Chapter 6

New Perspectives in the Diagnosis of Mild Cognitive Impairment and Alzheimer's Disease: Novel Uses of Biomarkers

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Additional information is available at the end of the chapter

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Abstract

Criteria for the diagnosis of Alzheimer's disease were established in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA). Commonly used since their implementation, these criteria are becoming obsolete for everyday practice, and a review is being claimed. Three groups of experts consisting of renowned experts from the National Institute on Aging (NIA) and the Alzheimer's Association proposed a set of recommendations to modify the criteria in this field of research. Two notable differences from the initial criteria were included: the incorporation of biomarkers and the formalization of different disease stages in the diagnostic criteria. From now on, mild cognitive impairment is incorporated in the diagnosis as another stage of dementia. However, the new criteria are still under revision and are currently of use for research purposes with the aim to get the definitive modification for the clinical criteria. This chapter presents the main developments in research concerning Alzheimer's disease and mild cognitive impairment to define these new research criteria.

Keywords: Alzheimer's disease, mild cognitive impairment, biomarkers, neuropsychology, dementia

1. Introduction

The concept of dementia makes us instantly think about a set of characteristic symptoms and the resulting repercussions for patients and their families. The objective of this chapter is to

update our ideas about Alzheimer's disease and get to know the beginning and evolution of the construct of mild cognitive impairment, as well as the new advances in genetics and biomarkers that, in not such a distant future, will be of common use in the diagnosis of cognitive impairment.

The Greeks were the first to study mental disorders from a scientific point of view by separating the study of mind from religion. The existence of dementia has been known since the times of Hippocrates (460–370 BC), although throughout history, it has been given different names: paranoia, idiocy, senility, senile psychosis, and so on. But it will not be until 1906 that Alois Alzheimer first described the disease that would be named after him and which has made history worldwide [1].

From Dr. Alois Alzheimer's first patient, Auguste D., until the current description and definition of the disease, more than a century has passed and many research studies have been carried out on it. Initially, it was considered to be a condition particular to young patients, and so it was given the name of presenile dementia. However, the progressive increase in life expectancy left uncovered that the symptoms present in Auguste D. were also found in older population, thus leading to a new approach to the disease. But it was not until the 1970s that the disease described by Alzheimer started to be a focus of attention. The real story of the concept of dementia and Alzheimer's disease can be consulted in different texts of reference [1–3].

Recently, knowledge on dementia in general and on Alzheimer's disease in particular has been remarkably expanded. The diagnostic process for Alzheimer's disease has benefitted from widely accepted consensus protocols [4]. Nevertheless, the clinical heterogeneity of this disease (age of onset, type of impairment, or the disease's progression pace) makes diagnosis extremely difficult.

2. Diagnosis of Alzheimer's disease

Alzheimer's disease is a neurodegenerative condition of insidious onset and progressive evolution, characterized by loss of memory and other cognitive functions, and by a set of noncognitive symptoms, among which depressive or psychotic-related symptoms and behaviour disorders stand out. Among the main neuropsychological features of this disease, we can point at the progressive impairment of memory and language, the decline in visuospatial and motor capacities, and the disruption of executive functions such as the capacity for abstraction and reasoning [5, 6].

The criteria for the clinical diagnosis of Alzheimer's disease were defined in 1984 by the National Institute of Neurological and Communicative Disorders (NINCD) and the Alzheimer's Disease and Related-Disorders Association (ADRDA). These criteria are based on the idea that Alzheimer's disease is a single clinicopathological entity [7], thus advocating that Alzheimer's disease always has a close correlation between clinical symptoms and their pathological basis; in most cases, it was thought that the typical anatomopathological presen-

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tation already described in 1910 and based on the presence of senile plaques, neurofibrillary tangles and cerebral arteriosclerotic changes [8] would be found at autopsy. Following this idea, the basic lines for the development of the disease were, in 1984, as follows:

1. The underlying pathology of Alzheimer's disease and clinical symptoms was developed concurrently.
2. Patients either had completely developed Alzheimer's disease symptoms (in this case, then, they clearly had a dementia), or they were free of this pathology and, therefore, had no dementia at all (at least no Alzheimer-like dementia as later identified).

Thus, 1984 criteria required the presence of cognitive impairment and dementia to be confirmed by neuropsychological assessment in order to establish the diagnosis of possible or probable Alzheimer's disease, although histopathological confirmation was still needed for a final diagnosis (via autopsy or biopsy) (see **Table 1**).

