REVIEW ARTICLE

Alzheimer's disease: new guidelines for diagnosis

Doença de Alzheimer: novas diretrizes para o diagnóstico

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ABSTRACT

For 27 years, the clinical diagnosis of Alzheimer's disease was based on the criteria established in 1984 by the National Institute of Neurological and Communicative Disorders and Strokes (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA). However, over the years, scientific advances allowed a better understanding of its pathophysiology as well as about other forms of dementia - culminating in the need for a revision of the old criteria. Thus, in 2011, four articles with new recommendations from the NINCDS-ADRDA were published. The main changes in the new guidelines involve the identification of non-dementia stages for disease and incorporation of biomarkers.

Key words: Alzheimer's Disease; Dementia; Neuropsychiatric; Aging.

RESUMO

Durante 27 anos, o diagnóstico clínico da doença de Alzheimer foi baseado nos critérios feitos, em 1984, pela National Institute of Neurological and Communicative Disorders and Strokes (NINCDS) e pelo Alzheimer's Disease and Related Disorders Association (ADRDA). Contudo, com o passar dos anos, os avanços científicos permitiram melhor compreensão da sua fisiopatologia, bem como melhor entendimento sobre as outras formas de demência - que culminaram na necessidade de revisão dos antigos critérios. Por isso, em 2011 foram publicados quatro artigos com novas recomendações da NINCDS-ADRDA. As principais mudanças nas novas diretrizes envolvem a identificação de estágios não demenciais para doença e a incorporação dos biomarcadores.

Palavras-chave: *Doença de Alzheimer; Demência; Neuropsiquiatria; Envelhecimento.*

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INTRODUCTION

In the current Brazilian context, the relevance of population aging and its consequences are unquestionable. Neuropsychiatric disorders are evident - in increasing progression - among the diseases that significantly contribute to morbidity and mortality in the Brazilian population.[1] This is revealed by the increased mortality by dementia standardized by age, which in 1996 was 1.8 per 100,000 and in 2007 it was 7.0 per 100.000.[1] The incidence of death due to Alzheimer's disease (AD) increased significantly, approximately 66% between 2000 and 2008.[2]

Dementias are often degenerative and progressive morbidities causing bio-psychosocial disorders.[3] The most common types of dementia are AD and vascular dementia, followed by dementia with Lewy's bodies and frontotemporal dementia.[4] AD represents more than 50% of dementia cases, although in many situations it is associ-

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ated with another dementia. The cognitive manifestations in AD culminate in progressive impairment that lead to disability and even death.[4,5]

Herrera[6] evaluated 1,660 people, aged over 65 years, and identified 118 cases of dementia (7.1%), 54.1% as AD. In the United States, AD is the fifth most prevalent cause of death in people over 65 years old.[2] It affects approximately 1.5% and 30% of people near 65 years old and 80 years old, respectively.[7] The current risk of 65 years old individuals developing AD is approximately 10.5% [8]

The annual rate of AD increases significantly with increasing age. In the age groups 65 to 74; 75 to 84; and over 84 years old it is approximately 53; 170; and 231 new cases per year in 1,000 individuals, respectively.[2]

It is estimated that one in seven patients with AD lives alone,[2] exposed to greater risks such as inadequate self-care, malnutrition, non-adherence to medical conditions, falls and accidental deaths, when compared to the risks related to patients with AD living with caregivers.[2] These data reinforce the value of bio-psychosocial support and social strategies to improve the quality of life of patients with AD.

