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Misdiagnosis of Alzheimer's Disease

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(Abstract) The purpose of this report is to discuss the implications of the misdiagnosis of Alzheimer's Disease (AD). One of the major barriers to the accurate diagnosis of AD is that AD is a clinically-

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defined disease with no medical evidence. Since there are no known biochemical markers for AD without postmortem confirmation, dependence on clinical criteria has resulted in inaccurate diagnosis. With the absence of universally accepted AD mental test and the definitional ambiguity of AD, a mismatch between clinical performances and autopsy confirmation is frequently reported. To achieve a high percentage of accurate diagnoses of AD, more rigorous research is needed to develop a valid mental test appropriate for AD as well as universally accepted diagnostic criteria.

I. Introduction

As the numbers and proportion of older people increase, greater numbers of individuals will be at risk for dementia. One of the most common dementias, Alzheimer's Disease (AD), is found misdiagnosed at an alarming percentage of 30% and over 50% (Somerfield, Weisman, Ury, Chase, & Folstein, 1991). Although AD is currently known as untreatable, other forms of curable dementias can be detected at an early stage to provide appropriate medical and behavioral treatments. Despite the importance of differentiating AD from other forms of treatable dementias, the incidence of misdiagnosis has been routinely reported (Katzman, Lasker, & Bernstein, 1988; Somerfield et al., 1991).

In part, the misdiagnosis of AD is attributable to under-utilization of available diagnostic criteria. Two most frequently used diagnostic criteria, DSM-IV and NINCDS-ADRDA, are not used very frequently. In the U.S. a dementia patient with poor cognitive performance scores is determined to have AD after eliminating other possible medical, neurological, and psychiatric causes. Technically, patients with AD can only be diagnosed after

a brain autopsy. In short, AD is a clinically-defined disease with no medical evidence.

With the absence of medical proof, clinical diagnosis has always invited misdiagnoses of AD (Kendell, 1974; Nott & Fleminger, 1975; Risse, Raskind, Nochlin, Sumi, Lampe, & Bird, 1990; Ron, Toone, Garralda, & Lishman, 1979;). Misdiagnosis of AD becomes clear when there is a mismatch between the clinical assessment of a patient and underlying brain abnormalities at autopsy. Since no single laboratory test is available for the diagnosis of AD symptoms, the purpose of laboratory evaluation is to identify other treatable conditions that may imitate AD. Although brief cognitive tests have been used to detect the degree and progress of AD patients' cognitive impairments, performance scores also depend on other factors such as socioeconomic status and educational attainment (Katzman, Terry, DeTeresa, Brown, Davies, Fuld, Renbing & Peck, 1988).

The purpose of the paper is to discuss the implications of the misdiagnosis of AD. This paper concludes that better criteria of AD and development of appropriate mental test for AD will help care providers to set up appropriate cares according to the progress of the disease.

II. Definition and Diagnostic Criteria of Alzheimer's Disease

One of the most common dementias in the elderly is AD which accounts for approximately 60% of all dementing illnesses (Kane, Ouslander & Abrass, 1989; Katzman et al., 1988). The neuropathological hallmark of AD is neurofibrillary tangles and neuritic plaques (Terry and Katzman, 1983). About 5% of the population over 65 may suffer from AD. AD has an insidious onset, a gradual decline, and progressive impairments of daily activities in addition

to all conditions of other dementias. In the literature, AD is commonly used to refer to all cases regardless of age of onset. However, it is sometimes reserved for neuropathologically confirmed cases, with the term dementia of the Alzheimer type being used for those where the diagnosis has been on clinical grounds alone (Jorm, 1990). In this paper, the term AD will be used to avoid any confusion raised by the terminology: AD broadly comprises dementia with clinical symptoms of AD being defined by the DSM IV criteria, regardless of age of onset including both pre- and post-senile dementia of the Alzheimer type (SDAT).