NINCDS-ADRDA (1984) criteria for the clinical diagnosis of Alzheimer's disease	
Diagnostic criteria for probable Alzheimer's disease: Presence of dementia: - Established by clinical examination - Documented by the Mini-Mental Cognitive Examination Test, Blessed Dementia Scale or similar - 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 - Absence of systemic disorders or other brain disease that could cause dementia	**Diagnostic criteria for possible Alzheimer's disease:** - Dementia syndrome in the absence of other causes and in the presence of variations in the onset, in the presentation, or in the clinical course - Presence of another systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia - Presence of a single, progressive severe cognitive deficit
Criteria that support the diagnosis of probable Alzheimer's disease: - Progressive deterioration of specific cognitive functions (e.g., language, motor skills, perception - Impaired activities of daily living (ADL) and altered patterns of behaviour - Family history of similar disorders - Consistency in analytic results (lumbar puncture, EEG, CT)	**Diagnostic criteria for definite Alzheimer's disease:** - Meeting the clinical criteria for probable Alzheimer's disease with histopathologic evidence
Features nonconsistent with the diagnosis of Alzheimer's disease: - Sudden onset - Focal neurologic signs - Seizures or early gait disturbances	

Source: Adapted from Carrasco [21].

Table 1. Criteria for the diagnosis of Alzheimer's disease.

Some aspects of these criteria have been set aside by new research and daily clinical practice has also pointed at ideas to be revised. The pathological histology present in Alzheimer's disease can also be found in a wide set of alternative clinical conditions [9, 10], from patients without cognitive symptoms to patients with mild cognitive impairment (MCI) or other types of impairment. Therefore, the initial concept of Alzheimer's disease has to be less restrictive than that developed in 1984.

The capacity to recognize some clinical symptoms in other disorders with a similar development as in Alzheimer's disease was limited two decades ago, thus resulting in diagnostic confusions. In this respect, for example, reversible systemic disorders such as vitamin B12 deficiency, which may have similar symptoms to a dementia, were not taken into consideration [11]. Although frontotemporal dementia was considered to be an entity, others such as Lewy body dementia or vascular dementia were not taken into account [12]. Likewise, the concept of aphasia linked to neurodegenerative disorders, despite being described some years before the NINCDS-ADRDA criteria [13], was not fully developed until two decades later [14].

The implication that memory impairment must always be considered as the primary cognitive deficit for the diagnosis of Alzheimer's disease is also being put into doubt, as clinical experience has showed that Alzheimer's disease may be developed in a nonamnesic way [15]. Clinical experience has also pointed at the need to revise cut-off points by age for the diagnosis, as age-related pathologies such as dementia are more and more frequent due to the overageing of population. Finally, the inclusion of new results from neuroimaging exploration and biomarker clinical analysis in the new criteria will allow us to get to know the individual characteristics of every cognitive impairment from an integral approach of the same construct.

Since the establishment of the NINCDS-ADRDA criteria 32 years ago, it has been proved that Alzheimer's disease underlying pathology and clinical symptoms are not always present concurrently, thus dismissing one of the main assumptions of the 1984 diagnostic criteria. Research has evolved remarkably since then and, among other events, it has been identified, for example, that in the absence of any apparent symptom, there can be a wide pathological presentation (particularly of amyloid plaques) [16, 17].

Knowledge about the neuropathology of Alzheimer's disease has been expanded in the last 25 years of the twentieth century; new sets of diagnostic criteria to establish a diagnosis of this disease from its neuropathological basis have been developed and applied more or less successfully. Among others, we have to consider those by the National Institute on Aging (NIA) [18], those by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [19], and those by the NIA-Reagan Institute [20]. There are no basic differences among these three classifications; they all stand out the need to carry out an inclusive diagnosis, establish the priority for the cognitive diagnosis—with special emphasis on memory—and consider other noncognitive or psychiatric symptoms to be "accessory" [21]. These approaches present two main problems: first, they downplay cognitive symptoms, as they only focus on amnesic manifestations, with the other cognitive functions and psychopathological impairments being left in the background; second, they are limited by the inability to categorize certain symptoms present in this kind of dementia [22]. Nevertheless, there are two main research aspects that have evolved from the very first description of this disease: using biomarkers and formally

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establishing different stages for the disease. Literature on mild cognitive impairment has exponentially increased since the 1990s in order to document the gradual impairment of cognitive functions preceding the point when there is a significant interference with activities of daily living [23]. As previously mentioned, the 1984 criteria did not consider cognitive impairment that does not reach the dementia threshold, thus passing over that the Alzheimer's disease underlying pathology slowly develops for years—or even decades—before there is a clinical manifestation of the disease.

