Early Clinical Diagnosis:
Status of NINCDS-ARDA Criteria

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Introduction

During the past decade there has been a significant improvement in the accuracy of the clinical diagnosis of Alzheimer's disease (AD). Whereas early series of diagnostic accuracy reported error rates of 30-40% (Marsden and Harrison, 1972; Rodron, et al., 1975; and Nott and Fleminger, 1975), more recent studies have verified the correct diagnosis over 90% of the time (Martin, et al., 1987; Morris, et al., 1988). This improvement has largely resulted from the development of specific criteria for AD which specify inclusion criteria and appropriate evaluation, rather than merely excluding so-called 'treatable' dementias and designating the remainder as AD.

The criteria currently recommended for use in theraputic trials were developed by the Work Group on the Diagnosis of Alzheimer's Disease established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhann, et al., 1984). The intention was to provide uniform definitions for meaningful comparisons in theraputic trials regarding diagnosis and response to treatment. The criteria were also designed to be useful for comparative studies of AD patients in other types of investigations including case control studies, evaluation of new diagnostic laboratory tests, and clinicopathologic correlations. It was recognized that insufficient knowledge about the disease made the criteria tentative and subject to change after additional studies for validation had been performed.

Criteria of the NINCDS-ADRDA Work Group

In 1984, the NINCDS-ADRDA Work Group published inclusion/exclusion criteria for the categories of DEFINITE, PROBABLE and POSSIBLE Alzheimer's Disease. These are outlined

Table 1. NINCDS-ADRDA Criteria for the clinical diagnosis of Alzheimer's Disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

dementia established by clinical examination and documented by the Mini-Mental Test,(Folstein, et al., 1975) Blessed Dementia Scale,(Blessed, et al., 1968) or some similar examination, and confirmed by neuropsychological tests;

deficits in two or more areas of cognition;

progressive worsening of memory and other cognitive functions;

no disturbance of consciousness;

onset between ages 40 and 90, most often after age 65; and

absence of systemic disorders or other brain diseases that of themselves could account for the progressive deficits.

The diagnosis of PROBABLE Alzheimer's disease is supported by:

progressive deterioration of specific cognitive functions;

impaired activities of daily living;

family history of similar disorders; and

laboratory results of:
- normal lumbar puncture,
- normal pattern or nonspecific changes in EEG, and
- evidence of cerebral atrophy on CT with progression.

II. Clinical diagnosis of POSSIBLE Alzheimer's disease:

may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;

may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia.

III.Critieria for diagnosis of DEFINITE Alzheimer's disease are:

the clinical criteria for probable Alzheimer's disease and histopathologic evidence obtained from a biopsy or autopsy.

in Table 1. DEFINITE AD requires histological (autopsy or biopsy) confirmation and is therefore rarely useful in early diagnosis. The diagnosis of PROBABLE AD is made if there is a typical insidious onset of dementia with progression, and if there are no other diseases which could account for the deficits. Motor, sensory, or coordination deficits should not occur early in the disease. The diagnosis of POSSIBLE AD is utilized for cases where the presentation or course is somewhat aberrant. No prospective studies of unselected populations currently exist showing the relative percentages of each of these categories among AD patients. Theraputic trials generally require patients to have PROBABLE (or typical) AD.

Comparison of NINCDS-ADRDA Criteria with DSMIIIR Criteria for Primary Degenerative Dementia

Prior to the development of the NINCDS-ADRDA criteria, the most commonly used definitions were those of the current Diagnostic and Statistical Manual of Mental Disorders (DSMIIIR) for Primary Degenerative Dementia. While compatible, there are several notable differences in the NINCDS-ADRDA criteria:

1) At least two areas of cognition (unspecified) are required for diagnosis but, unlike the DSMIIIR, memory does not necessarily have to be one of them.

2) Intellectual dysfunction must be demonstrable on formal mental status/neuropsychological testing. Major cognitive processes that are impaired in AD are specified and examples of tests are provided for assessing each process. See Table 2.

3) Specific evidence of deterioration in social or occupational functioning is not required.

4) Other DSMIIIR diagnoses, such as depression, do not have to be excluded to make a diagnosis of AD.

The advantages and disadvantages of these changes will be discussed later.