In AD, the hippocampal formation is the initially injured brain region; hippocampus, subiculum, and entorhinal cortex; mainly responsible for memory. The deterioration of hippocampal formation in advanced stages of AD reaches up to 60%. Associative cortical areas are subsequently affected by alterations in language, executive function, visuospatial skills, and social behavior. The primary cortical areas responsible for motricity are usually preserved until its later stages. Therefore, the apparent initial symptomatology is constituted of behavioral and cognitive disorders and not related to motricity.[4]

Atrophy of cortical regions is observed in neuroimaging and autopsy examinations, especially in the medial part of the temporal lobe and areas of the frontal and parietal lobes association. The brain weight in an autopsy examination is reduced by about 15 to 35%. On microscopic examination, the nerve tissue shows signs of normal aging but with increased intensity. There is a reduction in number of neurons, dendritic branching, and synapses besides the formation of senile plaques and neurofibrillary tangles.[9]

The histopathology of AD suggests the extracellular deposition of the insoluble β-amyloid protein forming senile plaques with the toxic effect on neurons. This accumulation occurs due to mutations in genes of enzymes that cleave the amyloid precursor protein to produce β-amyloid. The anatomopathology also identifies neurofibrillary tangles caused by a mutation in the Tau protein gene, a cytoskeletal component and responsible for the formation and maintenance of axonal processes and interneuronal contacts, leading to the neuronal lesion. In this mutation, the Tau protein is phosphorylated in excess, which reduces its affinity for tubulin, the microtubule protein, leading to microtubule degradation. The severity of AD is more related to neurofibrillary tangles than senile plaques.[3,10]

The growing importance of dementias as a prevalent human disease, associated with current scientific advances in understanding them, has initiated discussions about the possibility to revise and improve the diagnostic criteria for mild cognitive impairment, in dementia and AD.

LITERATURE REVIEW

Guidelines for the diagnosis

The diagnosis of dementia in Brazil follows the criteria from the Mental Illness Diagnostic and Statistical Manual of the American Psychiatry Association IV (DSM-IV). However, the diagnosis of AD is based on the guidelines proposed by the National Institute of Neurological and Communicative Disorders and Strokes (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA).[11] The NINCDS-ADRDA criteria for AD were mentioned in 71% of Brazilian studies and those from the DSM III-R and DSM IV in 21 and 29% of articles, respectively.[11]

For 27 years, the diagnosis of AD was based on the criteria established in 1984 by McKhann et al. of the National Institute on Aging and Alzheimer's Association (NINCDS-ADRDA), with sensitivity of 81.5% and specificity of 70%.[12] However, over time, it became necessary to include the new advances in AD research that changed the understanding of the disease. Several studies about genetic discoveries, examinations (MRI, PET, cerebrospinal fluid study), and AD disease have emerged in this period, which led to the need for a review of the old criteria.[13,14]

Thus, in 2009, 40 researchers and clinicians from around the world began the analysis of the original criteria to establish the need for their change; and in 2011, new recommendations from the NIN-CDS-ADRDA emerged on how to establish the diagnosis of AD.[13]

New criteria: what differs with regard to the criteria from 1987

The 1984 criteria were mainly based on clinical judgment regarding symptoms presented by the patient; considering reports from patients, family and friends; results on cognitive examinations, and neurological evaluation.[2] The new criteria include the diagnostic aid from imaging and biomarkers exams.

The main changes in the new guidelines for the diagnosis of AD involve the identification of three stages: pre-clinical, mild cognitive impairment, and dementia; the first stage being asymptomatic.[2] In addition, the criteria from 1984 included the presence of mnemonic decline for diagnosis. The new criteria state that the evidence of memory impairment is not necessary for diagnosis. In the old criteria, AD was diagnosed only when there was dementia; in the current criteria, the first two phases without dementia were included.

The preclinical stage corresponds to the asymptomatic stage of AD that can begin years or decades before the onset of dementia symptoms.[15] Although it may show - in the future - considerable relevance for early diagnosis of AD, currently, it does not have clinical utility but importance for research.[12,15]

The mild cognitive impairment stage (CCL) was created to include individuals with deficits in one or more cognitive domains – executive function, memory, visuospatial skills, attention or language – who however, remain independent for performing daily activities and did not meet the criteria for the diagnosis of dementia.[12-17]