3. Mild cognitive impairment

Different nosological entities have been defined in order to characterize cognitive impairment processes that represent an intermediate stage between cognitive decline observed in the ageing process and changes that meet the criteria for the diagnosis of dementia [24]. The most used concept is that of "mild cognitive impairment" (MCI) coined by Petersen et al. [25], although initially described by Flicker et al. [26] according to Reisberg's Global Deterioration Scale [27].

MCI is a syndrome that shows up as a cognitive dysfunction greater than expected for the patient's age and cultural and educational level, that develops without major interferences in activities of daily living and does not meet criteria for dementia [25, 28]. The main diagnostic difference between Alzheimer's disease and mild cognitive impairment lies in the degree of interference in the patient's capacity to develop daily work or regular tasks. This is, unavoidably, a determination to be carried out by an expert on the basis of individual circumstances and the description of daily routines obtained by both the patient and a close informant. For a further development of this differential diagnosis, please see Albert et al. [29].

The definition in Petersen [21] describes MCI as a degenerative process that precedes dementia —on the basis of the *cognitive continuum* construct (**Figure 1**), where the main deficit concerns memory and the other cognitive functions seem to be stable. Later studies have expanded the MCI construct by describing different subtypes not only limited to amnestic symptoms [30].

Nelson and O'Connor [31] described, through postmortem histopathological studies with MCI patients, that a wide majority of cases evolved to a process of dementia, although a small percentage did not. These results put into question the assumption that MCI may always be considered as an initial stage of Alzheimer's disease.

As we get closer to the definition of the earliest stages of cognitive impairment, the dissociation between the connotations of the concept of early Alzheimer's disease and MCI is more obvious. It is becoming clearer and clearer that both Alzheimer's disease pathophysiological process and symptoms are better explained as a continuum (linking both Alzheimer's disease and MCI at the same time), as these processes can concurrently evolve and even overlap in time [32]. Hence the need to revise both constructs further.

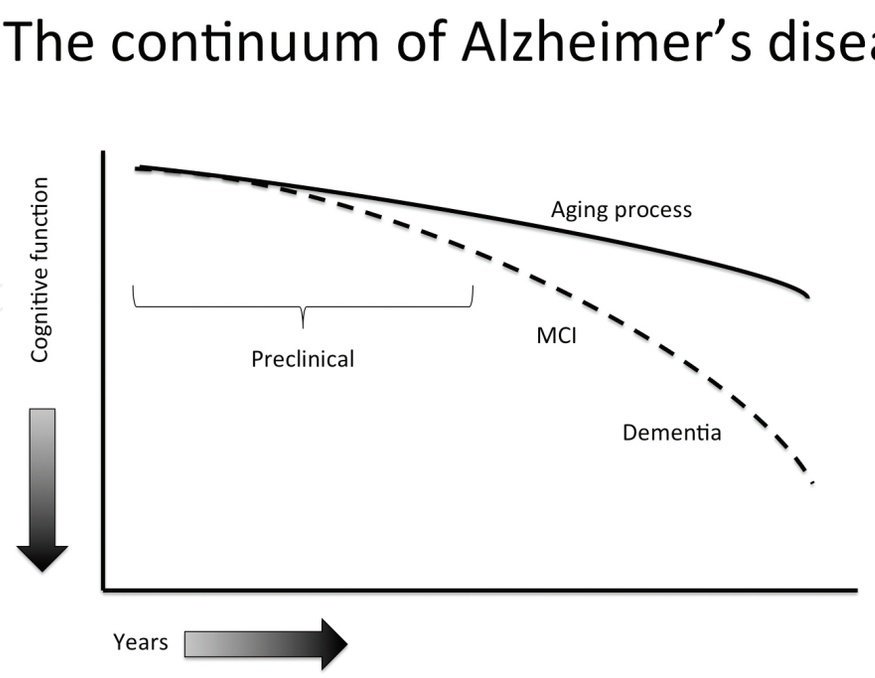

Figure 1. Model of cognitive continuum. Adapted from Sperling et al. [32].

