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REVIEW

Dementia Screening in Light of the Diversity of the Condition

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Dementia is a general term, not a specific diagnosis. There are many different causes of dementia, and the different etiologies are associated with different neuropsychological profiles. This complicates the problem of dementia screening. Detection of dementing conditions at the earliest possible stage requires batteries of tests, rather than a single test. The cognitive domains that must be addressed include the following: visual and verbal memory, sustained attention and complex attention, working memory, processing speed, reaction time, psychomotor speed and executive function.

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In my previous contribution to *JIM,*[1] I addressed the issue of dementia screening using computerized tests. Computerized neurocognitive testing is not a new technology. It has been used for many years in aerospace and military medicine, occupational and sports medicine, and pharmaceutical research. But its application to clinical diagnosis in the general physician's office is altogether new. It is driven by an abiding new concern over dementia in general and Alzheimer's disease in particular. Also, it is driven by the availability of new treatments for dementia. At this point, they are no more than symptomatic treatments, but commercially available treatments and new compounds currently under development hold promise of ''disease-modifying'' effects.[2–5]

It is well established that the preclinical phase of dementia usually precedes clinical diagnosis by many years.[6] If not to prevent dementia, early detection of dementing conditions during the preclinical phase can at least slow its course or mitigate disability. The possibility of disease-modifying treatment makes the issue of early detection crucially important.

In the last paper, we argued that conventional tools for dementia screening, like brief office-based tests, telephone interviews or dementia rating scales are gross measures and inadequate to today's clinical requirements. They only detect dementia when the symp-

Table 1. A Neurocognitive Key to the Dementias

Cortical Dementia (amnesia, aphasia, agnosia and apraxia)
Alzheimer's disease: early deficits in recent or episodic memory, either verbal or visuo-spatial; in complex attention; and speed of cognitive processing.
Fronto-temporal dementia: early deficits in executive control functions.
Subcortical Dementias (low arousal, deficits in vigilance, complex problem solving and psychomotor speed)
Lewy body dementia: attention, reaction time, working memory and visuo-perceptual ability.
Huntingon's disease: memory, cognitive flexibility, abstraction, manual dexterity, attention, and concentration.
Wilson's disease: perceptual-motor speed
Multiple sclerosis: episodic memory, working memory
Vascular Dementia (one of the subcortical dementias)
Tests of attention, memory and psychomotor speed are associated with cardiovascular risk factors like hypertension and diabetes, and represent early manifestations of cerebral vasculopathy.

toms are overt, and the disease is well established. They are virtually obsolete now that reliable and sensitive computerized screening batteries are available.

We also addressed the sometimes confusing issues of ''benign senescence,'' or normal age-related memory decline, and ''mild cognitive impairment'' (MCI), a general term that has been pre-empted by dementia investigators. MCI is a diagnosis for patients with more cognitive impairment than should normally occur with aging but without any significant associated disability. Many, but not all, patients with MCI ultimately ''convert'' to a state of dementia. The rate of conversion is about 10%-15% per year.[7]

Office-based dementia screening tests, like the Mini-mental State Exam, and telephone-based interviews, like the Minnesota Cognitive Acuity Test, have limited sensitivity for detecting the mild cognitive dysfunction that characterizes MCI. Additionally, they have not been standardized in enough elderly people to differentiate reliably between benign senescence and MCI.

The third problem is one that we shall address in this paper: that dementia is not a unitary construct, but a general term, like ''anemia'' or ''arthritis.'' Even if we focus on the so-called ''irreversible'' dementias, ie, dementias caused by neurological deterioration, rather than nutritional or metabolic abnormalities, there are many different causes. And, the different kinds of dementia have different neuropsychological profiles.

The diversity of both the dementias (Table 1) and their neuropsychological symptoms mean that a battery of neurocognitive tests are necessary for screening purposes. Different forms of dementia may present in different ways.

ALZHEIMER'S DISEASE

It has long been believed that the most common early deficit in patients with Alzheimer's disease (AD) is in recent or episodic memory (ie, memory for personal experience in one's recent past). Examples are remembering what you had for breakfast, what you went to the grocery store to buy, or how to find your way back to the hotel after you go for a downtown stroll. The memory deficit may be verbal (the grocery list) or visuospatial (the way back to the hotel).

