

USVH Disease of the Week #3: Dementia in Older Adults and Veterans

“Differential Diagnosis of Dementing Diseases”

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Introduction

Dementia in the adult population is a major and growing medical and social problem. It occurs at all ages but increases with advancing age, so that the largest group of demented patients is in the older age groups. Dementia has its highest rate in the population over age 75, the age group that is increasing at a higher rate than any other. Recent scientific advances give promise of major increases in knowledge and skills that will result in better diagnostic tests and better methods of treatment.

Dementia, because it interferes with the dignity and independence of the person, causes widespread suffering, not only for the person affected but also for families, friends, and caretakers. The expense of long-term care, either at home or in a nursing facility, can be overwhelming: It has been estimated at \$40 billion a year for people age 65 and older.

Proper identification of the disease state responsible for dementia in the individual patient is critical to management. Some diseases that produce dementia can be arrested or reversed (e.g., benign mass lesions of the brain, intoxication, infections, and metabolic and nutritional disorders). Some dementing diseases are infectious, and the tissues and bodily fluids require special handling to prevent transmission. Some dementing diseases are inherited, and this has important social and ethical consequences. The value of therapeutic trials for dementia that are now in progress, and of the epidemiologic studies of prevalence and incidence under way in delineated populations, is limited by the criteria and accuracy of diagnosis.

It is important to distinguish the early stages of dementia, the clinical behavioral state, from the nonprogressive cognitive changes known to occur in otherwise normal aging. This is not always possible. Serial examination of the patient over a period of time is still the best way to do this. Neuropsychological tests have been developed, and efforts continue to refine them so that dementia can be identified and distinguished from other mental states that may be confused with it. It is important to identify the specific pathological state that produces dementia in the individual patient. The usual clinical methods for doing this are sufficient for certain conditions. Brain-imaging methods and biochemical and genetic markers have advanced a long way and show a stunning promise for the future.

At the present time, diagnoses of many of the important dementing diseases can be confirmed or denied with certainty only at autopsy. Pathological diagnosis is the standard of accuracy of clinical diagnosis. Very few of the dementing diseases can be studied in an animal model. Pathological studies, while monitoring clinical diagnosis, are providing new knowledge that can

be expected to lead to effective antemortem diagnosis of dementing diseases that are now indistinguishable while the patient is alive.

In an effort to assess the current state of knowledge about the differential diagnosis of the dementias, the National Institute on Aging, the National Institute of Neurological and Communicative Disorders and Stroke, and the National Institute of Mental Health in conjunction with the NIH Office of Medical Applications of Research convened this conference. Following 10 days of presentations by experts in the relevant fields and presentations by public organizations involved with the dementias, a consensus panel consisting of representatives from neurology, psychiatry, geriatric medicine, epidemiology, psychology, family practice, neuropathology, nursing, and the public considered the evidence and formulated a consensus statement responding to these questions:

1. What is dementia?
2. What are the dementing diseases, and which of them can be readily arrested or reversed?
3. What should be included in the initial evaluation of dementia?
4. What diagnostic tests should be performed, and when are these tests indicated?
5. What are the priorities for future research on diagnosing the dementias?

What Is Dementia?

Dementia is a clinical state with many different causes, characterized by a decline from a previously attained intellectual level. It is more or less sustained in time, arbitrarily measurable in months or years rather than in days or weeks. Although long lasting, some varieties of dementia may be arrested or reversed. The term "dementia" is not applied to isolated focal loss of function such as occurs in amnesia, aphasia, agnosia, or apraxia. The decline usually involves memory, other cognitive capacities, and adaptive behavior. There is usually no major alteration of consciousness. The patient may or may not be aware of the dementia. In almost all cases, there is significant deterioration of memory and of one or more other intellectual functions such as language, spatial or temporal orientation, judgment, and abstract thought. Some criteria for dementia require defects in one or more components of intellectual function other than memory; some require that the defect be global, that is, involve all components of intellectual function.

Dementia is a consequence of dysfunction of the brain, particularly of those parts of the cerebrum known collectively as the association areas, which integrate perception, thought, and purposeful action so that the person can adjust to and survive in the environment.