Although some agreement has been reached in the last few years, the current MCI diagnosis is complex as there are no precise and standardized criteria with general consensus. As main characteristics, we can stand out the complaints about memory loss from the beginning of the process, reported either by an informant or by the patients themselves. Patients often report other symptoms, such as difficulties to find needed words, loss of personal objects, disorientation, or loss of continuity in usual tasks, for example, in a conversation [31].

There have been attempts to formalize these clinical observations as diagnostic criteria. We can stand out those by the Study Group on Dementia and Behavioral Disorders of the Spanish Society of Neurology [33] or those by Mayo Clinic [25] that correspond to the amnestic subtype only. Also worth highlighting are those by the International Psychogeriatric Association (IPA) [34], described in **Table 2**.

Despite the efforts to agree on diagnostic criteria for MCI, there are still some difficulties deriving, in many cases, from conceptual limitations of the nosological entity itself [24]. Since the Montreal Consensus [35], criteria became more flexible, with the inclusion, for instance, not only of patients in a cognitive normality dementia transition stage but also very prevalent intermediate conditions secondary to other aetiologies (e.g., vascular dementia) or other conditions, also very frequent, such as those secondary to mood disorders [36].

One of the facts that has always been an object of attention is the relationship between MCI and dementia, in particular, Alzheimer's disease [30, 37]. A recently published study [38] reports the prevalence for mild cognitive impairment between 3 and 42% depending on the construct. We should remember now that, before Petersen et al.'s definition of MCI [25], other constructs had been considered such as age-associated memory impairment (AAMI) [27] or cognitive impairment no dementia (CIND) [39]. In particular, according to Ward's study,

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AAMI prevalence is between 3.6 and 38.4%; the prevalence for CIND ranges between a bit more than 5 and 35.9%, whereas studies using the concept of MCI (as described by Petersen) show population prevalence between 3 and 42%. Moreover, if we consider that MCI patients have a three times higher risk to develop Alzheimer's disease in a period of 4.5 years after diagnosis [40], the need for some criteria that are agreed upon, global and useful for the diagnosis of cognitive impairment in all of its stages, from onset to more serious stages, becomes particularly important.

Diagnostic criteria according to the International Psychogeriatric Association (IPA) and World Health Organization (WHO)
1. No age restriction
2. Decline of cognitive function reported by patient or informant
3. Decline is gradual and present for at least 6 months
4. Deterioration in any major cognitive domain: - Memory and learning - Attention and concentration - Language - Thinking - Visuospatial functioning
5. Lower scores in mental state evaluations or neuropsychological tests, a standard deviation below the mean value of a control group
6. No presence of brain processes, either systemic or psychiatric, that can account for the impairment

Source: Adapted from Sánchez-Rodríguez and Torrellas-Morales [28].

Table 2. IPA criteria.

Since 2009 there has been a consensus among the main research centres, that diagnostic criteria for Alzheimer's disease, as well as those for dementia and mild cognitive impairment, should be revised. For this reason, the National Institute on Aging (NIA), together with the Alzheimer's Association, sponsored a deep revision of criteria, thus establishing a revision of old criteria by three independent groups of experts. The first group undertook to establish and describe diagnostic criteria for dementia and Alzheimer's disease; the second group focused on the symptomatic stage prior to Alzheimer-like dementia; finally, the third group dealt with the asymptomatic stage prior to dementia and mild cognitive impairment. The recommendations of the three groups were presented at the 2010 International Conference on Alzheimer's Disease and later published [41]. This new proposal of criteria has integrated research on dementia, MCI, and Alzheimer's disease carried out in the last 25 years of the twentieth century. In particular, the inclusion of genetic breakthroughs, biomarkers, and final formalization of the different stages in the development of dementia are worth standing out.

4. New advances in research

The role of genetics in the diagnosis of the different types of cognitive impairment is more and more active and important. At present, there is no doubt about the existence of genetic risk factors to develop Alzheimer's disease, as some genes have been identified that are not only responsible for the genetically pure forms of the disease but also some sporadic and late-onset forms [42].

Although the most important risk factor related to Alzheimer's disease is the ageing process of the patient, the second risk factor is the family history of the disease. Thus, Alzheimer's disease is a complex pathology with a clear genetic component. Up to now, three genes have been found to be responsible for early onset familial Alzheimer's disease: the gene for amyloid beta precursor protein (APP), the gene for presenilin-1 (PS1), and the gene for presenilin-2 (PS2). Taking this into account, if the predominant autosomal form of Alzheimer's disease is present in a patient with MCI, then this MCI is more likely to be a prodrome of early onset Alzheimer's disease [43].