Selective impairment of episodic memory is not only the first sign of AD, it is a preclinical marker for AD, as well. There is convergent data to this effect from studies of people who are genetically predisposed, longitudinal studies of patients with MCI, and epidemiological studies of incident AD cases.[2,8,9] Presymptomatic memory deficits are most readily apparent in tests of learning new material, both verbal and visuospatial. There is relative sparing of immediate mem-

ory such as working memory (eg, digit span), but the rate of forgetting is rapid within the first several minutes after exposure to a verbal or figural stimulus.[10] In one study, patients who later developed AD showed presymptomatic deficits on a computerized test of verbal memory (Paired Associate Learning).[11]

Memory impairment is not the only early sign of AD, however. Attention is also affected in the early stages. Measures of complex attention (eg, divided attention, selective attention, set-shifting, response selection) are particularly sensitive while measures of sustained attention (eg, vigilance, continuous performance) are relatively preserved.[12]

Complex attention is a component of executive control function, and frontal control tests, such as Trails, the Stroop test, Halstead Categories and the Wisconsin Card Sort are among the ''most sensitive and useful'' indicators of early AD.[13–17] Frontal-temporal dementia, a familial condition caused by a mutation on chromosome 17, is typified by frontal executive dysfunction but not memory deficit. Executive control deficits were apparent in some of the youngest mutation carriers, who were evaluated many decades prior to the expected onset of dementia.[18]

Cognitive slowing is another early sign of AD.[19–27] Even before ''slowing'' is subjectively apparent to the patient or the patient's family, it can be demonstrated in the latency of evoked potentials or in psychological tests that measure reaction times, especially choice or complex reaction times.[1,23,27–34] (Slowed reaction times and delayed EP latencies can be demonstrated in HIV-infected individuals long before there is clinical evidence of cerebral deterioration.)[35,36] To measure cognitive slowing in these paradigms, however, it is necessary to generate millisecond accuracy, which is not attainable in a paper-and-pencil test or even in a ''formal'' battery of neuropsychological tests.

Therefore, AD even in its earliest stages is not just a disease of memory. Long before clinical signs are apparent and even before a skilled neurologist or neuropsychologist can detect the condition, there are signs of cognitive weakness in various cognitive areas. Supportive evidence continues to accrue, for example, from PET studies of people with a genetic predisposition, who show evidence of reduced glucose metabolism in the temporal lobes,[37] and from longitudinal studies, like the ''Nun Study.''[38] The earliest ''detectable cognitive deficits'' are not only tests of verbal and visual memory but also measures of complex attention, executive control, and reaction time/information processing speed. Table 2 summarizes a representative neuropsychological test battery for AD screening.

Table 2. A Neuropsychological Test Battery for AD Screening

Episodic Memory
• Verbal memory (ie, list learning)
• Visual memory (geometric figures)
• Prose memory (sentences, stories)
Complex attention (eg, shifting attention test)
Executive function (eg, Stroop, categories, multitasking)
Processing speed, reaction time

Episodic memory is the ability to remember recent events, for example a list of words, a series of geometric figures, or the factual elements of a story. A test for immediate episodic memory may have you recall as many items as you can as soon as the list is presented and a delayed episodic memory test would have you recall the items after a delay of 5–30 minutes, depending on the test.

Complex attention is the ability to pay attention to a complicated series of stimuli, and/or rules, at the same time. For example, press the left shift key if the two figures on the screen are the same color, press the right shift key if the two figures are the same shape, and press the space bar if the two figures are the same color and shape.

Executive functions are elements of frontal lobe function: the ability to do two things at once (multitasking), the ability to suppress or inhibit a normal response and to activate an unfamiliar response quickly and efficiently (the Stroop test), or the ability to deduce similarities from a series of abstract figures (Cat-

egories test). Other executive functions are planning, organization and abstract problem solving.