The following terminologies for the diagnosis of dementia associated with AD were proposed in order to classify affected individuals in the best possible way: probable dementia due to AD, possible dementia due to AD, and probable or possible dementia due to AD with evidence of the pathophysiological process of the disease. The first two contain criteria for the clinical diagnosis, which can already be used by physicians; and the last classification, which involves evidence of the pathophysiological process, is still in the research stage.[12]

When the first criteria were published, there was no information on the genetics of AD. Genetic alterations in AD patients, including the ones arising from mutations in genes encoding the precursor protein of β-amyloid, apolipoprotein E and presenilins 1 and 2, were identified in recent years.[18] The apolipoprotein polymorphism is the most common change found in patients with AD. This protein participates in cholesterol transportation to nerve cells helping to keep membranes and myelins. One of the alleles of the gene, called ε4, produces a less efficient protein, which increases the number of senile plaques and cholinergic deficiency.[3,12]

Biomarkers are molecules with measurable characteristics that indicate a biological or pathogenic process, or pharmacological response to therapeutic interventions.[12,19] The AD biomarkers detect the β-amyloid peptide (Aβ42) and Tau protein, with reduction and increase, respectively, of these substances in the cerebrospinal fluid compared to a normal elderly person. In addition to liquor analysis, the biomarkers can be used in neuroimaging exams.[12,19]

Patients who present these biomarkers in the CCL stage have 17 times more chances of developing AD than those without alterations in the patterns of these liquor markers.[20] Bouwman[21] found that 94% of patients with altered biomarkers detected in the liquor, and with atrophy of the medial temporal lobe on MRI developed AD.[21]

The use of biomarkers is still under research; however, it is possible to outline a promising future in the diagnosis of AD, especially in the early stages. Its clinical use is not yet indicated due to the lack of standardization between different laboratories, lack of definitions on cut-off points, and difficulty of accessing this new technology.[22]

In addition to these changes, the new guidelines recognize that the neuropathological lesions occur decades before the appearance of symptoms. The age group affected by this disease increased, now with the recognition of patients under 40 and over 90 years of age.[12] The neuropathological criteria for AD were reviewed in 2012 because those published in 1997 were considered outdated.[23] The main changes involved, above all, recognition of neuropathological alterations in individuals without dementia.[23]

When the first criteria were established, there was no knowledge to determine other forms of dementia affecting the elderly population, such as Lewy's bodies, vascular and frontotemporal dementias. In the new criteria, these other forms of dementia are considered in the diagnosis of AD.[12] Therefore, the diagnose of dementia associated with AD and classification as probable dementia associated with AD, requires that the diagnostic criteria for other forms of dementia are not met.[12] However, if the diagnostic cri-

teria of other forms of dementia are met, it is still possible to diagnose dementia associated with AD but it would be classified as possible dementia due to AD.[12] This happens because considering the existence of associated forms of dementias is necessary.

With regard to memory impairment, it is important to note that the decline in this cognitive domain is no longer an indispensable factor for the diagnosis of AD, other forms of manifestations can be verified such as posterior cortical atrophy and syndrome of primary aphasia.[12] The non-amnestic presentations include decline in the domains of language, visuospatial abilities, and executive functions.[12]

Whitwell et al..[14] analyzed the three neuropathological subtypes of AD: typical, with a predominance of limbic impairment, and with predominance cortical impairment. In 78% of patients with typical AD after death diagnosis, and 94% of patients with AD with limbic impairment predominance, there were initial clinical manifestations of AD before death with cognitive memory impairment. However, only 42% of patients with neuropathological diagnosis of AD with predominant cortical impairment and less limbic impairment showed memory impairment as the initial clinical manifestation.[14]

Dementia diagnosis

The diagnosis of dementia established by DSM-IV considers the need for memory impairment associated with at least one other cognitive decline (language, gnosis, praxis, or executive functions) affecting the daily activities of patients.[11] However, lately, with the determination of other forms of dementia without amnesic impairment in its early stages, it was necessary that the NINCDS-ADRDA would change the wording of dementia in the new guidelines published in 2011.[12] The current definition states that the patient must present two of the following affected areas: decline of memory, visuospatial skills, reasoning, management of complex tasks, judgment, and communication, and changes in personality and behavior, without the requirement that one of them is memory impairment.[12,17]

