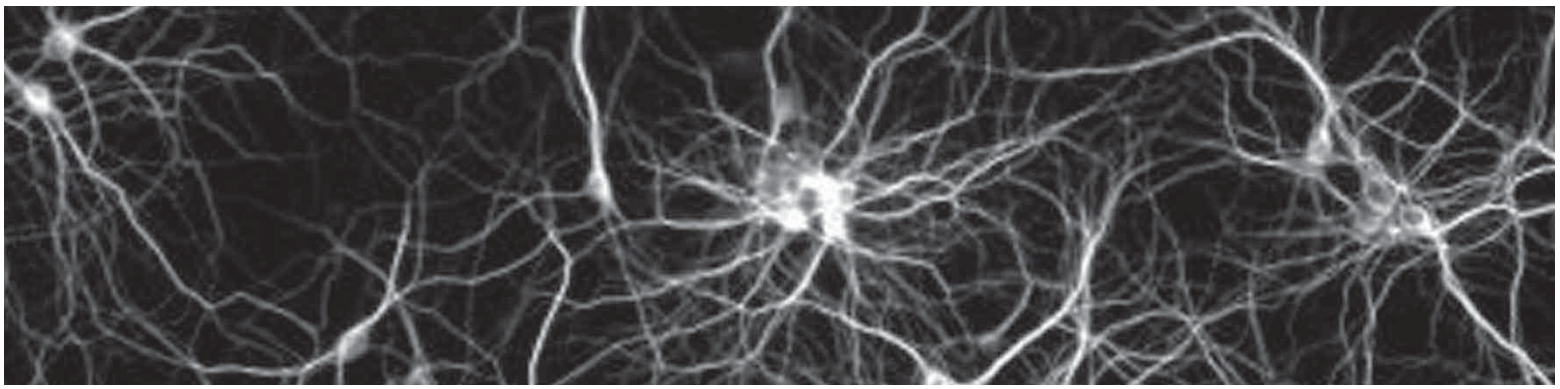

New diagnostic criteria for Alzheimer's disease

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ABSTRACT – The goals of this review were to investigate the previously published criteria for the diagnosis of Alzheimer's dementia which are used in clinical practice. Today, we are able to explore environmental factors and genetic predisposition for developing Alzheimer's dementia, to detect biomarkers in cerebrospinal fluid, to find neuroimaging characteristics of the disease, and eventually to notice a number of clinical manifestations of the pre-dementia and dementia phase. The criteria for the diagnosis of probable Alzheimer's dementia have been based on the National Institute on Aging and the Alzheimer's Association (NIA-AA) diagnostic criteria from 2011 and The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria from 2013, and they appear to have similar accuracy in clinical practice. Further research is needed to define more specific and sensitive diagnostic criteria and more effective treatment.

Key words: Alzheimer's disease, diagnostic criteria, biomarkers

INTRODUCTION

Alzheimer's disease (AD) is the most common form of neurodegenerative dementia, accounting for 50-60 percent of cases (1). Dementia is a disorder characterized by a decline in cognition involving one or more cognitive domains (learning and memory, language, executive function, complex attention, perceptual-motor, social cognition) (2). Age remains the strongest risk factor for dementia, particularly for AD. The incidence of AD approximately doubles every 10 years after the age of 60 (3). The challenge and yet perhaps the greatest promise in effectively treating neurodegenerative disease lies in prompt diagnosing. The reality is that the pathophysiological process begins more than a decade prior to the stage of clinically detectable symptoms (4).

Regarding diagnosis, the clinical criteria established in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) (5) have been revised by the National Institute on Aging and the

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Alzheimer Association (NIA-AA) (6, 7). These criteria for AD incorporate two notable differences. First, the AD process is considered as a continuum that encompasses three different disease stages: 1) preclinical phase, in which subjects are cognitively normal but have AD pathology; 2) symptomatic pre-dementia phase: mild cognitive impairment (MCI); and 3) dementia phase: AD (6). The original 1984 clinical criteria for AD defined it as having a single stage, dementia, while the diagnosis relied solely on clinical symptoms. It assumed that people free from dementia symptoms were disease-free. Diagnosis was confirmed only on autopsy, when the hallmarks of the disease, i.e. abnormal amounts of amyloid proteins forming plaques and tau proteins forming tangles, were found in the brain. Since then, research has determined that AD may cause changes in the brain a decade or more before the symptoms appear and that symptoms do not always directly relate to abnormal changes in the brain caused by AD. For example, some elderly people are found to have abnormal levels of amyloid plaques in the brain on autopsy, yet having never shown signs of dementia during life. It also appears that amyloid deposits begin early in the disease process but that tangle formation and loss of neurons occur later and may accelerate just before the clinical symptoms appear (6,8).