But not only is early onset Alzheimer's disease linked to genetic influence. Approximately, 40% of diagnosed individuals have a family history of the disease, and epidemiological studies show that the risk of developing the disease if a first-degree relative already has it is between two and three times higher than that of general population [44]. The genetic component of late-onset Alzheimer's disease has been targeted in many studies, but at the moment only a genetic component, APOE, has been considered as a risk factor associated with the disease [43]. Thus, up to now, the presence of one or two ε4 alleles in the gene for apolipoprotein E (APOE) has been the only genetic variation widely accepted as a risk factor to develop late-onset Alzheimer's disease, whereas the presence of the ε2 allele would have the opposite effect [45]. Evidence suggests, then, that an individual meeting clinical, cognitive, and etiological criteria for MCI and carrier of the ε4 allele of the APOE gene is more likely to progress towards developing Alzheimer's disease, eventually, than any other individual without this genetic characteristic.

Genetic research has also allowed us to know that the molecular mechanisms that start Alzheimer's disease, both clinically and pathologically, correspond to a metabolic disorder of amyloid beta (Aβ) [46]. A key point is the concept according to which some usually soluble neuronal proteins can misfold and aggregate, for instance, in neurofibrillary tangles, thus producing high levels of cell cytotoxicity [47]. Recent data suggest that although familial Alzheimer's disease is characterized by Aβ overproduction, sporadic late-onset forms are characterized by a decrease in Aβ recycling capacity. And Aβ traffic is controlled by APOE, so the genetic data available at the moment overwhelmingly point at the amyloid cascade hypothesis as the starter of the cognitive impairment process [48].

To facilitate the theoretical discussion of the MCI construct as a preclinical stage of Alzheimer's disease, the group revising the criteria [32] proposed a theoretical model to explain the relationship between cognitive decline and the basic pathophysiology of Alzheimer's disease (see **Figure 2**). As will be seen later, genetic factors are not the only determinants in the development and progression of mild cognitive impairment, as other risk factors, such as

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vascular factors or the history of personal development, as well as environmental factors and cognitive reserve, which can positively influence the development of cognitive symptoms of decline, also have to be considered.