Reaction time is how fast the mind can respond to a simple stimulus (eg, press the space bar as soon as you see a shape appear on the screen). Processing speed or complex reaction time is how fast the mind can respond to a complex stimulus (eg, press the space bar if the sentence you see on the screen is true). For each of these psychological functions, there are numerous tests in the literature; some tests can address more than one function. For example, the Stroop test is a test of complex attention, executive function and information processing speed.

SUBCORTICAL DEMENTIAS

AD and frontotemporal dementia are cortical dementias. In contrast, the diseases considered in this section are considered to be subcortical dementias. The primary pathology is in the basal ganglia or subcortical white matter. Examples are dementia with Lewy bodies (DLB), Huntington's disease (HD), Parkinson's disease (PD), Wilson's disease (WD), progressive supranuclear palsy, and vascular dementia (VaD), ie, multi-infarct dementia or leukoaraiosis. Cortical dementias are typified by cortical symptoms, such as amnesia, aphasia, agnosia and apraxia. Subcortical dementia has different symptoms such as low arousal, deficits in vigilance, complex problem solving and psychomotor speed. The neuropsychological tests that are most sensitive to subcortical degeneration are time-dependent tests.[39]

Subcortical dementias that affect the basal ganglia are also associated with impairment in functions that are usually associated with the prefrontal cortex (attention tests, executive function tests). This is because the basal ganglia participate in virtually all of the complex function systems that reside in the frontal lobes, a relationship that is reflective of the evolution of the frontal lobes, phylogenetically and developmentally.[40]

Ultimately, the neurocognitive deficits of patients with cortical and subcortical dementias converge. As cortical disease advances, it inevitably involves subcortical tissues. As subcortical disease advances, it inevitably compromises cortical function. But early in the course of both disorders, their neurocognitive profiles are differentiated. A neurocognitive battery that is sensitive to early manifestations of cortical dementia should emphasize memory, selective attention and cognitive flexibility. A subcortical dementia battery should include measures of reaction time and information processing speed such as motor speed, working memory, and sustained attention. An ideal battery for dementia screening should include the tests summarized in Table 3.

Table 3. Neurocognitive Tests for Subcortical Dementia

Psychomotor Speed: Coding, Finger Tapping Test
Reaction Time Tests
Sustained Attention: Continuous Performance Test
Working Memory: Digit Span, Digit Ordering

Psychomotor speed is the ability to execute a complex motor task. The finger-tapping test is how fast a subject can press the space bar with the index finger in 10 seconds. Coding is how fast a subject can match abstract symbols to their matching digits, according to a pre-set instruction.

Sustained attention, or vigilance, is the ability to maintain one's attention, free from distraction, over a long period of time. In the continuous performance test, one has to press the space bar when the letter B appears on the screen, but not for any other letter. The test can go on for 5–20 minutes and is incredibly onerous to do.

Working memory is one's span of immediate attention. Think of trying to keep a phone number in one's mind just long enough to dial it. In digit span, one has to repeat a series of digits; most of us can handle seven digits, which is why phone numbers are seven digits long. It is harder to do if you have to repeat the numbers backwards. For example, the stimulus is 3-5-8-1-7-2 and correct re-

sponse should be 2-7-1-8-5-3. It is even harder if you have to repeat the digits in their proper sequential order (1-2-3-5-7-8), which is called digit ordering.

Parkinson's Disease

Parkinson's disease (PD) is a disease of the basal ganglia characterized by progressive motor impairment such as tremor, bradykinesia, mask-like facies, and abnormal gait. PD is almost always associated with some degree of cognitive impairment. A substantial number of PD patients become demented but by no means all of them.

Two types of dementia can occur in PD patients. One has the characteristics of a subcortical dementia, and another shares the typical characteristics of AD. Cognitive domains that are impaired early in the course of PD include sustained or shifting attention, memory, visuospatial ability, sustained attention, reaction time and processing speed.[41,42]

Lewy Body Dementia

Another type of dementia is associated with mild or moderate Parkinsonism, which is dementia with Lewy bodies (DLB). Lewy bodies are spherical intraneuronal inclusions that are present in PD mainly in the substantia nigra. In DLB, they are also found in the brain stem and the neocortex. The severity of dementia is correlated with the density of Lewy bodies.[43] It is not understood why or how Lewy bodies are formed, but their appearance is associated with cellular degeneration. They have specific antigenic characteristics and are stained by anti-ubiquitin and anti-synuvlein antibodies. Also, mutation of the synuclein gene has been identified in cases of familial PD.[44–46]