In this review, we provide an overview of current diagnostic criteria for Alzheimer's dementia including preclinical phase, available biomarkers and clinical features.

BIOMARKERS OF ALZHEIMER'S DEMENTIA (in preclinical phase)

Preclinical AD refers to the stage of AD in which the molecular pathology is already present in the brain but is not yet clinically expressed (9). Neuropathologically, it is characterized by amyloid plaques, tau containing neurofibrillary tangles, activated microglia around amyloid plaques, and amyloid angiopathy and microhemorrhages in some individuals with AD (10).

The genetic basis of AD is best understood in the early-onset form, which accounts for less than one percent of cases and typically follows an autosomal dominant inheritance pattern related to mutations in the genes that alter amyloid-beta (Aβ) protein production, aggregation, or clearance. The genetic basis of late-onset AD (sporadic AD) is more complex, with susceptibility likely conferred by a variety of more common but less penetrant genetic factors, such as apolipoprotein E (*APOE*) alleles. Those genetic factors are interacting with many environmental and epigenetic influences such as age, hypertension, hypercholesterolemia, diabetes, tobacco smoking, obesity, lifestyle, social, mental and physical activity, level of education and cognitive reserve, head trauma, obesity, high alcohol consumption, depression, etc.

Newer criteria place emphasis on using biomarkers to provide an earlier and more specific diagnosis (8).

Structural imaging (CT or MRI)

In AD, the typical imaging appearance is global brain atrophy with early disproportionate symmetric involvement of medial temporal lobe structures including the hippocampi (11). It can differentiate AD from aging and from dementia with Lewy bodies (DLB) and vascular cognitive impairment (12, 13). Medial temporal lobe atrophy can predict which individuals will develop clinical AD from MCI state (12, 14). Progressive atrophy of the parietal/occipital lobes is supportive of AD and in particular in distinguishing AD from frontotemporal dementia (FTD); incorporating visual ratings of posterior atrophy can improve distinction of AD from other causes of dementia (11). Rates of whole brain and hippocampal atrophy, calculated from serial volumetric MRI are sensitive markers of progression of neurodegeneration and are increasingly used as outcome measures in trials of potentially disease modifying therapies in AD (14).

Functional imaging (PET, SPECT, fMRI, amyloid PET tracers)

Functional brain imaging with 18F-fludeoxyglucose positron emission tomography (FDG-PET), functional MRI (fMRI), perfusion MRI or *single-photon emission computerized tomography (SPECT)* reveals distinct regions of low metabolism (PET) and hypoperfusion (SPECT, fMRI) in AD. These areas include the hippocampus, the precuneus (mesial parietal lobes), and the lateral parietal and posterior temporal cortex (15-21). Amyloid PET tracers (F18-florbetapir, F18-flutemetamol, F18-florbetaben) that measure amyloid lesions in the brain have been developed as tools to aid in the diagnosis of AD *in vivo*, aid in prognosis, speed development of anti-amyloid drugs and differentiating AD from other causes of dementia (22-24). Currently, the availability and cost of amyloid PET imaging still limit its use in clinical practice (25).

Cerebrospinal fluid's biomarkers (β-Amyloid, Tau, Phospho-tau 181)

The CSF levels of Aβ1-42, thought to be one of the key pathological forms of Aβ in brain tissue, are reduced in AD, with the degree of reduction correlating with the brain amyloid plaque load (26). Reduction of CSF Aβ1-42 occurs years before symptom onset (27), and has good positive predictive value for conversion from MCI to clinical AD (28); accordingly, CSF Aβ1-42 is now included in the new diagnostic criteria for MCI due to AD (7). In clinical practice, normal CSF Aβ1-42 in a demented individual should prompt re-evaluation of the AD diagnosis. Other forms of β-amyloid, notably Aβ1-40, can be measured in CSF and may better reflect both total brain Aβ burden than Aβ1-42 (29) and may improve differential diagnosis in certain circumstances (30, 31), but this has not yet entered routine clinical practice.

The CSF levels of t-tau and tau phosphorylated at 181 (p-tau) are both increased in AD. T-tau is increased after stroke, in inflammatory conditions and in other neurodegenerative diseases, most notably in Creutzfeldt-Jakob disease, where the levels are often in the orders of magnitude higher than in AD; p-tau elevation is thought to have high specificity for AD (32). Stability and reproducibility of t-tau and p-tau levels are good, and the levels remain stable over periods of up to 6 months (33), suggesting that these biomarkers may be capable of detecting small biochemical changes induced by treatment.

