

Diagnosis of Alzheimer's Disease and Mild Cognitive Impairment

a report by

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As America ages, dementing illnesses are becoming increasingly important since they can majorly impact quality of life of individuals, families, and society in general. The major risk factor for dementia is age – particularly Alzheimer's disease (AD) – and with the 'baby boomers' reaching the age of risk for dementia, this topic is receiving great attention. Research on dementia is also increasing rapidly and new diagnostic techniques are being developed; consequently, a review of the diagnosis of AD and mild cognitive impairment (MCI) is timely.

Terminology

Dementia refers to a change in intellectual function including a memory impairment, along with an additional cognitive deficit in at least one other area of function (such as language, attention, concentration, visuospatial skills, or problem solving). These impairments have to be of sufficient magnitude to affect the activities of daily living and are not thought to be due to a change in the sensorium, e.g. delirium. The Diagnostic and Statistical Manual IV criteria for dementia are outlined in *Table 1*.¹ The clinical diagnosis of AD is similar to that developed for dementia but adds the dimension of a presumed degenerative etiology. The most common research criteria for AD have been described by McKhann et al. (see *Table 2*). It is apparent that the dementia criteria were strongly influenced by AD, e.g. the requirement for a memory disorder to be present, and this aspect of the criteria is being reconsidered.² The American Academy of Neurology (AAN) concluded in a recent evidence-based medicine review of the literature that the clinical diagnoses of dementia and AD were actually quite accurate when compared with post-mortem findings.³ In spite of the lack of a biomarker for AD, clinicians are usually quite accurate. As previously mentioned, technology has assisted in making this diagnosis, meaning that some of these newer diagnostic techniques need to be reviewed.

Clinical Evaluation

The fundamental diagnosis of dementia or AD remains clinical, i.e. without a biomarker the ultimate diagnostic

call is a clinical judgment. This can be accomplished with accuracy by following standard procedures.

History

A history from the patient and from someone who knows the patient well is of paramount importance. It is critical to inquire about daily activities, how well the person is performing activities of daily living, if performance of these activities is changed, and whether that change is secondary to an alteration in intellectual function. Since these disorders increase with age, it is important to determine that the changes in function are secondary to cognitive difficulties and are not due to medical co-morbidities. The typical course of the change is important to determine since AD is typically of insidious onset and gradual progression. Cognitive changes of a vascular etiology may appear in a more abrupt fashion, although vascular disorders involving certain types of vascular insults can progress slowly.

It is also important to inquire about non-cognitive behaviors. A personality change and other alterations in behavior can alert the clinician that the dementia may not be due to AD. Frontotemporal dementias typically present with an alteration of behavior with lack of insight into the clinical state and occasionally present with apathy. Inappropriate social behaviors may also be a feature of this disorder. It is also important to inquire about sleep habits. Individuals with dementia and Lewy body syndrome may be prone to snoring and may exhibit dream enactment behavior. This disorder is also frequently characterized by daytime hallucinations, which are often non-threatening, and wide fluctuations in behavioral performance. These features can be very useful in differentiating among the various dementias.

Examination

It is important to perform a medical and neurologic examination to determine any clues as to the etiology of the dementia syndrome. Typically, the general neurologic examination without a mental status examination component is largely normal in early AD. However, if there are subtle features of Parkinsonism, this may suggest a Lewy body component either leading to dementia



Table 1: DSM-IV Diagnostic Criteria for Dementia¹

The development of multiple cognitive deficits manifested by:

- memory impairment; and
- one, or more, of the following cognitive disturbances:
 - aphasia;
 - apraxia;
 - agnosia; and
 - disturbance of executive functioning.

These cognitive impairments are of sufficient severity to compromise social or occupational function and represent a decline from a previous level of function

These deficits do not result from an altered sensorium

Table 2: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Criteria for the Diagnosis of Alzheimer's Disease²

The criteria for the clinical diagnosis of probable AD include:

- dementia;
- deficits in two or more areas of cognition;
- progressive worsening of memory and other cognitive functions;
- intact level of consciousness;
- onset between ages of 40 and 90; and
- absence of other medical conditions or brain diseases thought to account for the changes in cognition.