The diagnosis of dementia requires that the patient presents undermined functional capacity at work or usual activities, in addition to decline in at least two of the cognitive domains considered, as well as reduction of his former level of functionality and performance.[12,17] It is also important to consider that cognitive impairment is detected by considering the patient's and his informant's reports, combined with objective cognitive tests. It is also important to exclude delirium or some major mental illness.[12,17]

Dementia diagnosis associated with AD

Probable dementia associated with AD

The diagnosis of probable dementia associated with AD is fundamentally performed through reports or careful observation of cognitive impairment, together with the exclusion of other forms of dementia or other diseases resulting in cognitive impairment.[12] Diagnostic confirmation can only be achieved by the histopathological examination of neural tissue for the evaluation of senile plaques and neurofibrillary zones obtained from biopsy or necropcy[12,17] Because obtaining this material is difficult in living patients, in most cases the confirmation of AD can only occur after death. The reliability of this diagnosis can be increased with positive biomarkers, evidence of cognitive impairment, and typical genetic mutations for AD.[12,17]

The disease should begin insidiously (gradual, taking months or years), with noticeable cognitive deterioration. The amnestic presentation is the most common form, with recent memory impairment and incapacity of learning new facts. There can also be problems in the non-amnestic presentation: language, visuospatial abilities, and executive functions;[12,17] being necessary to exclude cerebrovascular diseases; dementia with Lewy's bodies; frontotemporal dementia; other diseases; or the use of any drug that affects cognition.[12,15]

Possible dementia associated with AD

The diagnosis of possible dementia associated with Alzheimer's disease is achieved when there is uncertainty about the evolution of cognitive decline in the patient, when the course of the disease is abnormal, or there is any illness or use of medications that affect cognition, such as fulfilled diagnostic criteria for other forms of dementia, or when the onset occurs suddenly and not gradually.[12,17]

The evidence of a definitive diagnosis of dementia associated with AD occurs only by the histopath-

ological study of cerebral tissue through biopsy or necropsy with the finding of neurofibrillary tangles and senile plaques above the normal level expected during aging.[12,17]

Probable or possible dementia associated with AD with evidence of the pathophysiological process of AD

The diagnostic certainty that the clinical dementia is associated with AD[12] depends on the clinical criteria for probable dementia associated with AD and biomarkers indicating its pathophysiological process.

People who meet the diagnostic criteria for other forms of dementia, but have biomarkers for the pathophysiology of AD or evidence of neuropathological alterations, can receive the diagnosis of possible dementia associated with AD, with the evidence of pathophysiological process. In this case, the identification of both types of biomarkers is necessary.[12] It is important to note that this diagnosis does not exclude the possibility that other pathophysiological processes are also present.[12]

Mild cognitive impairment (CCL)

Patients with CCL are in transition between normal aging and dementia. The new criteria from NINCDS-ADRDA characterize CCL by the decline in one or more cognitive domains, not necessarily in the mnemonic domain, however, without losing the autonomy for daily functional activities. Slowness and difficulty for complex activities might occur, such as paying for purchases, preparing meals, but without the dependence manifested in dementia.[17,22]

It is estimated that 10 to 20% of people over 65 years old have CCL;[2] and over 15% of those who are concerned about the symptoms of CCL and seek medical care will develop dementia every year.[2] From this estimative, it is possible to state that half the people who seek medical care complaining of CCL symptoms will develop dementia within three to four years.[2]

Morris (2001)[24] followed up 277 people with average age of 76.9 years during nine years and six months. He reported that out of 25 patients with CCL submitted to the autopsy, 96% showed evidence of dementia and 84% of AD. He associated CCL to the early stage of AD and found that this diagnosis should be considered as soon as possible with the patient and his family, so that they can prepare for a possible progression to the dementia stage at the moment that the patient still has enough cognitive ability to make decisions.[24]

