Alzheimer's disease: a review of diagnostic criteria

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Introduction

Dementia is a syndrome in which affected individuals have impairment of memory and at least one other cognitive area, for example, orientation or comprehension. The diagnosis of dementia corresponds to a variety of etiological domains, from cerebrovascular disease to neurodegenerative disease. However, Alzheimer's Disease (AD), which is a neurodegenerative disease of uncertain origin and pathogenesis, is the most common form of dementia in the elderly.

First described by Alois Alzheimer in 1906, AD is a currently incurable neurodegenerative disease that primarily affects adults. Estimated to affect over 4 million Americans, AD places a heavy burden on the healthcare system. It is very unusual for this disease to occur in individuals less than 60 years of age, and it is reported to have a slight predilection towards affecting women rather than men.

Early AD typically presents with an insidious onset of mild cognitive impairment, often in the form of short term amnesia, which may be confused with the effects of aging or stress. This is followed by progressive functional and cognitive impairment in multiple domains, with some studies reporting that the mean survival post AD diagnosis is around 3-8 years, depending on factors such as the severity of cognitive impairment and functional deterioration. In later stages, AD can manifest with non-cognitive neurological symptoms, such as myoclonus and seizures.

The progress of AD clinically is often measured by mental status scales such as the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating Scale. However, these scales have their own limitations in terms of correspond with the rate of clinical decline.

Currently, the only definitive way to secure a diagnosis of AD is through histopathological examination of brain tissue. However, this is neither feasible nor is it practised clinically except for confirmation of diagnosis at autopsy. Rather, the mainstays for establishing a working diagnosis of AD are clinical assessment criteria. In this paper, we explore these tools and discuss their shortcomings in AD diagnosis. We also review some of tests that are useful in differentiating AD dementia from other major types of dementia.

Clinical criteria for a diagnosis of Alzheimer's Disease

While a number of diagnostic criteria for AD based on clinical grounds have been proposed, two major sets of clinical criteria are used in North America to reach a working diagnosis of AD. Both these criteria take into account some well established features of AD, such as the history of insidious onset and progressive course of deterioration, as well as evidence of cognitive impairment in multiple areas. Conducting a detailed cognitive and general neurological examination and evaluating the level of cognitive impairment and dementia using the MMSE provide the essential clinical information to which these criteria may be applied.

NINCDS-ADRDA criteria

In 1984, a task force established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) put forth a set of clinical criteria for diagnosis of probable AD. These are provided in Table 1. Additionally, the criteria put forth by the same group for possible AD, where the degree of suspicion is lower than with probable AD, are also provided in Table 1.

<table>
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<tr>
<th>Probable Criteria</th>
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<tr>
<td>Dementia established by clinical examination and standardized brief mental status examination and confirmed by neuropsychological tests</td>
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<tr>
<td>Deficits in two or more areas of cognition</td>
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<td>Progressive worsening of memory and other cognitive function</td>
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<td>No disturbance of consciousness</td>
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<tr>
<td>Onset between 40 and 90 years</td>
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<tr>
<td>Absence of other systemic or neurologic disorder sufficient to account for the progressive cognitive defects</td>
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<th>Possible Criteria</th>
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<tr>
<td>Atypical onset, presentation, or progression of dementia without known etiology</td>
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<tr>
<td>Presence of another potentially causative systemic or neurologic disorder that is not thought to be the etiology of dementia in this case</td>
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<tr>
<td>Progressive deterioration in a single cognitive domain in the absence of any other etiology</td>
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Table 1. NINCDS-ADRDA criteria for diagnosis of AD. Adapted from Feldman et al.
Alzheimer’s disease

The validity and reliability of these criteria have been investigated by a number of studies, with some yielding optimistic conclusions. For example, one study showed that diagnoses of AD made based on these criteria are confirmed by autopsy in 87% of cases. A study by the National Institute of Mental Health Genetics Initiative found these criteria to have good reliability and validity, with a diagnostic sensitivity of 80%. However, some criticisms of these criteria have also been made. For example, one study showed that the interrater reliability for AD diagnosis using these criteria was only low to moderate. Another study showed that these criteria were not effective in distinguishing frontotemporal dementia from AD dementia in a group of 56 patients. This lack of specificity has been attributed to be a result of inadequate emphasis of the saliency of the amnesia component of AD. Furthermore, since the NINCDS-ADRDA criteria are fairly old, they may not reflect recently discovered biomarkers and genetic findings that can help support an AD diagnosis.

**DSM-IV-TR criteria**

The other commonly used clinical criteria for AD diagnosis are derived from the current version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) published by the American Psychiatric Association. These criteria are provided in table 2.