The onset of dementia is usually but not always insidious. The patient or family observes minor forgetfulness, restlessness or apathy, an increasing tendency to misplace things, small inconsistencies in some of the ordinary tasks of daily living, and repetitiousness of word or action. If the dementing process worsens, more disorganization of cognitive function takes place. Patients may fail at work, become lost in their own neighborhoods, fail to recognize people familiar to them, or reverse their sleep cycles. There may be hallucinations, delusions, or overt paranoid behavior. Some patients retain the shadows of their personalities even into severe dementia; others behave inappropriately and even antisocially. Depending on the pathological

state that causes dementia, there may or may not be indications of brain disease beyond the cognitive and behavioral change. In some demented patients, changes in motor, sensory, and visual systems appear; concomitant disorders of extrapyramidal function are especially common.

Dementia is a very variable state. A patient may or may not be aware of his dementia. It may be progressive, as in the degenerative diseases, or static, as in a postbrain injury state. Even when progressive, the duration of decline may be slow or rapid, ranging from a few months to many years. The manifestations vary from disease to disease and from patient to patient within a given disease. There may be more than one underlying cause in the same patient. Patients may or may not have evidence of neuronal dysfunction other than that producing the dementia.

Dementia is distinguished from mental retardation, but a person who is mentally retarded can become demented when he declines from a previously attained level, as happens so often in Down's syndrome. Dementia is not psychosis: a patient with dementia may or may not be psychotic; a patient with psychosis may or may not be demented.

Many different disease states are capable of producing dementia. In this sense, we refer to dementing diseases. These diseases are divisible into two groups. In one group, the process inevitably produces dementia if it progresses through its full course; these are the conditions thought to affect the brain primarily or exclusively, such as Alzheimer's disease, Huntington's disease, and Parkinson-dementia complex. Other diseases may or may not produce dementia, depending upon whether or how the brain is affected. Examples are liver disease with portacaval encephalopathy, metabolic disorders such as hypothyroidism, or infectious disorders such as syphilis or acquired immune deficiency syndrome.

What Are the Dementing Diseases, and Which of These Can Be Readily Arrested or Reversed?

Dementia, a clinical syndrome, can be produced by numerous pathological states that affect the brain. These pathological states can be divided into those that appear, on the basis of our present knowledge, to be primary in the brain, such as Alzheimer's disease or Pick's disease, and those which are outside the brain and affect it secondarily, such as the encephalitides or exogenous intoxications. A clinically useful division of dementia-producing pathological states is made into those that are progressive or fixed, such as Alzheimer's disease and hypoxic-ischemic encephalopathy of cardiac arrest, and those that are arrestable or reversible, such as chronic subdural hematoma or myxedema.

Some pathological states, if allowed to run their course, result inevitably in dementia; others may never go on to dementia or may produce only fragments of the dementia syndrome. Frequently, more than one pathological cause is operating to produce the dementia in an individual patient. The commonest example of this is the person with a progressive degenerative dementia who is taking an excess of a psychoactive medication that is having a potentiating effect upon the primary process.

The investigation of the patient is determined by these nosological considerations. The physician initially seeks out those causes of dementia that can be arrested or reversed. They may be found

in all the classical categories of disease: intoxicant, infectious, metabolic, nutritional, vascular, neoplastic, genetic, and traumatic.

Arrestable or Reversible Causes of Dementia

Intoxications

Intoxications may result from medication or from nonmedication chemicals deliberately or accidentally ingested. Medications capable of producing dementia include the increasingly large number of neuroactive and psychoactive agents, the opiate analgesics, and the adrenocortical steroids. These are the obvious ones; however, even less obvious, frequently used medications may cause or aggravate dementia: anticholinergic preparations such as are used in movement disorders, allergic reactions, or gastrointestinal disorders; drugs used for cardiovascular purposes, such as antihypertensives; and even digitalis and its derivatives. Finally, multiple drugs in combination may have more than an additive effect.

Virtually all of the chemicals used in substance abuse from heroin to glue are capable of producing dementia. Other exogenous chemicals include carbon monoxide, carbon disulfide, lead, mercury, and manganese.

Any of these intoxicants, of whatever sort, may have lethal or irreversible consequences, but they are high on the list of the common causes of arrestable or reversible diseases that affect the central nervous system.