Several studies have demonstrated that the combination of low CSF Aβ1-42 and elevated t-tau and p-tau could distinguish individuals with MCI/incipient AD from those without it with 95% sensitivity and 87% specificity (34). On the research basis, the combination of low Aβ42, elevated tau and p-tau has also been used to predict future cognitive decline in healthy older individuals (35). In clinical practice, the combination of low CSF Aβ1-42 and elevated tau (or p-tau) to Aβ1-42 ratio is often used to support the diagnosis of AD, with one recent study suggesting the tau:Aβ42 ratio to be the most robust single biomarker combination (36).

CLINICAL FEATURES

Symptomatic pre-dementia phase: mild cognitive impairment

The MCI stage is marked by symptoms of memory problems, enough to be noticed and measured, but not compromising the person's independence. People with MCI may or may not progress to Alzheimer's dementia (6-8, 37).

There should be evidence for lower performance in one or more cognitive domains that is greater than would be expected for the patient's age and educational background. This change can occur in a variety of cognitive domains, including memory, executive function, attention, language, and visuospatial skills. Impairment in episodic memory (i.e. the ability to learn and retain new information) is seen most commonly in MCI patients who subsequently progress to the diagnosis of AD. Persons with MCI commonly have mild problems performing complex functional tasks which they used to perform previously, such as paying bills, preparing a meal, or shopping. They may take more time, be less efficient, and make more errors on performing such activities than in the past. Nevertheless, they generally maintain their independence of their daily life functioning, with minimal aid or assistance. These cognitive changes should be so mild as to show no evidence of significant impairment in social or occupational functioning. The person should not meet the criteria for dementia (37).

Dementia phase: Alzheimer's disease

Memory impairment is an essential feature of AD and is often its earliest manifestation. Declarative memory for facts and events, which depend on mesial temporal and neocortical structures, are profoundly affected in AD, while subcortical systems supporting procedural memory and motor learning are relatively spared until quite late in the disease. A subset of declarative memory, that of specific events and contexts (episodic memory) is more profoundly impaired in early AD, compared with memory for facts such as vocabulary and concepts (semantic memory), which often becomes impaired somewhat later. Semantic memory is encoded in neocortical (nonmesial) temporal regions. Within episodic memory, there is a distinction between immediate recall (e.g., mental rehearsal of a phone number), memory for recent events (which comes into play once material that has departed from consciousness must be recalled), and memory of more distant events. Memory for recent events, served by the hippocampus, entorhinal cortex, and related structures in the mesial temporal lobe, is prominently impaired in early AD (15, 38, 39). In contrast, immediate memory (encoded in the sensory association and prefrontal cortices) is spared early on, as are memories that

are consolidated for long periods of time (years), which can be recalled without hippocampal function. Memory deficits develop insidiously and progress slowly over time, evolving to include deficits of semantic memory and immediate recall. Impairments of procedural memory appear only in late stages of AD.

Verbal disfluency and anomia are often early features and sometimes the presenting feature of AD (40). The first manifestations of language dysfunction usually include word-finding difficulties, circumlocution, reduced vocabulary in spontaneous speech, and anomia on confrontational naming tests, which progress to include agrammatism, paraphasic errors, impoverished speech content, and impaired comprehension. Patients can usually repeat phrases verbatim until the disease is quite advanced (41).

Loss of visuospatial skills is an early feature of AD that is sometimes very prominent at presentation (42-44). Visuospatial impairments manifest as misplacement of items and difficulty navigating in first unfamiliar, and as deficits progress, familiar terrain. Visual agnosia (inability to recognize objects) and prosopagnosia (inability to recognize faces) are later features. Some clinicians have noted hemispatial visual neglect in their patients with AD (45, 46).

In early stages of AD, impairment of executive function is usually subtle (47); family members and coworkers may find them less motivated, less engaged, and apathetic. As the disease progresses, a more manifest alteration of personality, poor judgment and planning occurs, and inability to complete tasks typically emerges. Reduced insight into deficits (anosognosia) is a characteristic feature of AD and has been linked to frontal lobe pathology (48, 49). Those with relatively preserved insight are more likely to be depressed; those with more impaired insight are likely to be agitated, disinhibited, and exhibit psychotic features such as hallucinations, delusions or misidentification syndromes (50, 51). Neuropsychiatric symptoms are common in AD, particularly in the middle and late course of disease.

Other signs and symptoms worth mentioning are dyspraxia and apraxia, which usually occur later in the disease after deficits in memory and language have become apparent, then changes in olfactory function, sleep disturbances (fragmented sleep), seizures, and pyramidal and extrapyramidal motor signs, which are typically late-stage findings.