Clinical diagnosis of possible Alzheimer's disease:

- may be made on the basis of a dementia syndrome in the absence of other medical or neurologic causes of dementia and in the presence of variations in onset, presentation, or clinical course;
- may be made in the presence of a second medical or brain disorder but not considered to be the primary cause of the dementia; and
- could be used in research studies where a single gradually progressive cognitive decline is identified.

Criteria for the diagnosis of definite Alzheimer's disease:

- clinical criteria for probable Alzheimer's disease; and
- autopsy confirmation.

with Lewy body syndrome or perhaps Parkinson's disease with dementia. The examination can also reveal features that might suggest a vascular contribution such as asymmetrical reflexes, hemiparesis or a visual field defect. These features may direct a further investigation into the certain causes of the clinical findings.

Mental Status Examination

An essential part of the evaluation is the mental status examination. The clinician can use one of several evaluations in the literature such as the Mini-Mental State Exam (MMSE) or the Short Test of Mental Status (STMS) but the precise instrument used is less important than familiarity with a single measure.⁴ If the clinician becomes comfortable with the performance of a particular mental status examination, this can be quite useful in the diagnostic workup. The mental status examination is not diagnostic by itself but can document the degree of cognitive impairment and

suggest additional tests to be ordered. Typically, AD will have a prominent memory impairment, whereas other syndromes may have different presentations. The STMS can also be useful as a baseline for future examinations.

Neuropsychological Testing

An important adjunct to the evaluation of cognition involves neuropsychological testing. Neuropsychological testing can be particularly important in very mild cases such as those found with MCI. Neuropsychological testing can differentiate the cognitive changes of normal aging from incipient disease states and can also provide a cognitive profile, which may be useful in sorting different dementing illnesses. In well-established cases of dementia, neuropsychological testing is probably less relevant, although it can be useful for identifying areas of strength and weaknesses as well as following progression. Finally, as previously stated for the STMS, neuropsychological testing can provide a useful baseline for future reference.

Neuroimaging

The AAN in its most recent recommendations for the evaluation of dementia recommended neuroimaging as an essential component of the diagnostic assessment.³ Generally, a head computed tomography (CT) scan is adequate for most 'rule out' purposes. However, MRI scans are being increasingly more relevant as a means of providing exclusionary information as well as positive predictive indices of a diagnosis and its progression. Measures such as volumetric quantitation of the hippocampal formation and entorhinal cortex can be useful in the AD spectrum of diseases as can measures of whole brain volume or ventricular dilatation. More developmental measures such as the boundary shift integral, arterial spin labeling, and diffusion tensor imaging may be of value in the future with respect to the assistance in diagnosis as well as in predicting progression over time. A current large effort called the Alzheimer's Disease Neuroimaging Initiative (ADNI) has just been sponsored by the National Institute on Aging (NIA) and industry with additional support of the Alzheimer's Association (AA) and should provide important diagnostic information regarding certain neuroimaging measures for the future.

Laboratory Studies

Depending on the specific clinical situation, certain laboratory studies might prove useful in determining the etiology of a cognitive impairment. The AAN recommended assessing thyroid function studies and a vitamin B₁₂ level, not because they are likely to be the sole cause of a dementia, but because abnormalities on these tests are common in aging, and these disorders may influence cognitive function. Other previously

recommended tests such as a syphilis serology are only recommended in particular situations where this is a clinical suspicion. In certain clinical contexts, more extensive evaluations may be indicated (see *Table 3*). For example, if the patient is young and/or has experienced a subacute decline, the likelihood of an Alzheimer process is less likely and other explanations should be entertained. Perhaps a cerebrospinal fluid analysis assessing possible infections, neoplasms, or inflammatory markers might be revealing. If the person has had a recent diagnosis of cancer, a more exhaustive evaluation may be entertained. Rarely, in rapidly progressive, fluctuating clinical conditions, auto-immune disorders may indicate a steroid responsive condition and should be considered.

There are no specific biomarkers for AD at present. Susceptibility polymorphisms pertaining to certain genes such as the apolipoprotein E gene can be indicative of a risk but are not recommended for screening asymptomatic individuals. It can be helpful to use apolipoprotein E4 carrier status in the differential diagnosis of a dementia. Several studies have indicated that measures of cerebrospinal fluid amyloid or tau can be useful, and while these markers can be suggestive, they are not diagnostic of an AD process. Usually, the clinical judgment based on the aforementioned criteria is adequate.

