Clinical studies are ongoing in the USA and China.

Alcohol

In population case–control comparisons, self-reported light-to-moderate wine consumption was associated with a reduced risk of coronary artery disease [105] and AD [106,107]. Among men older than 65 years, self-reported current light-to-moderate (<7 drinks/week) alcohol consumption was associated with better cognitive performance [108]. However, the results of this study are difficult to interpret as current drinkers were compared with a small number of teetotalers (4% of the study group) and 'former drinkers' who were screened for alcoholism using only self-reported information. Among women, moderate alcohol consumption (up to 1 drink/day) may not impair cognitive function and may actually decrease one's risk of cognitive decline independent of the type of alcohol (e.g., beer, wine, liquor) [109]. Resveratrol, a polyphenol compound found in grapes and red wine, is thought to be the agent that exerts a wide range of anti-inflammatory, antioxidant, anticarcinogenic and antimutagenic effects attributed to regular wine intake [97]. Owing to the high incidence of alcoholism in the USA, the neurotoxic effects of excess drinking on the brain [110] and the likelihood that alcohol abuse may go undetected in the elderly, we do not encourage alcohol consumption in our patients. We screen regular drinkers for alcohol abuse even if wine is the only alcoholic beverage consumed.

Box 4. Examples of pharmacological agents used in patients with dementia.

- Acetylcholinesterase inhibitors
  - Tacrine
  - Donepezil
  - Rivastigmine
  - Galantamine
- Memantine
- Selective serotonin reuptake inhibitors
  - Fluoxetine
  - Sertraline
  - Citalopram
  - Paroxetine
- Antipsychotics
  - Haloperidol
  - Risperidol
  - Quetiapine
- Anticonvulsants
  - Valproate
  - Carbamazepine
  - Lamotrogine

Docosahexaenoic acid

Epidemiological research has suggested a relationship between higher serum docosahexaenoic acid (DHA) levels and reduced risk of AD. DHA can be obtained by consumption of fish and/or fish oil [111]. Dementia has been linked with low serum DHA levels [112] and decreased fish intake [111,113]. A prospective study of 899 subjects showed that a diet incorporating an average of three servings of fish per week and DHA intake of 0.18 g/day had a significant 47% reduction in the risk of developing all-cause dementia [111].

Vaccination

The pathological hallmark of AD is the finding of NFTs and NPs. Immunization of transgenic mice with synthetic amyloid-β 1–42 reduced amyloid accumulation in young mice. In older mice, additional deposition was blocked and there was some evidence of clearance [114]. Phase I and II studies of active immunization in humans showed promise but were stopped for safety reasons after several cases of meningoencephalitis [115,116].

Therapies

The majority of patients with dementia have underlying neurodegenerative disease processes that are not curable. Therefore, the goal of therapy is to improve function. Degenerating brains are known to be deficient in a variety of neurotransmitters, in particular, acetylcholine. Agents developed to inhibit acetylcholinesterase activity are thought to increase acetylcholine levels at degenerating synapses and have been shown to effective in favorably improving some aspects of cognition and behavior [117].

Pharmacological approaches

BOX 4 lists examples of pharmacological agents used in patients with dementia.

Acetylcholinesterases

Tacrine

Tacrine was the first acetylcholinesterase inhibitor to be approved in 1993. Its inconvenient dosing schedule and concerns about hepatotoxicity have seen this agent replaced by newer agents. Meta-analysis suggests a lack of convincing evidence proving efficacy of tacrine for symptoms of AD [118].

Donepezil

Donepezil is a selective acetylcholinesterase inhibitor, which was approved in 1997. It is dosed once daily and does not require regular laboratory monitoring. Donepezil may be better tolerated than rivastigmine or galantamine but no clinical difference was shown when compared to rivastigmine at 12 weeks or galantamine at 52 weeks [117].

Rivastigmine

Rivastigmine is an acetyl butyrylcholinesterase inhibitor approved in 2000. It is administered once or twice daily and laboratory monitoring is not needed. Its efficacy is similar to donepezil and galantamine [4,117].

Galantamine

Galantamine, approved in 2001, is dosed twice daily, does not require laboratory monitoring and has activity at nicotinic receptors, as well as acetylcholinesterase activity. Meta-analysis of ten trials, comprising 6805 subjects, concluded that galantamine treatment (in doses >8 mg/day) resulted in a significantly greater proportion of subjects with improved or unchanged global rating scale than placebo in mild-to-moderately impaired AD. Galantamine is not recommended in MCI [119].