The criteria for the diagnosis of probable AD dementia have been established by the National Institute on Aging and the Alzheimer's Association (NIA-AA) and most recently updated in 2011 (5, 7). Probable AD dementia is a syndrome of dementia defined by the following characteristics:

- interference with the ability to function at work or at usual activities;
- a decline from the previous level of functioning and performing, not explained by delirium or major psychiatric disorder;
- cognitive impairment established by history-taking from the patient and a knowledgeable informant; and objective bedside mental status examination or neuropsychological testing;
- cognitive impairment involving a minimum of two of the following domains: impaired ability to acquire and remember new information; impaired reasoning and handling of complex tasks; poor judgment; impaired visuospatial abilities; impaired language functions; changes in personality, behavior or comportment;
- insidious onset;
- clear-cut history of worsening;
- initial and most prominent cognitive deficits are one of the following : 1) amnestic presentation (i.e. impairment in learning and recall of recently learned information); 2) nonamnestic presentations include either a language presentation, with prominent word-finding deficits; a visuospatial presentation, with visual cognitive deficits; or a dysexecutive presentation, with prominent impairment of reasoning, judgment and/or problem solving); and
- no evidence of substantial concomitant cerebrovascular disease, core features of dementia with Lewy bodies, prominent features of behavioral variant frontotemporal dementia or prominent features of semantic or nonfluent/agrammatic variants of primary progressive aphasia, or evidence of another concurrent, active neurologic or non-neurologic disease or use of medication that could have a substantial effect on cognition (5,7).

The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for AD are also commonly used and were revised in 2013 (52). The DSM-5 definition of probable AD (now called major neurocognitive disorder due to AD) and include the following:

- evidence of significant cognitive decline from a previous level of performance in one or more

cognitive domains (learning and memory; language; executive function; complex attention; perceptual-motor; social cognition);

- cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications;
- cognitive deficits do not occur exclusively in the context of a delirium;
- cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia);
- there is insidious onset and gradual progression of impairment in at least two cognitive domains; and
- either of the following:
  1) evidence for a causative AD genetic mutation from family history or genetic testing; and
  2) all three of the following are present: (a) clear evidence for decline in memory and learning and at least one other cognitive domain; (b) steadily progressive, gradual decline in cognition, without extended plateaus; (c) no evidence of mixed etiology (i.e. absence of other neurodegenerative disorders or cerebrovascular disease, or another neurologic, mental or systemic disease or condition contributing to cognitive decline) (52).

CONCLUSION

Alzheimer's dementia is the most common form of neurodegenerative dementia. As age remains the strongest risk factor for AD, the incidence of AD increases exponentially after the age of 60. The pathophysiological process begins more than a decade prior to the clinically developed symptoms and this period may be the optimal time to intervene. Old diagnostic criteria from 1984 were based entirely on clinical symptoms, while the new criteria from 2011 onwards consider AD as a continuum that encompasses three different disease stages: preclinical phase, symptomatic pre-dementia phase (MCI) and dementia phase (AD). Newer criteria place emphasis on using biomarkers to provide an earlier and more specific diagnosis in order to ensure effective treatment.

The role of laboratory (CSF biomarkers) and imaging (CT, MRI, PET, SPECT, fMRI, amyloid PET tracers) is to exclude other diagnoses, to support the diagnosis of AD or some of them are used in research settings in an effort to better define prodromal and preclinical forms of AD and identify candidates for early, intervention clinical trials. Effective strategies for early diagnosis, prevention and treatment are urgently needed.

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Novi dijagnostički kriteriji za Alzheimerovu bolest

SAŽETAK - Cilj ovoga pregleda bio je istražiti dosad objavljene kriterije za dijagnosticiranje Alzheimerove demencije koji se primjenjuju u kliničkoj praksi. Danas smo u mogućnosti istraživati okolišne čimbenike i genetsku predispoziciju za razvoj Alzheimerove demencije, otkriti biomarkere u cerebrospinalnom likvoru i neuroadiološke karakteristike same bolesti te na kraju uočiti brojne kliničke manifestacije pred-dementne i dementne faze. U upotrebi su dijagnostički kriteriji NIA-AA (*National Institute on Aging and the Alzheimer's Association*) iz 2011. godine te kriteriji DSM 5 (*The Diagnostic and Statistical Manual of Mental Disorders*) iz 2013. godine koji imaju približno podjednaku učinkovitost u kliničkoj praksi. Potrebna su daljnja istraživanja kako bi se definirali još specifičniji i osjetljiviji dijagnostički kriteriji te što učinkovitiji način liječenja.

Ključne riječi: Alzheimerova bolest, dijagnostički kriteriji, biomarkeri