1. The development of multiple cognitive deficits manifested by both:
   - Memory impairment
   - One or more of the following cognitive disturbances: aphasia, apraxia, agnosia, disturbance in executive functioning.
2. The cognitive deficits cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
3. The course is characterized by gradual onset and continuing decline.
4. The deficits are not due to another brain, systemic, or psychiatric condition.
5. The deficits do not occur exclusively during the course of delirium.

Table 1. DSM-IV-TR criteria for diagnosis of AD.
Adapted from Feldman et al.

One argument in favour of the DSM-IV-TR criteria is that they do not necessitate neuropsychological testing in making a diagnosis. However, in a study of 200 patients that compared the NINCDS-ADRDA criteria and the then-current DSM criteria (DSM III-R) against the gold standard of histopathological examination, the NINCDS-ADRDA probable and possible criteria together were found to be 61% specific, 96% sensitive, and 85% accurate in detecting AD while the DSM criteria were found to be 51% sensitive, 96% specific, and 66% accurate in detecting AD. Another study showed that the interrater reliability between the NINCDS-ADRDA and the DSM-III criteria are comparable, and an evidence-based review written by the American Academy of Neurology (AAN) in 1994 concluded that both sets of criteria for AD diagnosis were sufficiently reliable and valid and that they should be used. More recent evidence indicates that documenting an objective progression of cognitive decline over a 12-18 month period is both highly specific and sensitive for AD, however, this is logistically hard to execute.

**Excluding other causes of dementia**

As mentioned earlier, dementia can be present in a wide variety of neurological disease entities. Excluding depression is an important part of diagnosing dementia. Depression is more common in old age than dementia, and is treatable. Chronic pain and medication side effects can also be confused with dementia, therefore, clinical assessments need to be thorough in order to delineate these other non-AD causes of cognitive decline.

Laboratory and imaging technologies can also be helpful in ruling out non-AD diagnoses of dementia. For example, according to guidelines issued by the AAN, brain imaging, preferably MRI, is indicated in those patients with suspected AD. This is important because imaging can reveal structural problems (e.g. hematomas), brain atrophy, and cerebrovascular disease, which can all present similarly to AD. Specific imaging features for AD diagnosis have not been firmly established, though some studies have reported reduced hippocampal volume to be correlated with AD. However, there is also evidence that AD and aging exhibit substantially overlapping atrophy patterns in the hippocampus and entorhinal cortex, so age-specific criteria are required. Special imaging techniques (e.g. fluorodeoxyglucose-positron emission tomography) have been developed that can highlight areas of hypoperfusion in AD or that can reveal imaging features that distinguish AD from other diseases causing brain atrophy. However, these techniques need to be evaluated further for their ability to provide information that affects therapeutic decision making; distinguishing between clinical entities whose treatment is the same does not help. They are also not universally available, and they are not routinely used for AD at present.

Laboratory tests are useful in ruling out other factors that can contribute to dementia. For example, B12 deficiency, which affects homocysteine and methylmalonyl-CoA metabolism, is associated with irreversible neurological damage. Hypothyroidism can also contribute to a dementia-like presentation, therefore screening for B12 deficiency...
and hypothyroidism is important. However, clinicians should not order multiple laboratory tests unnecessarily: some studies show that this is not a cost-effective process, owing to the relative rarity of a treatable metabolic cause of dementia.20 Given the right clinical picture (e.g. a patient with chronic alcoholism, in whom B12 deficiency is likely), laboratory tests are warranted. A number of studies have revealed that serum or CSF levels of a beta-amyloid peptide (called Aβ 42), which is suspected to play a role in AD pathogenesis, may be predictive for AD in patients with mild cognitive impairment, but these measurements have not been formally included in clinical practice guidelines yet.21 Genetic testing does not have a routine role in AD diagnosis, but some evidence suggests that testing for presenilin-1 mutations may be considered on a case-by-case basis in unusual presentations of disease, for example in young patients with a strong family history, when appropriate genetic counselling is provided.22

Conclusion

In this paper, we have reviewed some major clinical criteria that are used in making a provisional diagnosis of AD and reported on the literature evaluating the credibility of these criteria. While the NINCDS-ADRDA guidelines have been used for a long time and have been shown to have reasonable validity and reliability, they are lacking in specificity, and need to be updated to incorporate the latest advances in diagnostic technology. Studies have found the DSM-III-R criteria to be comparable to the NINCDS-ADRDA diagnostic criteria, however, there is a clear dearth of research in evaluating the value of the DSM-IV-TR criteria for AD. In addition to these clinical criteria, other tests such as neurological imaging and serum B12 tests, can be valuable in excluding non-AD differential diagnoses of dementia. Given that the DSM-V is slated for publication in 2012, we hope that the AD criteria published therein will incorporate the merits of existing criteria with additional criteria that reflect our expansion of diagnostic knowledge and tools in this area.

References

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