Validity Studies: NINCDS-ADRDA Criteria

Clinicopathological Studies

Several clinicopathological series (Joachim, et al., 1988; Morris, et al.,1988; Tierney, et al., 1988; and Wade, et al., 1987) have recently reported excellent validity for NINCDS-ADRDA criteria. Morris, et al., (1988) noted 100% accuracy in a clinicopathological series of 26 post-mortem examinations from a longitudinally studied research cohort. Seventeen of these individuals were diagnosed when only 'mildly' demented. Martin, et al., (1987) performed cortical biopsies on 11 patients with PROBABLE AD and also reported

Table 2. Recommended Neuropsychological Evaluation (NINCDS-ADRDA) (McKhann, et al., 1984)

The major cognitive processes that are impaired in Alzheimer's disease, with examples of the kinds of tests used to assess these functions, include:

orientation to place and time, graded by a test such as the Mini-Mental State Examination (Folstein, et al., 1975);

memory evaluated by tests such as a free-recall test of concrete nouns, a 3-4 paired-associated learning test (verbal and nonverbal) by use of a recognition paradigm, the Recognition Span Test (Moss, 1984), and the Brown-Peterson Distractor Test (Peterson and Peterson, 1959; and Armak and Butlers, 1972);

language skills tested by examination of verbal fluency of the semantic or category type, with the examiner writing responses, and by other tests such as the Boston Naming Test (Kaplan, et al., 1978), the Boston Diagnostic Aphasia Examination (Goodlass and Kaplan, 1972), the Western Aphasia Test (Kertesz, 1979), and the Token Test (DeRenzi and Vignolo, 1962; Spellacy and Spreen, 1969) with Reporter's Test (DeReazi and Ferrare, 1978);

praxis evaluated by tests such as those in which the patient copies a drawing (cube, daisy, clock, or house) or performs the block design subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1981);

attention monitored by tests such as a reaction-time task or by the Continuous-Performance Test (Rosvold, et al., 1956);

visual perception studies by use of a variety of tasks, such as the Gollin Incomplete-Pictures Test (Gollin, 1960) and the Hooper Test (Hooper, 1958);

problem-solving skills determined by tests such as the Wisconsin Card Sorting Test (Milner, 1963) or the Poisoned Food Problem Task of Arenberg (Arenberg, 1968); and

social function, activities of daily living, and instrumental activity of daily living, assessed by methods similar to those described in the Philadelphia Geriatrics Center Forms (Lawton, et al., 1982).

100% diagnostic accuracy. The results of these studies however, cannot be generalized since they are small series of highly selected research subjects.

Joachim, et al., (1988) reported a larger series of 150 cases of clinically diagnosed Alzheimer's Disease donated to a brain research program over a three year period. Although diagnosed by over 100 physicians using unknown criteria, 87% of the cases fulfilled histological criteria for AD. While encouraging, these results suggest the relative ease of diagnosing end-stage AD even in the absence of specific criteria. The diagnostic challenge to the clinician and the researcher is to accurately diagnose AD in the early stages of this disease.

Clinical Studies

Huff, et al., (1987) studied the utility of cognitive deficits detected by neuropsychological tests for the clinical diagnosis of PROBABLE AD (NINCDS-ADRDA criteria). Of subjects who had 2 or more deficits on testing, 96% had clincally diagnosed AD (96% sensitivity). Of subjects with fewer deficits, 14% had been diagnosed as having AD (86% specificity). Follow-up testing after one year improved sensitivity to 100% and specificity to 89%. Of note, 19% of patients with clinically diagnosed AD had Mini-Mental State Examination (MMSE) scores of 27 or higher, well above the published criteria of below 24 as abnormal (Folstein, et al., 1985). Defining a MMSE score below 27 as abnormal, the sensitivity of the MMSE was 80%; specificity was 95%. Utilizing a cut-off score of 24, sensitivity dropped to 44%. Therefore the MMSE and other mental status tests are relatively insensitive to early cognitive changes.

The patients in this study were felt to be relatively 'early in the disease course' since they were required to give informed consent and be testable neuropsychologically. Twelve percent of patients had only one area of cognitive deficit on neuropsychological examination and would not have met NINCDS-ADRDA criteria. If DSM III criteria requiring memory loss had been used, 4% of patients diagnosed as AD would not have qualified. Hence, the earlier in the course of illness, the less likely they were to meet criteria.

Reliability Studies

In a multicenter study, Forette, et al., (1989) studied the reliability of clinical diagnosis using criteria comparable to NINCDS-ADRDA criteria. Diagnoses made at one year intervals were compared and found to have 95% reliability. Although this study did not attempt to establish validity, it showed sufficient reliability to allow comparison of groups at different centers for the purpose of research, including research on the efficacy of pharmacologic treatment.