DLB is a fairly common dementing disease, accounting for 12%–36% of dementia cases. It is less common than AD but almost as prevalent as vascular dementia.[45,47,48] The wide range of prevalence data probably reflects the difficulty even dementia specialists have in distinguishing among DLB, AD and PD dementia, and the validity of the diagnostic criteria have been questioned.[49] The overt characteristics of the condition, however, are striking and belie the contention that it is just one more neuropathological oddity. They include marked fluctuations of alertness and cognitive performance, moderate Parkinsonism, visual hallucinations, unexplained falls and syncopes, delirium, and adverse (sometimes severe) reactions when the patients are treated with conventional neuroleptic drugs. Mean age of onset is between 60–68 years. In contrast to AD, males are more commonly afflicted.[44]

The neuropsychological profile of DLB is only gradually coming into focus, but it seems to have a subcortical profile. Compared to AD patients, DLB patients are more likely to have problems with attention, reaction time, working memory and visuoperceptual ability.[50–52]

Huntington's Disease

Huntington's disease (HD) is a progressive hereditary disorder that usually appears late in life. It is characterized by abnormal movements, usually choreiform, dementia and psychiatric disturbances. Neuropathologically, the basal ganglia (especially the caudate nucleus) are the most severely affected structures. Neurons are also lost in the cerebral cortex, and at postmortem examination the brain is shrunken and atrophic.

The first symptoms of HD are typically choreic movements or behavioral aberrations, and cognitive decline only becomes obvious later on.[53] Sometimes, memory problems are the first overt symptoms of the disease.[42] The dementia of HD is profound and diffuse (affecting virtually all cognitive functions) and is compounded by concomitant symptoms of rigidity, mood instability or psychosis.

A meta-analysis of neuropsychological studies of HD patients indicated that they are most deficient on tests of delayed recall, followed by performance on measures of memory acquisition, cognitive flexibility and abstraction, manual dexterity, attention/concen-

tration, performance skill, and finally verbal skill.[54] Patients with mild or early HD have been found to have prominent deficits in memory,[55] visuospatial ability[56] and cognitive flexibility (eg, Stoop test).[57] The pattern is one of diffuse impairment of frontostriatal functions.

Although overt dementia is a relatively late symptom of HD, the gradual erosion of intellectual abilities begins long before clinical signs (ie, choreic movements) become evident. This has been established by studies of asymptomatic carriers of the HD gene on chromosome 4. The identification of excessive trinucleotide repeats (CAG) is central to the genetic defect. But even before the HD gene was identified, it was clear that it did not simply ''turn on'' at the time involuntary movements begin to appear. Subtle neurocognitive impairments can be demonstrated many years earlier.[58]

Neuropsychological deficits in presymptomatic carriers of the HD gene have been noted in several areas, again consistent with frontostriatal pathology, which includes the following:

- Memory[53] and verbal learning[59]
- Visuospatial abilities, especially visuospatial memory
- Executive abilities (eg, Wisconsin Card Sort Test)[60]
- Attentional set shifting and verbal fluency[45]
- Attention, learning and planning[61]
- Information processing speed[59]

Wilson's Disease

Wilson's Disease (WD) is an inborn error of copper metabolism that is associated with cirrhosis of the liver and degenerative changes in the basal ganglia. Dramatic physical signs characterize the disease. However, in a substantial number of WD patients, the first signs are behavioral or psychiatric in nature.[62]

Patients with untreated WD ultimately develop diffuse cognitive impairments, including intelligence, memory, perceptual speed, word fluency, rule finding and mental rotation.[63] Overt neurocognitive deficits do not usually arise in WD until after neurological or psychiatric problems are manifest.[63] As a result, patients' performance on neuropsychological tests is complicated by the co-occurrence of motor impairment, which can compromise the speed and accuracy of responding.[64] However, cognitive impairment is not necessarily correlated with neurological signs.[65] If one controls for motor impairment, subtle deficits in perceptual speed can be detected even in patients who are asymptomatic.[66]