Memantine

Memantine was approved for AD therapy in 2003. A low affinity *N*-methyl-D-aspartate receptor blocker, memantine may prevent excitatory amino acid neurotoxicity, without interfering with the physiological actions of glutamate necessary for memory and

Box 5. Nonpharmacological interventions used in patients with dementia.

- Exercise
  - Aerobic
  - Strength training
- Cognitive training
- Aromatherapy
- Music therapy
- Massage

Box 6. Patient and family education topics.

- Diagnosis
  - Subtype
  - How diagnosis was made
- Treatment plans
  - Medications
  - Exercise
  - Nonpharmacological interventions
- Prognosis
  - Natural history of disorder
  - Clinical expectations of progression
- Safety considerations
  - Fall precautions
  - Driving restrictions
  - Medication compliance
  - Other potentially dangerous activities – firearms, power tools, heights
  - Wandering
- Living arrangements
  - Recommendations on appropriate type of living environment
  - Financial management
  - Supervision
  - Home modifications to facilitate safety and ADLs
- Legal considerations
  - Power of attorney
  - Living wills or advanced directives
- Support options
  - Respite care options
  - Coordination with social work
  - Local support groups
  - Alzheimer's Association contact information

learning [120]. The manufacturer recommends twice-daily dosing, and it does not require regular laboratory monitoring. Several trials have shown that memantine is safe and results in modest improvements in cognition and behavior in patients with moderate-to-severe AD [121,122]. Earlier studies suggested that memantine was beneficial for patients with vascular dementia [208]; but, a recent meta-analysis of available research could not find a clinically detectable difference at 6 months for mild-to-moderate vascular dementia. Its efficacy in mild-to-moderate AD is unclear [123].

Combining memantine with cholinesterase inhibitors appears to have a synergistic effect on cognition, ADLs and behavior in moderate-to-severe AD [124,208]. Theoretically, memantine may have neuroprotective and indirect dopaminergic activity and may thus be helpful for vascular and atypical dementia syndromes (PDD); however, controlled trials for these indications are still underway.

Antipsychotics

As dementia progresses, disability expands from memory difficulties to inability to perform ADLs, loss of bowel/bladder continence and behavioral symptoms ranging from agitation to aggression and psychosis [125]. Behavioral issues place a large burden on families and may influence decisions to institutionalize patients [126]. Low-dose atypical antipsychotics, such as risperidone, olanzapine or quetiapine, may be helpful for severe agitation, hallucinations, delusions and bizarre behaviors. Antipsychotics are considered by some to be more effective than other classes of medications [127]; however, this is debatable [209]. Meta-analysis did not show a clear benefit favoring first-generation antipsychotics (FGAs) in patients with dementia [128]. Atypical or second-generation antipsychotics (SGAs) have shown modest efficacy [126,128,129,209], but are associated with increased mortality risk [130]. Results from the Clinical Trials of Intervention Effectiveness (CATIE) trial and Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) 1 studies suggest that there is little difference in effectiveness between FGAs and SGAs to justify the expense of SGA [131,132]. In our practice, we attempt to avoid antipsychotics if possible owing to the increased risk of mortality and side effects. With that said, in the appropriate clinical situation, and after discussing the risks and benefits with the family, we believe there is still a time and place for these medications in treating acute psychosis and aggressive behaviors. We start these agents at the lowest dose and treat for the shortest time possible.

Selective serotonin-reuptake inhibitors

Selective serotonin-reuptake inhibitor (SSRI) antidepressants are often administered to control neuropsychiatric symptoms. While considered beneficial for managing depression, a 2005 systematic review of five randomized controlled trials did not show clear evidence to support the efficacy of SSRIs in managing neuropsychiatric symptoms in AD patients [128]. Likewise, the use of anticonvulsants, such as carbamazepine or valproate has not proven particularly effective in treating neuropsychiatric symptoms [128].

Nonpharmacological considerations

Nonpharmacological considerations for patients with dementia syndromes are listed in BOX 5.

Exercise

Exercise is an underutilized intervention in managing dementia patients [133]. Regular aerobic exercise (30 mins/day), when combined with strength training, has been shown to improve behavior, functioning and reduce depression in AD [133,134]. Exercise has been shown to improve cognitive function in the healthy elderly as well as patients with cognitive dysfunction [133–135].

Cognitive training

Another nonpharmacological intervention that is receiving attention these days is cognitive training. Can such an intervention lead to improved outcomes? The answer may be yes but results have been specific to the type of cognitive task trained and studied in relatively high functioning individuals [133]. With modest amounts of practice, older adults can improve their ability to switch tasks equal to the performance of younger adults [136]. Recent data from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) study suggest that cognitive training, concentrating on memory reasoning, or speed of processing results in long-lasting (at least 5 years in this study), self-reported improvements in cognitive ability and individual ADLs [133,137].