The two major standard criteria have been widely used for the diagnoses of AD: the DSM-IV and NINCDS-ADRDA. More recognized diagnostic criteria for dementia is the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 1994). In this revised manual, the dementia is described as the patient having impairment of short- and long-term memory in addition to abnormalities in at least one of the areas of mental function: abstract thinking, judgment, language, praxis, visual recognition, constructional abilities, or personality. Also, these disturbances must be severe enough to interfere with work, social activities, or relationships with others.

On the other hand, the NINCDS-ADRDA criteria categorizes AD into three stages; probable, possible, and definitive (McKhann, Drachman, Folstein, Katzman, Price & Stadlan, 1984). The NINCDS-ADRDA criteria for probable AD are similar to the DSM IV criteria, but are more detailed. Possible AD is defined as patients with an atypical course, finding, or coexistent disease. Definite AD diagnosis is made when it is confirmed with brain biopsy or autopsy. These categorized criteria are preferred over the DSM IV criteria, primarily it offers a more systematic approach.

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Although the accuracy of clinical diagnosis has been greatly improved by virtue of NINCDS-ADRDA criteria, the relatively high degree of correct diagnoses may be the inclusion and exclusion features of the criteria (Katzman et al., 1988; Morris, McKeel, Fulling, Torack, & Berg, 1988). Morris et al. (1988) reported their 100% clinical accuracy using the NINCDS-ADRDA criteria. The 28 subjects (26 AD, 2 control) were selected from the 106 AD and 83 control subjects. All 26 AD subjects were identified as AD patients after autopsy. Seventeen of the 26 subjects was diagnosed clinically mild dementia. However, the results were affected by the characteristic features of the NINCDS-ADRDA criteria which applies rigid inclusion and exclusion criteria to enhance accuracy. Due to these strict criteria for participating in the clinical assessment, many persons ruled out of this experiment entirely. That is, subjects were preselected to be very likely to have AD. If they had included the AD-possible population as a whole, their diagnostic accuracy probably would have fallen below 100% accuracy.

In one report, NINCDS-ADRDA criteria reported a diagnostic accuracy rate of 72%. Patients who had mixed dementia with a 'degree' of AD were excluded. By strict application of inclusive and exclusive clinical criteria, they were not able to define all patients with pure presenile AD. Additionally, they admitted that if patients with mixed dementia had been included, the accuracy rate would have been even lower. NINCDS-ADRDA criteria illustrate that when restrictive criteria is used for the diagnosis of AD, a high degree of postmortem confirmation would be expected. Likewise, a less demanding diagnostic approach would lead to fewer confirmation upon brain autopsy. Future work on diagnostic consensus between the two competing criteria is needed.

III. Discrepancy in Clinical Diagnosis and Brain Autopsy

According to a survey done by Somerfield et al. (1991), over 75% of physicians did not use either DSM or NINCDS-ADRDA diagnostic criteria, and 42% of physicians did not perform any mental status tests themselves. In a similar report, an alarming 37% to 80% of demented elders were not examined for their cognitive impairments by physicians (Knights and Folstein, 1988), even though it would have taken only a few minutes to determine the elders' cognitive abilities. Gall, Reichel, and Anderson (1988) indicated that 26 out of 136 nursing home patients with a diagnosis of senile dementia actually had treatable disorders. They concluded that an adequate mental status examination should be a part of routine admission procedures to differentiate the possible causes of dementias. Instead of prematurely assuming that any signs of dementia will eventually lead to AD, careful differential diagnostic practices will avert misdiagnosis.

The definitive diagnosis of AD is determined by microscopic examination of the presence of neuritic plaques and neurofibrillary tangles. One source of misdiagnosis is that brain lesions appear in people with AD as well as older people without AD (Blessed, Tomlinson, & Roth, 1968; Katzman et al., 1988). Although Blessed et al. (1968) showed that significant brain damage was observed in AD patients, these types of brain lesions were also found in brain autopsies of the cognitively normal elderly.