Multiple Sclerosis

Although few multiple sclerosis (MS) patients are actually demented, cognitive dysfunction occurs in at least half of patients. General intelligence and language tend to be preserved in MS, but neurocognitive deficits are discovered in memory, attention, information processing speed, executive functions and visuospatial perception.[67] In MS patients, the extent of lesions on an MRI is correlated with deficits in memory, information processing speed, abstract reasoning, naming/verbal fluency and visuoperceptual organization.[68]

Patients with mild MS usually perform well on standard neuropsychological tests, apart from mildly reduced performance on tests of long-term memory. It has been suggested, however, that deficits in working memory are the earliest neurocognitive manifestation of the disorder.[69]

VASCULAR DEMENTIA

Vascular dementia (VaD) is the second most common form of dementia after AD. The diagnosis is based on evidence of cognitive loss (most often subcortical), vascular brain lesions demonstrated by imaging, and exclusion of other forms of dementia such as AD.[70] The term comprises a spectrum of conditions, depending on the magnitude of the cerebrovascular event(s). In ''strategic single-infarct dementia,'' post-stroke dementia and multi-infarct dementia the pathology is overt, if not catastrophic, and clinical diagnosis is

not given to any degree of subtlety. However, the development of multiple lacunar infarcts (white matter disease, small vessel disease or leukoaraiosis) is insidious and not necessarily associated with mild cerebrovascular events, like transient ischemic attacks. Lacunar infarcts are very small lesions, occupying tissue nourished by penetrating arteries, 50 μm to 200 μm in diameter in the subcortical nuclei and convolutional white matter.[71]

Cerebral small vessel disease is a very common condition. Its onset is insidious, and mild cognitive dysfunction may be the first clue to its presence. Indeed, the diagnosis is often serendipitous where multiple, small white matter lesions are identified on an MRI that is undertaken for some other reason. The clinical presentation may be pre-syndromal. For example, a middle-aged patient has a mild concussion, but complains of persistent, vague cognitive impairment, and so an MRI is ordered. White matter lesions are demonstrated that are not the result of trauma but of pre-existing small vessel disease. In such cases, the only overt consequence of small vessel disease is a reduction in the patient's ''cerebral reserve.'' In this example, it is the patient's capacity to recover quickly from a minor brain insult.[40]

The risk factors for small vessel disease in the brain are the risk factors that dispose to systemic vasculopathy such as aging, hyperlipidemia, hypertension, diabetes mellitus, obesity, cigarette smoking, hyperhomocysteinemia and C-reactive protein. In contrast to AD, which is a primary neurodegenerative condition, VaD is a secondary condition, the CNS manifestation of systemic disease. Although VaD is clinically and neuropathologically distinct from AD, the two conditions are also related. For example, in AD patients, the presence of VaD risk factors aggravates the course of their AD.[72] Conversely, in patients disposed to develop VaD, the presence of the ApoE4 genotype accelerates the course of their VaD.[73] In simple terms, when the aging brain is assailed from without and within, dementia is more likely to occur and to be more severe.

White matter disease is an MRI diagnosis. The typical finding is white matter lesions (WML) or lacunes in the basal ganglia, thalamus and periventricular regions. They may also be noted in the frontal lobes.[71] WMLs are so common in the MRIs of elderly people that the film may be read as ''normal for age.'' A few such lesions may, indeed, be a correlate of normal aging, but the number or extent of WMLs is correlated with cardiovascular risk factors, cognitive impairment and disability.[74–76] Even healthy, elderly subjects with WMLs have subtle disturbances in basic attention and selected frontal lobe functions, including digit span, divided attention (multitasking), sorting (categories) but not IQ, memory, language, visuospatial ability or information processing speed.[77]

One does not need an MRI to suspect the diagnosis of small vessel disease. A middle-aged patient with significant cardiovascular risk factors is likely to have the disorder to some degree. Fundoscopic examination of the retinal vessels can indicate vascular pathology. The retinal arterioles are as vulnerable to vasculopathy as the arterioles of the brain.