Infections

Any infection capable of involving the brain is capable of producing a dementing illness. Many cases of dementia are prevented from happening in the first place by the effective treatment of leptomeningitis and encephalitis, whether caused by bacteria, fungi, protozoa, or viruses. Chronic infectious processes, such as can be caused by bacteria (Whipple's disease), protozoa (syphilis), or fungi (cryptococcus), affect the brain in such a way that the process is reversible and arrestable, at least to a degree. Certain chronic viral illnesses, such as human immunodeficiency virus, are known to produce dementia with great frequency, but it is not known whether the agents that retard the process of AIDS will arrest or reverse the changes in the nervous system that lead to dementia. The agents responsible for conditions like Creutzfeldt-Jakob disease and progressive multifocal leukoencephalopathy are so far resistant to any kind of treatment.

Postinfectious encephalomyelitis, such as follows the viral exanthems, infrequently may produce enough damage to leave the patient demented.

Metabolic Disorders

Chronic diseases, tumorous or nontumorous, of thyroid, parathyroid, adrenals, and pituitary are subject to easy identification and generally are reversible. Pulmonary disease produces a dementia consequent upon hypoxia or hypercarbia. The encephalopathies of renal failure and

hepatic failure respond up to a point to measures directed at underlying causes. The diabetic becomes vulnerable to a multitude of metabolic mechanisms related to the disease or to the treatment. It must be remembered that dehydration is the commonest metabolic abnormality of the older person with or without dementia.

A number of hereditary metabolic diseases often associated with dementia make their appearance for the first time in adult life. Examples are Wilson's disease (hepatolenticular degeneration), metachromatic leukodystrophy, the adrenoleukodystrophies, and the neuronal storage diseases.

Nutritional Disorders

Thiamine deficiency produces Wernicke-Korsakoff's encephalopathy, out of which may emerge Korsakoff's dementia. The dementia of Korsakoff's, once established, may undergo a degree of remission, but the pathological changes are irreversible. Thiamine deficiency is a preventable nutritional deficiency seen in the context of alcoholism, pernicious vomiting of pregnancy, depression, or any other condition in which this deficiency occurs. There are different mechanisms by which pernicious anemia can produce dementia; not all of them are reversible. Folate deficiency is potentially reversible if recognized early. Pellagra, uncommon in developed countries but still a major problem in some parts of the world, shows a dramatic response to niacin even when the mental changes have been present for a long time.

Vascular

Management of the underlying states can arrest and sometimes reverse the dementias of cardiovascular origin. Hypertension, especially severe hypertension, is one of the most frequent causes of dementia. By producing cerebral infarctions, large and small, it is the commonest cause of multi-infarct dementia. Other causes are atherosclerosis and arteriosclerosis without hypertension, vasculitis, and emboli from the heart or elsewhere in the vascular system. Cardiac disease also produces dementia by single or repeated episodes of cerebral ischemia and hypoxia due to acute or intermittent disorders of cardiac function.

Chronic occlusion of extracranial arteries leading to the brain does not result in dementia in the absence of infarctions.

Space-Occupying Lesions

Chronic subdural hematoma may produce a dementia by itself, or it may complicate and add to the effects of other causes. It is not uncommon in dementias of older people, where the mode of presentation is often different from that seen in younger people.

Benign tumors of the brain produce dementia depending on their size and location. Notable are those on the orbital surface of the frontal lobe or on the medial surface of the temporal lobe because they may not be associated with other more familiar signs of cerebral tumor. Obstructive hydrocephalus may produce dementia in such benign lesions as cerebellopontine angle neurofibromas.

Malignant tumors of brain frequently produce dementia. Only rarely is the dementia relieved by palliative treatment.

Normal Pressure Hydrocephalus

Normal pressure hydrocephalus produces a dementia associated with gait disturbance and urinary and fecal incontinence. It is a rare but frequently discussed condition. Some patients respond dramatically to shunting of the ventriculosubarachnoid reservoir.

Affective Disorders

Depression may be so severe that it produces a true cognitive deficit that is reversible with successful treatment. Depression commonly is present with other causes of dementia, especially Alzheimer's disease.