Confounders for the Diagnosis of Early AD

Mental Status Scores/Functional Decline

As noted above, brief cognitive scales can be insensitive to mild degrees of cognitive impairment particularly in well-educated subjects. Although "cut-off" scores for dementia have been recommended for most of these tests, the experienced clinician frequently makes the diagnosis of dementia before these levels have been reached. For example, the published cut-off for the Mini-Mental State Examination (Folstein, et al., 1975) is <24. Most theraputic trials, however, permit entry of subjects with scores of 26 or less, recognizing the potential of patients with early disease to have such high scores. Similarly the Blessed IMC Test generally has a cut-off of >10 errors, but Katzman, et al., (1989) reported individuals with error scores >5 to have a high risk of subsequently developing dementia, suggesting early undetected disease for many of these subjects.

The requirement of the NINCDS-ADRDA criteria for formal testing to document cognitive deficits, while useful, may delay the diagnosis of some individuals. Morris and Fulling (1988) reported a case of early AD with pathological verification in which the majority of the subject's scores were within normal limits. A few scores had shown modest decline over time. One experienced clinician had been unable to detect dementia. Of prime importance in diagnosing this patient was his wife's report of functional decline: forgetting appointments, requiring help on tax preparation for the first time, and getting lost. Similarly, the study of Huff, et al., (1987) detected patients by history who did not yet demonstrate appropriate abnormalities on formal testing. Although the criteria established by the Work Group does not require evidence of functional decline, this information can often be invaluable in making early diagnosis, particularly when there has been no longitudinal follow-up.

Multiple Areas of Cognition

Dementia is a syndrome of global cognitive impairment; requiring the impairment of at least two areas of cognition would seem appropriate. Numerous patients, however, have been reported initially to have only one affected area such as memory (Neary, et al., 1986), language (Pogacar and Williams, 1984) or visuospatial ability (Crystal, et al., 1982). These individuals do not meet criteria for diagnosis until later in the course of their illness.

Depression

The relation of depression to dementia is complex. Early in Alzheimer's Disease, up to 1/4 of patients suffer significant depression. Many follow-up series of "pseudodementia" (dementia secondary to depressive symptoms) have reported the subsequent development of Alzheimer's Disease in up to half of the patients (McCallister and Price,

1982; Kral, 1983; and Reding, et al., 1985). The NINCDS-ADRDA criteria allows the diagnosis of AD in the presence of depression, but early in the illness, this distinction can be difficult to make.

Medications and Concurrent Illnesses

The distinction between dementia and delirium can be difficult to make. Delirium can occur in any person if the metabolic insult is sufficiently great, but older patients are more susceptible to this problem (Katzman, et al., 1988). Relatively minor intercurrent infections, such as urinary tract infections, can produce impaired cognition in the elderly patient. Similarly, toxic exposures (particularly medications) can create conditions easily confused with dementia. The older patient does not metabolize medications as well as their younger counterparts. For example, levels of sleeping medications can build up, leading to a persistant daytime confusion. These situations can present diagnostic difficulty for the clinician.

Determining AD in the Presence of Cerbrovascular Disease

The clinical diagnosis of mixed AD-multi-infarct dementia is problematic. No validated criteria currently exist for this frequent combination of illnesses. The Hachinski Ischemic Score (Hachinski, 1978) has been valuable in distinguishing AD from vascular dementia but cannot separate individuals with combined disease from the MID category (Molsa, et al., 1985). In the presence of cerebrovascular disease, the diagnosis of Alzheimer's disease cannot be made with reliability.

Early Dementia and Normal Aging

Perhaps the most difficult challenge in diagnosing dementia is distinguishing the memory and cognitive losses of early dementia from those of normal aging. On the one hand, it is well recognized that changes in memory accompany normal aging. On the other hand, 80% of patients with Alzheimer's Disease have insidious memory loss as their initial symptom. Thus far, these two types of memory loss have been indistinguishable. Longitudinal follow-up of these patients has been the only reliable means of determining the presence of a progressive dementia. Hence, the ability to make a diagnosis improves with multiple assessments demonstrating deterioration of specific cognitive abilities.

Summary

Clinical investigations of Alzheimer's Disease are dependent on diagnostic accuracy. The criteria developed by the NINCDS-ADRDA Work Group were in response to a need for specific and accurate inclusion criteria to improve the confident identification of subjects with AD. These criteria have contributed greatly by allowing the identification of a

homogeneous group of patients with probable Alzheimer's Disease who can be evaluated in theraputic trials. There are, however, numerous patients with Alzheimer's Disease who do not meet these criteria. Determining the presence of early dementia is a greater challenge than determining the condition producing a dementia. In particular, differentiating early dementia from depression or the memory loss of normal aging remains difficult. A peripheral marker for the diagnosis of early Alzheimer's Disease would be extremely useful and remains a high research priority.

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