COGNITIVE IMPAIRMENT ASSOCIATED WITH VaD RISK FACTORS

Subtle signs of subcortical dementia occur in patients who are at risk for VaD by virtue of cardiovascular risk factors. Hypertensive patients, for example, have significant deficits in attention and verbal memory, even when the effects of aging are controlled.[78] Primary systemic hypertension is correlated with cognitive impairment in reading, executive functioning, constructional- and memory-recall but not in memory recognition or language.[79] Elevated midlife BP and the resulting increase in white matter hyper-intensities increase the risk for MCI in older men to at least the same degree as the ApoE4 genotype.[80] Elderly patients with hypertension, but without dementia or stroke, have deficits in tests of reaction time, visual and verbal memory, and attention when compared to matched controls.[81]

Patients with hypertension are also at high risk to develop severe cognitive impairments following cardiac surgery.[80]

In a large multi-center longitudinal investigation of individuals with cardiovascular risk factors followed from middle age, hypertension and diabetes mellitus were found to be positively related with cognitive decline. The Coding Test was particularly sensitive.[82]

The performance of patients with Type-2 diabetes on a battery of neurocognitive tests, compared to controls, is somewhat complex. In one study, performance on measures of visual memory, attention, executive function, general mental functioning, and information processing was not impaired, but verbal memory was. The impairment in verbal memory was correlated with duration of the condition but not with indicators of recent glycemic control (eg, HbA1c).[83,84]

Patients with nonrheumatic atrial fibrillation who were neurologically asymptomatic were found in one study to have ''subclinical but significant impairment in attention and memory.'' This was possibly caused by minor ischemic episodes secondary to microembolization or by diffuse hypoxic damage due to hypoperfusion.[85]

Hyperhomocysteinemia (Hhcy) is a metabolic disorder associated with both atherosclerotic vascular disease and cognitive decline in elderly people.[86] Hyperlipidemia is also correlated with cognitive decline. For example, in a Finnish study of 1500 people followed from 1972, midlife cholesterol was the most significant risk factor for the subsequent development of MCI.[87] By the same token, lowering serum lipids clearly results in reduced risk for cerebrovascular events, major and minor.[10] Lipid lowering agents, especially the statins, are associated with a reduction of cerebrovascular disease. For some reason, they seem to be protective against the development of AD, as well.[88–91]

DEMENTIA SCREENING

The diagnosis of dementia is not made on the basis of neuropsychological testing alone. Cognitive testing is necessary to make the diagnosis, but it is not sufficient. Dementia is a clinical diagnosis. It is based on history (complaints of disabling cognitive deficits, evidence of progression), physical and neurological examination, imaging studies and laboratory tests. An appropriate work-up including neurocognitive testing will establish the diagnosis with confidence.

No such confidence, however, accrues to dementia subtyping. A definite diagnosis of Alzheimer's disease, for example, is only made at autopsy. Even in cases where there is strong evidence of a causative agent, the sub-type diagnosis is uncertain. If a patient with early dementia has a strong family history of Alzheimer's disease, a typical neuropsychological profile, and the ApoE4 allele, then chances are that patient has Alzheimer's disease. But he or she may also have a comorbid dementia such as vascular dementia. ''Mixed dementia'' refers to patients who have more than one likely cause of their dementing condition.

The purpose of describing the different subtypes of dementia is to illustrate the point that dementia screening has to take the diversity of the condition into consideration. Screening cannot rely on simply 1, 2 or 3 tests. Rather, it needs to address all of the cognitive domains that may be affected in the earliest stages of the disorder. These tests include:

- Episodic memory, both verbal and visual memory
- Sustained attention
- Complex or selective attention
- Working memory
- Processing speed and/or reaction time
- Executive function
- Psychomotor speed

To reiterate a point we have made already, these domains are not covered in the brief, office-based examinations that are so widely used by physicians. They can be addressed by administering a formal neuropsychological battery, but that is not really appropriate for screening purposes. They can be ad-

dressed more efficiently, and perhaps more precisely by utilizing one of several new computerized neurocognitive screening batteries, as discussed in the last issue.

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