The Progressive Degenerative Diseases

The most frequent of the dementing diseases are not arrestable or reversible. They are, as far as it is known, primary in the brain and are divisible into two groups, those with no important neurological findings other than dementia and those with other prominent neurological signs.

Alzheimer's disease is the classical example of the first category. It is the most common of all the dementing diseases, increasing in frequency in the older age groups. Although not diagnosable in life with total certainty, a high probability in diagnosis can be attained by using the criteria established by the NINCDS-ADRDA Work Group of 1984. Pick's disease is the other condition in this category, but it is far less frequent than Alzheimer's.

The second category includes a multitude of diseases of the nervous system in which dementia may or may not occur. They include diseases of the basal ganglia (Parkinson's, Huntington's), of the cerebellum (cerebellar and spinocerebellar degenerations, olivopontocerebellar degeneration), and of the motor neurone (amyotrophic lateral sclerosis). Some have more complicated anatomical distributions: Parkinson's-amyotrophic lateral sclerosis-dementia complex of Guam, progressive supranuclear palsy, progressive subcortical gliosis, and multiple system atrophy. It must be recognized that this is only a partial listing of these diseases. Taken all together, they do not compare with the very great frequency of Alzheimer's disease.

What Should Be Included in the Initial Evaluation of Dementia?

The history is the most important component of the initial evaluation; it should be obtained from both the family and the patient. Family members most responsible for and most often in contact with the patient should be consulted first, followed by other family members, friends, and neighbors. Community health workers, especially nurses and social workers, can provide important and objective information. Wherever possible, previous medical records should be reviewed.

A chronological account of the patient's current problems should emphasize the mode of onset, duration of disease, and specific cognitive, memory, and behavioral changes, including such problems as becoming disoriented or lost in a familiar place, having difficulties with driving, or becoming repetitious, irritable, or agitated. Symptoms suggesting cerebral disease should be investigated. The medical history should include inquiries about relevant systemic diseases, trauma, surgery, psychiatric disorders, nutrition, alcohol and substance use, exposure to environmental toxins, and the use of medication, both prescribed and nonprescribed. The Hachinski scale is useful in organizing the patient's history relevant to cerebral vascular disease.

Family history should include questions about relatives who suffer from dementia, Down's syndrome, or psychiatric disorders.

The significance of a patient's behavioral changes needs to be considered within the social context, including cultural, ethnic, racial, educational, occupational, marital, and family background. Additionally, a physician should inquire about changes in the functional abilities, including dressing, grooming, toileting, eating, housekeeping, shopping, preparing meals, and managing finances.

The aim of the physical examination should be to detect not only the primary cause or causes of dementia but also coexisting abnormalities that may exacerbate the patient's disability. The neurological examination should be geared to the detection of focal lesions and signs of general brain dysfunction. In assessing mental status, it is desirable to include a published mental status test with known psychometric characteristics that can provide a baseline for subsequent evaluations. Physicians should consider administering the test themselves because it offers the opportunity to observe the patient's response to questions. At the same time, they can observe and inquire about the patient's mood and the presence of any hearing or visual impairment that may affect the validity of the testing of the mental state.

Examples of published mental status tests are the Mini-Mental State, the Blessed Information-Memory-Concentration test, and the Short Portable Mental Status Questionnaire. These are brief tests, requiring only 5 to 15 minutes for administration. They carry a relatively high risk of both false positives and missed cases. No single test, of any kind, will by itself establish a definitive determination of the presence of dementia; brief tests will provide rough documentation of the patient's mental state.

Short screening batteries, which require 10 to 30 minutes to give in clinical settings, are more satisfactory in the sense that they produce fewer false positive results and miss fewer cases. Examples of such short batteries are the Washington University SDAT Screening Battery and the Iowa Screening Battery for Mental Decline.