Morris (2012) reported his study results following the new criteria[25] with the evaluation of more than 17 000 people with an average age of 75 years between 2005 and 2011. He found that most patients currently diagnosed with the very attenuated form of AD (99.8%) could be classified as having CCL.[25] He reinforces the premise that there is no difference between the early stages of AD and mild cognitive impairment.[25]

Pre-clinical Alzheimer's disease

It is undeniable that, according to the new NINCDS-ADRDA guidelines on the recognition that AD does not begin with the onset of symptoms, the understanding of this disease has changed significantly. The typical pathological lesions of AD appear years, if not decades, before the onset of symptoms.[12,13] Recent advances in neuroimaging research, liquor studies, and other studies on biomarkers allow predicting the disease process before the onset of clinical manifestations.[12,13,22] The use of pre-clinical diagnosis is still under research, however, current studies show positive results,[12,13,22] representing great challenges for application in the clinical practice to standardize the values of biomarkers.[22]

This stage is divided into three phases:[15,22]

1. **cerebral asymptomatic amyloidosis phase:** there is evidence of accumulation of β-amyloid peptide in the imaging examination through positron emission tomography (PET) and reduction in the liquor. Neurological or cognitive alterations are not observed;[15,22]
2. **amyloid positive phase, with evidence of synaptic dysfunction and/or onset of neurodegeneration:** there are positive signs of amyloid biomarkers and increased Tau protein in the liquor, with a decrease in flurodeoxglucosis 18f (FDG) in PET indicating hypometabolism related to synaptic dysfunction. Hippocampal atrophy can be detected by MRI. There is evidence that synaptic dysfunction studied by neuroimaging exams, such as FDG-PET, can be perceived before neuronal volume loss;[15,22]
3. **amyloid positive phase, with neurodegeneration and subtle cognitive decline:** this phase

marks the limits between the pre-clinical status and CCL. The patient presents a subtle cognitive decline, however, still remains in the normal range of cognitive tests. The patient still does not present the criteria to be classified as CCL.[15,22]

Unlikely dementia associated with AD

The diagnosis of unlikely dementia associated with AD occurs when the clinical criteria for AD are not met.[12] Unlikely dementia associated with AD is considered, regardless of meeting the clinical criteria for probable or possible dementia associated with this disease, when there is sufficient evidence of an alternative diagnosis such as dementia associated with the human immunodeficiency virus or Huntington disease, or when both categories of biomarkers are negative, both for beta-amyloid proteins and neuronal lesions.[12]

DISCUSSION AND COMMENTS

The limitation in the use of biomarkers, which mainly corresponds to a lack of experience in their application, currently partially restricts the pragmatic application of new knowledge about AD. However, this restriction does not limit the increased reliability of diagnosis according to the new criteria compared to the old criteria.

It is important to recognize that relevant updates on clinical criteria were also established raising the reliability of diagnostic criteria, which are still based on the clinical and not laboratory approach.

CONCLUSION

The latest advances in AD studies bring great opportunities to enrich knowledge about this disease improving diagnosis and understanding. The use of biomarkers and new knowledge about the pathophysiology of AD promises to contribute in the future to the early diagnosis and possibilities of effective therapeutic interventions.

However, it is necessary to consider currently the benefits of an early diagnosis. It is also important to recognize the potential adversities that may occur with early diagnosis such as increased risk of suicide, problems with employers, and precipitous decrease in the quality of life of patients with AD in the preclinical stage – since there are no effective interventions ensuring disease's non-progression into the dementia stage.

The importance of AD among the diseases that affect the elderly is undeniable, especially due to its increasing prevalence favored by the rapid demographic transition, which has been observed worldwide and especially in Brazil. Dementia compromises the well-being, quality of life, and morbidity and mortality in the elderly population, and therefore, every effort must be placed in researching, knowing, and better understanding how it occurs with the aim of improving the quality of life of patients, especially in elderly people.

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