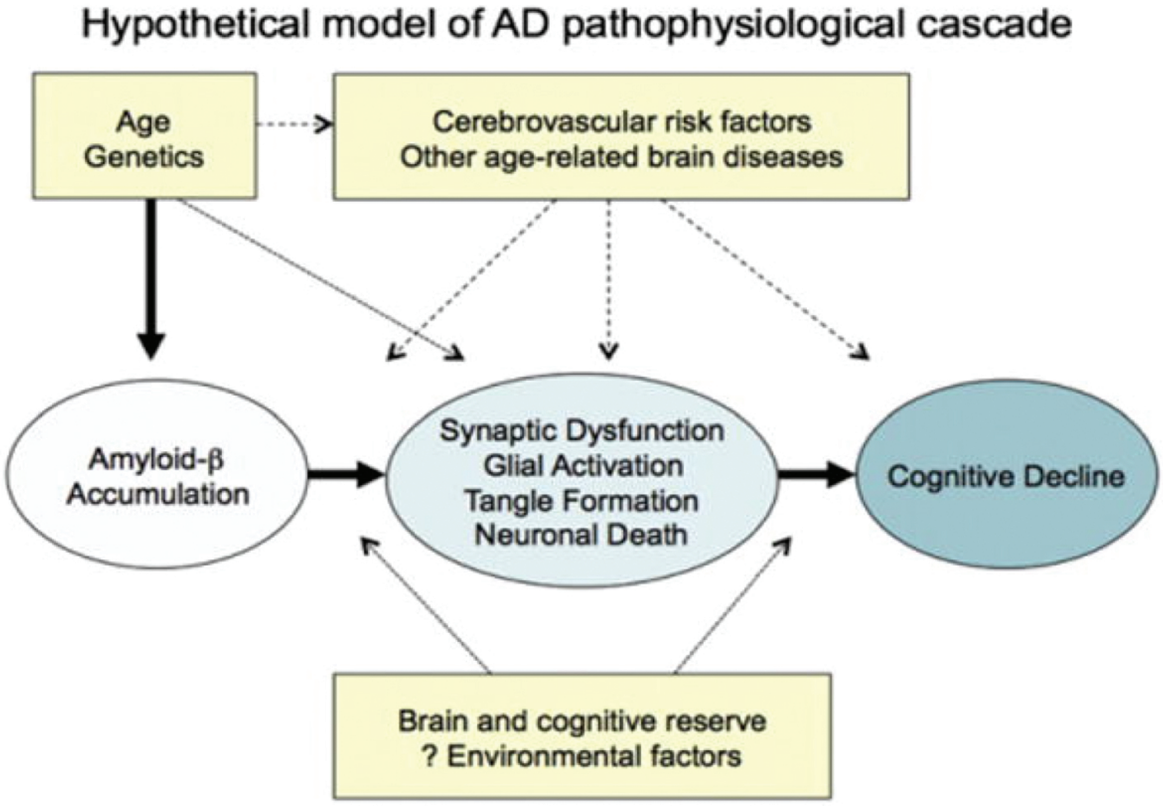

Figure 2. Relationship between cognitive decline and the basic pathophysiology of Alzheimer's disease. Based on Sperling et al. [32].

Another remarkable difference between the 1984 criteria and those revised in 2011 is the incorporation of biomarkers to diagnose cognitive impairment. Biomarkers are physiological, biochemical, or anatomic parameters that are measured in vivo and that reflect specific characteristics of pathophysiological processes related to a disease; in this case, MCI or Alzheimer's disease. It is important to incorporate new knowledge on biomarkers into the diagnostic framework of these diseases, as, on the one hand, they provide us with greater support when establishing the etiological bases of the cognitive decline process and thus allow us to better choose the intervention to follow when there are effective specific treatments; on the other hand, they allow us to determine the probability of the cognitive and functional progression of impairment towards a more serious stage of MCI or towards dementia, as well as the possibility that this progression develops in a defined period of time [29].

There are many biomarkers. Nevertheless, after a long and thorough study of the main markers, the study groups selected only two categories of biomarkers to be included in their recommendations. These are the biomarkers related to Aβ and the biomarkers reflecting neuronal injury [29].

The amyloid plaques (or senile plaques) are one of the most characteristic features of Alzheimer's disease and, therefore, those biomarkers that can detect and quantify Aβ protein or tau protein accumulated in brain tissue are vitally important for the pathological diagnosis of the disease and its precursors [49]. Aβ deposition markers include both measurements of the level of $A\beta_{42}$ in cerebrospinal fluid (CSF) as evidence of deposition via positron emission tomography (PET) imaging by using a variety of specific binding agents [50]. Tau protein accumulation markers can be obtained through measurements via CSF.

Among neuronal injury markers, there is a series of structural and functional measures, described in **Table 3**, together with Aβ biomarkers.

Biomarkers for the diagnosis of cognitive impairment
Biomarkers of Aβ deposition - CSF $A\beta_{42}$ - PET amyloid imaging
Biomarkers of neuronal injury - CSF tau/phosphorylated-tau - Hippocampal volume or medial temporal atrophy by volumetric measures - Rate of brain atrophy - FDG-PET imaging - SPECT perfusion measures *Other non-validated measures*: fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MR spectroscopy, and diffusion tensor imaging.

Abbreviations: CSF, cerebrospinal fluid; PET, positron emission tomography; FDG, fluorodeoxyglucose; SPECT, single photon emission tomography; fMRI, functional magnetic resonance imaging; BOLD, blood oxygen level-dependent; MR, magnetic resonance.
Adapted from Albert et al. [29].

Table 3. Biomarkers for clinical diagnosis.

Among the potential uses of biomarkers, there is the identification of people in the preclinical stages of the disease or the reduction in the heterogeneity of the disease in clinical trials. However, not all biomarkers are valid as indirect assessment criteria, as they can be difficult to validate and require different levels of validation depending on their expected use. In this respect, although the presence of high levels of tau protein is clearly associated with the pathophysiological process of Alzheimer's disease, changes in tau and phosphorylated-tau (p-Tau) are not exclusive to Alzheimer's disease and can also reflect more general neuronal and synaptic damage. The same can be said of Aβ depositions, as they are not exclusive to Alzheimer's disease. This is one of the main limitations of these biomarkers [51]. No conclusive determination has been reached either concerning whether the quantitative measure of these biomarkers provides us with more information than the dichotomous assessment (presence/absence; positive/negative). Nevertheless, the combination of both types of measures points

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at the higher probability that the pathophysiological process of the disease is the etiological base of underlying changes [29].