A patient should not be considered demented solely on the basis of a poor score on a mental status test or short battery. Identification of dementia in an elderly individual must take into account the cognitive changes that normally occur with aging; what is required for identification are changes that are greater than expected for the individual. Age-associated memory impairment (previously called "benign senescent forgetfulness") is a controversial condition that may be merely a manifestation of normal age-related changes in memory. Mild changes in memory are

thought to be normal at age 50 in some people. Slight changes in spatial perception and attention are similarly regarded as normal at age 60. Small changes in abstract thinking and language are considered normal at age 70. A score suggestive of dementia should be considered clinically significant only if it is corroborated by other components of the initial evaluation, such as strong evidence of deterioration by history or a clinical observation of deterioration on repeated visits. The clinician must be aware that premorbid mental dullness can produce a picture that may mimic early dementia. If there is an unresolved question of lifelong mental retardation, the patient should be referred to a psychologist who is experienced in testing such individuals.

The clinical diagnosis of dementia and the pathological state that causes it should not be considered a one-time or final process. Continuing observation over time is necessary to establish diagnosis for some patients and to identify complicating or superimposed conditions for others. Especially in patients with irreversible dementing diseases, continuing care requires repeated evaluations.

What Diagnostic Tests Should Be Performed, and When Are These Tests Indicated?

The best diagnostic test is a careful history and physical and mental status examination by a physician with a knowledge of and interest in dementia and the dementing diseases. Such an evaluation is time consuming, but nothing else can replace it. Subspecialty consultation proves helpful in selected cases.

The laboratory tests that are used should be individualized based on the history and physical and mental status examination. Overtesting may expose the patient to discomfort, inconvenience, excess costs, and the likelihood of false positive tests that may lead to additional unnecessary testing. Undertesting also has hazards, for example, in elderly persons, where medical diseases may have nonspecific presentations such as dementia.

All patients with new onset of dementia should have several basic and standard diagnostic studies, with modifications to be made according to individual circumstances:

1. Complete blood count.
2. Electrolyte panel.
3. Screening metabolic panel.
4. Thyroid function tests.
5. Vitamin B-12 and folate levels.
6. Tests for syphilis and, depending on history, for human immunodeficiency antibodies.
7. Urinalysis.
8. Electrocardiogram.
9. Chest x-ray.

Most of the readily reversible metabolic, endocrine, deficiency, and infectious states, whether causative or complicating, will be revealed by these simple investigations when combined with history and physical examination.

Other ancillary studies are appropriate in certain common situations:

1. Computed tomography of the brain (without contrast) is appropriate in the presence of history suggestive of a mass, or focal neurologic signs, or in dementia of brief duration. Unless such diagnosis is obvious on first contact, computed tomography should be done.
2. All medications that are not absolutely necessary should be discontinued.
3. Electroencephalograms are appropriate for patients with altered consciousness or suspected seizures, depending on the clinical circumstances.
4. Formal psychiatric assessment is desirable when depression is suspected.
5. Inpatient hospitalization should be considered when the history is unclear, if the patient is suicidal, when an acute deterioration has occurred without apparent cause, or if the social situation precludes adequate observation.
6. Neuropsychological evaluation is appropriate (a) to obtain baseline information against which to measure change in cases in which diagnosis is in doubt, (b) before and following treatment, (c) in cases of exceptionally bright individuals suspected of early dementia, (d) in cases of ambiguous imaging findings that require elucidation, (e) to help distinguish dementia from depression and delirium, and (f) to provide additional information about the extent and nature of impairment following focal or multifocal brain injury.
7. Speech and language analysis can be very helpful. In some patients, complex language disorders can simulate dementia; in others, the skillful speech pathologist can help the patient and family to communicate better.

The role of other studies is controversial, and firm rules for their routine use are not appropriate. Undue weight should not be placed on isolated laboratory findings unless they are consistent with previous clinical information. Examples of these other studies include the following:

1. Magnetic resonance imaging is more sensitive than computed tomography for detection of small infarcts, mass lesions, atrophy of the brainstem, and other subcortical structures; it also may clarify ambiguous computed tomography findings. Inexperienced interpreters may make too much of ambiguous or nonspecific findings on magnetic resonance imaging.
2. Regional cerebral blood flow and metabolism measurements (positron emission tomography and single photon emission computed tomography) are research techniques that have no proven routine clinical value at the present time. Their value in predicting Huntington's and Alzheimer's disease in individuals at risk is under investigation.
3. Lumbar puncture is not routinely required in the initial evaluation of dementia. It should be performed when other clinical findings suggest an active infection or vasculitis. At present, cerebrospinal fluid markers for Alzheimer's disease are not sufficiently well developed to justify routine lumbar puncture.
4. Electrophysiological techniques such as event-related potentials that are recorded using special electroencephalographic techniques are not recommended for routine use.
5. Brain biopsy for nontumorous and noninfectious diseases rarely is justified except in a small number of unusual clinical situations.
6. Biological markers for progressive degenerative dementing diseases are still in the investigative stage. Although some give promise, they are not ready for widespread or routine use.