In a similar study, Katzman et al. (1988) reported that cognitive test scores and neurodegenerative markers were not meaningfully associated. Katzman and his colleague (1988) administered a brief cognitive test to 137 nursing home residents. After their death, autopsies were performed in order to count number of cells having neuritic plaques and neurofibrillary tangles. Surprisingly enough,

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ten out of twenty-nine individuals who were not screened through the mental test had brain lesions responsible for AD. Perplexed by the high discrepancy rate, Katzman and his colleagues concluded that cognitive-intact individuals who were found to have neuropathological markers in their brains might have had "incipient AD", but they did not show it behaviorally because of "greater brain reserve." On the other hand, a number of clinically demented subjects did not show any evidence of AD-related brain pathology. Thus, future research will clearly answer why clinical diagnoses are not confirmed by brain autopsies at an acceptable level.

To further prevent misdiagnoses of AD, AD should be clearly distinguished from normal aging. However, a study suggests that high mortality rate among AD patients' could be a result of aging process. When age is statistically controlled, the differential longevity of demented and nondemented persons is diminished significantly. Why do some people with brain abnormalities not develop cognitive impairments, whereas others show clinical and behavioral deficits of the AD syndrome with no underlying brain disorders? Since the brain inevitably degenerates with advancing age, AD can be thought of as exaggerated form of normal aging. Further investigation should be spurred in this area. Otherwise, AD may be recognized as an inevitable consequence of aging, rather than a secondary result of aging.

If a person's behavior is suspected of having AD, a series list of medical examinations involve the following : prior medical history, physical examination, psychiatric evaluation, laboratory investigation, neurologic examination, and mental status examination. No consensus has been reached among primary care providers about the best procedure of excluding AD-mimic diseases. Several dementia specialized clinics across the U.S. might initiate a thorough differential work-up, but the vast majority of

hospitals simply rely on routine processes such as brief mental testing and a CT scan. Regardless of what kind of testing patients receive, it is important to remember that the diagnostic work-up does not pinpoint AD itself, but it serves to eliminate the possibility of other conditions that could be causing the patient's dementia.

IV. Problems of Testing and Clinical Definition of AD

A large number of assessment tools have been invented by geriatric clinicians to measure the degree of cognitive impairments (Blessed et al., 1968; Folstein, Folstein, & McHugh, 1975; Hasegawa 1983; Jacobs, Bernhard, Delgado, & Strain, 1977; Kahn, Goldfarb, Pollack, & Peck, 1960; Mattis, 1989; Pattie, & Gilleard, 1975; Pfeiffer, 1975). The Mini-Mental State Examination (MMSE) created by Folstein et al. (1975) has gained the most popularity among other tests. It has an excellent test-retest reliability (Cockrell, & Folstein, 1988). The MMSE is a 30-item cognitive screening instrument which assesses orientation to time and place, attention/concentration, language, constructional ability, and immediate and delayed recall. However, even the most popular test, the MMSE, is cautioned that it may not be appropriate for individuals with a low educational attainment, different cultural backgrounds, and a poor command of English (Katzman et al., 1988).

While a large number of mental screening tests have been developed, consensus is lacking about the use of screening tests for AD. Four similar mental tests for senile dementia were analyzed to compare potential differences; AMTS (Abbreviated Mental Test Score), MMSE, MSQ (Mental State Questionnaire), and SPMSQ (Short Portable MSQ) (Hooijer, Dinkgreve, Jonker, &

Lindeboom, 1992). These tests were administered and their performance was compared. The results did not show that one test was superior in predicting the diagnosis of dementia. There were only slight differences between the 4 tests on detecting mild to advanced cases of dementia. Currently, more research needs to focus on how to maintain the mini-mental test that is appropriate for AD patients.

Problems arise when clinicians only use standardized mental status examinations. Testing performance to determine the degree of the patient's cognitive impairment could be affected by several elements: sex, age, education, culture, and socioeconomic as well as other biases. Koivisto, Helkala, Reinikainen, and Hanninen (1992) administered a battery of neuropsychological tests, including the MMSE to screen dementia. The difference between various education groups (less than 3 yrs, 4-6 yrs, more than 7 yrs.) was statistically significant, even after adjustment for the effect of age.