One of the main drawbacks in Alzheimer's disease research is that the symptoms of the disease appear after significant neuronal loss. The objective of current research with biomarkers is to manage to prevent this loss before the final emergence of symptoms, in order to develop really efficient treatments against this disease, as current medication can only provide patients with short-term improvements of their cognitive function [52].

5. New criteria for research on mild cognitive impairment and Alzheimer's disease

After thoroughly analysing the background and revising the main research studies carried out at the epidemiological, neuropsychological, genetic levels, and with biomarkers, the group of experts of the National Institute on Aging and the Alzheimer's Association proposed a working framework (**Figure 3**) to provide specialists, and the scientific world in general, with a specific and common language to move towards the knowledge of the preclinical and clinical stages of Alzheimer's disease.

The objective of the group of experts is to contribute with some operational research criteria in order to help select future target groups at risk of developing Alzheimer's disease, by considering the presence of Aβ biomarkers (either in isolation or in combination with other neurodegeneration markers). We have to consider that, at the moment, the use of these new criteria is for research only and that an inappropriate use in other fields may lead to wrong results and misinterpretations, as so far these criteria are still under revision.

These new criteria are based on the assumption that Alzheimer's disease is characterized by a sequence of biological events that begin much before the clinical symptoms of the disease appear. Considering the genetic evidence, the hypothesis of Aβ accumulation in a first stage of amyloidosis, which would be the first moment when cognitive impairment can be measured, is gaining strength. This first stage occurs before any other symptomatic manifestation and, therefore, would allow for a first diagnosis, which would indicate that a still indefinable process has started. At the same time, the new criteria acknowledge that the preclinical stages of Alzheimer's disease represent a continuum, including those cases that will never go beyond stage 1 or 2. The presence of one or two biomarkers, once the MCI stage has been reached, would indicate that an individual is experiencing a neurodegenerative process that in further stages will be defined.

As the group of experts highlights in their conclusions [32], at the moment, these criteria are to be used only in research and have no diagnostic utility; the objective of the new criteria is to allow researchers to better characterize the biological sequence that triggers Alzheimer's disease from the first moments. Therefore, these criteria have to facilitate the standardization of data collection in new studies, whose results will modify the very same criteria.