MCI

In recent years there has been an increasing emphasis on making the diagnosis of cognitive impairment at an earlier point in the clinical spectrum.⁵ Many investigators believe that by the time the clinical symptoms warrant the diagnosis of AD, considerable damage has been done to the central nervous system (CNS). If clinicians can diagnose these conditions at an earlier point in time, and as effective therapies are developed, treatment could therefore be initiated at a point when the damage may be prevented.

At this point, this rationale is theoretical, but there are practical advantages to making an early diagnosis. For example, if patients were to learn that they had a certain probability of progressing to AD over the coming years, they may be able to make decisions regarding financial planning, retirement and family issues. All of this information may be beneficial to patients if displayed in the appropriate context.

With this as a rationale, the concept of MCI has come to designate the intermediate stage of impairment between the cognitive changes of aging and the earliest clinical manifestations of AD. Mild cognitive impairment can be diagnosed using the following criteria:

Table 3: Evaluation of Dementia

Imaging studies

- CT
- MRI
- PET, SPECT

Electroencephalogram

Cerebrospinal fluid analysis:

- microbiology;
 - gram stain;
 - bacterial cultures;
 - fungal cultures;
 - AFB cultures;
 - viral cultures;
 - PCR-herpes, simples encephalitis; *Borrelia burgdorferi*;
- chemistry
 - protein
 - glucose
 - VDRL
 - FTA-Abs
 - IgG index
 - oligoclonal bands
- cell count; and
- cytology.

Blood studies:

- chemistry group including glucose;
- hematology group;
- sedimentation rate;
- vitamin B12, folic acid;
- thyroid function studies;
- syphilis serology;
- toxicology screen; and
- alcohol level.

Optional:

- ANA;
- ENA;
- heavy metal screen;
- HIV;
- lyme serology;
- copper;
- ceruloplasmin;
- anticardiolipin antibody;
- lupus anticoagulant;
- anti-Purkinje cell antibody;
- antineuronal nuclear antibody; and
- arterial blood gas.

CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single-photon-emission tomography; AFB = acid-fast bacillus; PCR = polymerase chain reaction; VDRL = Venereal Disease Research Laboratory; FTA-Abs = fluorescent treponemal antibody-absorption; ENA = extractable nuclear antigens; ANA = antinuclear antibodies; HIV = human immunodeficiency virus; IgG = immunoglobulin G. (Adapted from Reference 9.)

- cognitive complaint, preferably corroborated by an informant;
- memory impairment for age and education;
- essentially preserved general cognition;

- intact activities of daily living; and
- not demented.⁶

It should be emphasized that these criteria are to be fulfilled using clinical judgment in much the same fashion as the criteria for dementia and AD are implemented (see *Table 1* and *2*). That is, while neuropsychological testing can be quite useful in aiding the diagnosis, the testing itself does not make the diagnosis. There are no specific tests or cut-off scores that indicate the diagnosis of MCI. To fulfil the criteria previously listed, the clinician should:

- take a history from the patient and informant to determine if there has been a change in cognition in recent months and years;
- measure memory function using appropriate mental status examinations or neuropsychological testing to determine if the person has a memory impairment with respect to the appropriate age and education of the individual;
- use the mental status examination or neuropsychological testing to determine that general cognition, defined by performance in non-memory cognitive domains is largely preserved, i.e. not significantly impaired to indicate a clinically significant abnormality;

- by history or use of an appropriate instrument, the activities of daily living are largely preserved and the person is functioning essentially normally in the community; and
- the person does not fulfil the criteria listed for dementia or AD.

Individuals with MCI are commonly seen in clinical practice and the AAN has recommended that these individuals be followed for their risk of developing dementia.⁷ Recently, several clinical trials in MCI have been completed and one study demonstrated a potential beneficial effect at reducing the risk of progressing to AD from MCI for up to one year in subjects treated with donepezil, and for up to two to three years for Apolipoprotein E4 carriers.⁸ While effective treatments are being studied, it is therefore apparent that the field of aging and dementia research is moving toward an earlier identification of the patients' symptoms.

In summary, the diagnoses of dementia, AD, and MCI can be made with a high degree of accuracy when compared with subsequent post-mortem examinations. Even in the absence of a biomarker, the clinician can be quite astute. As more effective therapies are developed, it will become increasingly important for the clinician to be able to identify dementing illnesses at their earliest clinical juncture. ■

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