Another obstacle to a correct diagnosis of AD is the resemblance of AD and MID (multi-infarct dementia) which is another common form of dementia. Unlike an insidious onset with progressive course characteristic of AD, MID is described as "typically abrupt onset" and a "step-wise deteriorating course." Clinicians rely on their own judgements to determine whether the patient is MID or AD according to suggested criteria. Problems arise when patients belong neither criteria or have overlapping behavioral deficits of either area. One study shows that some patients do not fit into either criteria. Nussbaum, Treves, and Korczyn (1992) obtained 98 patients who met the DSM criteria of dementia. When they were broken down into different type of dementia suggested by the DSM criteria, 53 patients did not belong to either area. are also supported by neuropathological studies. Using the DSM criteria, Fischer, Gatterer, Marterer,

Simanyi, and Danielczyk (1990) reported that a number of patients had overlapping symptoms of AD and MID. Of the MID patients, 29% showed a clinical feature of AD such as insidious onset with progressive course.

V. Suggestions for Accurate Diagnosis

In order to achieve accurate diagnosis, clinicians need to have universally approved criteria. Currently, no consensus has been reached about how to assess AD. Smith, Byrne, Arie, and Lilley (1992) reported that a majority of clinicians did not utilize available standard guideline such as the MMSE and the NINCDS-ADRDA. Only 11% of respondents used the NINCDS-ADRDA criteria. Compared to the MMSE, the NINCDS-ADRDA criteria is more stringent which may cause under-diagnosis by excluding potential AD patients. The development of universal criteria is still in the beginning stages.

Furthermore, although the MMSE is widely applied to identify AD, it is not effective in discriminating AD from other kinds of dementia. there is no agreement on the use of tests for mental screening. A consensus needs to be reached about the use of mental testing tools.

As previously mentioned, one element that prevents proper diagnosis is the patients' educational level. People with fewer years of schooling are also known to have poorer performance scores on most mental status exams (Berkman, 1986). To correctly determine the degree and stage of dementia, a few points could be added to the scores of less educated people whereas a few points could be subtracted from the scores of higher educated people. To predict dementia with the brief mental status exams, other predictors such as socioeconomic status and education should be taken into

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consideration. Ideally, instruments should be less sensitive to educational differences and more sensitive to changes associated with the dementia process (Berkman, 1986).

To enhance the evaluation, the family members' behavioral observations reported over the last few months and years could be sought out. These observations could add to the information used by the geriatrician to diagnose the elder.

One of problems with misdiagnoses of AD is that physicians reported that they did not use formal mental status such as the MMSE and a large number of primary care physicians did not apply standardized criteria (e.g., DSM IV and NINCDS-ADRDA). Although the perfect diagnosis of AD remains difficult, an adequate diagnosis of different types of dementias will help caregivers and health professionals manage demented patients. Good documentation of mental functioning is useful for identifying the presence and severity of cognitive impairments and for tracking the progression of dementia over time. Although researchers have not yet identified the cause of AD, research has already provided much useful information about the characteristic features of AD and how to provide care for AD patients.

Prior to the discovery of AD, symptoms associated with AD had been considered manifestations of senility and accepted as an unavoidable part of normal aging. With the successful identification of abnormal brain structures in patients of AD, acceptance of AD as "normal aging" has declined. However, clinical diagnosis of AD has been a major source of misdiagnosis as well. Although the standardization of diagnostic criteria for AD (DSM IV and NINCDS-ADRDA) has significantly reduced error rates, no general consensus about diagnostic criteria has been achieved. Also, despite the importance of valid and reliable psychometric tests to assess AD, no psychometric tools are found to be suitable for measuring

adequately AD. Although medical treatments of AD cannot be achieved in a foreseeable future, the accurate clinical diagnosis of the disease will help family and care providers to meet the needs of AD patients.

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