Environmental changes

Anxiety and agitation can often be managed with behavioral techniques that attempt to reduce the level of impersonal, task focused and intrusive care methods. In addition, aromatherapy, pet therapy and music therapy have also shown some efficacy [209]. All of these techniques have stressed the importance of maintaining a stable and safe living environment, with nonthreatening, hands-on personalized care.

Caring for family members with dementia can be stressful on families. In our practice, we routinely discuss options for families beyond placement in a nursing facility (BOX 6). Common topics include respite care, support groups and education about the illness. We encourage close coordination between our patients, their families and social workers.

Conclusion

We have presented an overview of the most common dementia diagnoses, to include neurodegenerative, vascular and potentially reversible variants. AD is the most common subtype, followed by vascular dementia. Evaluation requires a thorough history to identify the type of cognitive dysfunction present, the estimated time of onset and rate of progression. Cognitive evaluation using measures, such as the MMSE and bedside screening, for focal cognitive dysfunction are useful. Meeting with a dementia specialist or attending a neuropsychological consultation may be helpful. All patients should have a complete physical and neurological examination as well as brain CT/MRI. Laboratory evaluation should exclude vitamin B12 deficiency and hypothyroidism at a minimum. Further testing should be tailored to the individual patient.

Treatment is supportive and includes counseling of patients and families. We recommend providing written information and additional opportunities for family follow-up. Treatment with an acetylcholinesterase inhibitor with or without memantine is recommended. SSRIs are indicated, at therapeutic doses, to treat symptoms of depression. Environmental modification with or without the use of low-dose atypical antipsychotics can be helpful for behavioral issues. Other important interventions include attempts to ensure adequate nutrition, addressing safety concerns (e.g., fall precautions), exercise and end of life planning.

Expert commentary

We feel that it is likely that cholinesterase inhibitors have reached their maximum utilization by geriatricians and general care practitioners. This is unfortunate as a very large proportion of people with AD are still not receiving them. Further impact on the overall incidence and prevalence of dementia is likely to require a new class of agents, especially an agent that might be administered to the healthy aged at risk or to patients with MCI. However, we think that a small but significant impact on the incidence of dementia may be made by increasing attention to physical activity, nutritional status and appropriate treatment of depression in the elderly. We also think that an expanding range of behavioral care options for AD (e.g., increasing numbers of day programs tailored to different deficits, premorbid group affiliations and social interests) will become available over the next 5–10 years, augmenting the caregiver's role, increasing public awareness of AD-related problems and improving the likelihood that people with dementia may be able to function in the home setting for longer periods.

Key issues

- Dementia is characterized by memory loss that occurs in combination with impairment of other cognitive functions (e.g., behavior, personality changes, social functioning and/or the inability to perform activities of daily living).
- Alzheimer's disease is the most common type of dementia syndrome. Dementia secondary to cerebrovascular disease (i.e., vascular dementia) is the second most common type.
- Evaluation and diagnosis requires a thorough history, physical and neurological examination. Brain imaging (i.e., computed tomography or magnetic resonance imaging) as well as a basic laboratory screen for thyroid disease, vitamin B12 deficiency and infectious etiologies (e.g., syphilis and/or HIV in appropriate cases) is recommended.
- Referral to a neurologist specializing in cognitive/behavioral disorders should be considered, particularly in atypical cases.
- Patient and family education and planning are essential components of disease management.
- Pharmacological treatment involves the use of anticholinesterase medications, and glutamate antagonists, in combination with lifestyle modification. Concomitant illnesses, such as hypothyroidism, vitamin deficiencies and depression, should be treated appropriately at therapeutic dosing.

Five-year view

It is likely that within 5 years we will have a great deal more information about general health conditions and systemic illnesses conferring increased and decreased risks of developing dementia. It will be interesting to learn whether acute or chronic infections (e.g., gingivitis) will be associated with an increased risk of AD. More sophisticated neuroimaging studies, such as functional 2-(^{18}F)-fluro-2-deoxy-D-glucose PET or utilization of novel markers for amyloid and NFTs, may allow earlier and more precise diagnosis and prognosis, as well as serve as useful biomarkers in the study of future interventions. We are likely to have a large amount of additional information regarding appropriate early management of cognitive symptoms in PD and cognitive evaluation is likely to be performed routinely in moderate PD in 5 years, which is not current practice. As our population and thus our cultural icons age, it is likely that a famous person will be affected by stroke-related aphasia, spatial disorder or vascular dementia, and increased funding and attention to vascular cognitive impairment by the USA medical culture may follow.

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