7. Significant major findings have been made on the molecular genetics of conditions like Huntington's and Alzheimer's diseases, but these findings have restricted usefulness at present.
8. Carotid ultrasound is of no value except sometimes in the search for the cause of infarcts.

What Are the Priorities for Future Research on Diagnosing the Dementias?

Diagnosis of the dementing diseases has improved over the past 10 years. Nevertheless, there is room for improvement in accuracy of diagnosis. Advances in genetics and molecular biology have opened the door to new areas of research but are not immediately applicable to clinical diagnosis. While awaiting the development of definitive in vivo diagnostic tests, it is necessary to rely on autopsy correlation and validation. These remain essential for studies concerned with the search for diagnostic markers, neuropsychological findings, neuroimaging results, outcome of clinical therapeutic trials, and delineation of clinical-pathologic syndromes. Although it is impossible to list all the approaches to future research that may prove fruitful, the panel recommends that highest priority should go to research on the following:

1. Exploration of potential biological diagnostic markers, innovative as well as logical extensions of ongoing research, with special emphasis on families with autopsy-diagnosed dementias.
2. Evaluation of neuroimaging by long-term followup of patients, correlation with clinical and neuropsychologic findings, and tissue histopathology. Families with autopsy-diagnosed dementias should be given special attention.
3. Evaluation of results obtained with current neuropsychologic instruments in populations that differ in age, education, ethnic composition, and social or cultural background, using long-term followup and correlation with clinical, neuroimaging, and neuropathologic findings.
4. Assessment of the role of vascular disease in dementia by combining clinical, neuropsychologic, neuroimaging, and neuropathologic findings as well as by examining vascular risk factors.
5. Investigation of neuropsychologic test profiles characteristic of specific dementias and validation by means of clinical, neuroimaging, and neuropathologic findings.
6. Design of multivariate studies to determine the optimal combination of diagnostic strategies, including elements of the history and physical examination, mental status, and specialized tests needed to differentiate the dementias common in each age group.
7. Investigation of the mechanisms by which various drugs, nonpsychoactive as well as psychoactive, induce or precipitate a dementia syndrome.
8. Exploration of the mechanisms by which depression induces or precipitates a dementia syndrome.
9. Investigation of the less common degenerative diseases, such as Pick's disease, progressive supranuclear palsy, olivopontocerebellar degeneration, and progressive subcortical gliosis.

Conclusion

Dementia is a clinical state, diagnosable only by clinical methods. Every patient with dementia deserves precise assessment, not only of the fact of dementia, but of the manifestations and the

manner in which the disability is produced. Dementia can be caused by a multitude of different dementing diseases, some of which are arrestable or reversible, and many of which are preventable.

The first approach to a patient with suspected dementia is a careful clinical evaluation. A laboratory test, whether chemical, biological, imaging, or psychological, should never be used as a substitute for the physician's time, expertise, and clinical judgment. Because dementia is primarily a behavioral diagnosis, the initial medical evaluation should include an assessment of how well the patient functions in his or her daily life as well as a family history and neurological and standardized mental status examinations. Relatives, friends, and neighbors often can provide information especially valuable in assessing a patient suspected of having dementia.

The diagnosis of dementia has become more accurate over the past 10 years, but thorough assessment still cannot be done rapidly. Because serious implications are inherent in making a diagnosis of irreversible dementia and in missing any conditions that may be arrested or reversed, physicians are urged to take the time necessary to make this thorough evaluation and to refer patients to specialists when they want further confirmation of clinical findings.

Because large gaps still exist in current knowledge on the diagnosis of dementia, the panel has made specific recommendations for further research that will result in improving the differential diagnosis of dementing diseases.

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