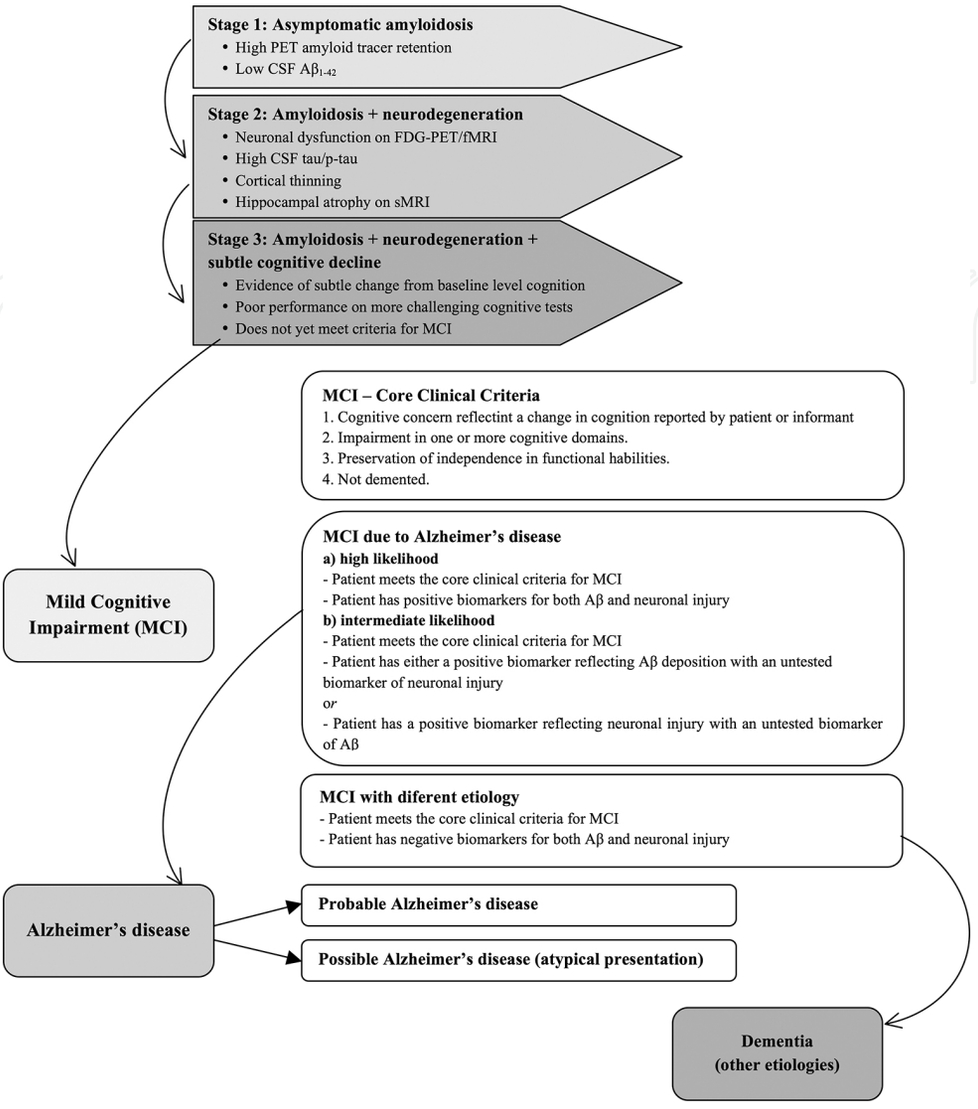

Figure 3. New proposal for research criteria for MCI and Alzheimer's disease.

6. Neuropsychological contributions to the early detection of cognitive impairment

Research has highlighted, beyond the genetic base, a series of factors that have a crucial significance in the development and course of cognitive impairment and Alzheimer's disease. There is great interest in knowing, for example, the association between two facts: cognitive impairment and metabolic and vascular alterations, such as cardiovascular diseases, high blood pressure, diabetes, or obesity, on the one hand, and the establishment and course of the disease, on the other. Understanding these relationships and obtaining data via clinical studies can help us understand that the fact of reducing risk factors associated to these pathologies may be also useful to control Alzheimer's disease. Moreover, a healthy balanced diet, physical

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exercise, social commitment, and mentally challenging activities can help people to keep healthy as they get older [53].

With regard to environmental factors, included in the diagram of **Figure 2**, different studies show that a higher educational level, complex working activities or a socially integrated lifestyle are factors that can help to postpone the onset of clinical cognitive impairment [54, 55]. It has also been shown that physical exercise and cardiovascular activity have long-term benefits on cognition [56]. Actually, physical activity has been proved to reduce the risk of developing dementia and to improve cognition [57].

On the other hand, vascular risk factors are associated, by definition, to vascular dementia. In contrast, the relationship between vascular risk factors and the development and progression of cognitive impairment associated with Alzheimer's disease is less clear. For more than three decades, Alzheimer's disease has been described as a primary neurodegenerative disorder with scarce, or none, vascular foundation [5, 58]. Nevertheless, in the last few years, knowledge about this relationship has increased a lot and many current studies relate vascular risk factors to the pathogenesis of mild cognitive impairment and Alzheimer's disease (see De la Torre for a thorough theoretical revision [59]).

Knowledge about the risk factors of Alzheimer's disease has expanded a lot, and at present, they include not only risk factors particular to the ageing and adulthood process but also risk factors particular to all life stages. For example, perinatal conditions, brain development, growth factors, socioeconomic conditions, or cognitive reserve are factors that have been shown to have an influence on the process of developing dementia [60, 61].

The identification of prodromal neuropsychological markers in cognitive impairment is based on the idea that neuronal loss starts much earlier than clinical symptoms. For this, it is essential to clinically detect individuals in the first stages of impairment, as starting treatment in these early moments would help to maximize the impact on maintaining cognitive functions and functional skills. Hence, the importance of having adapted tests to detect cognitive impairment at early stages, as an early diagnosis of cognitive impairment at prodromal stages is still a very important objective, considering the probability that this stage will be susceptible to treatments designed both to stop and to slow down the progression of the impairment.

In summary, literature suggests that the risk of starting a process of cognitive impairment linked to Alzheimer's disease is not determined only by a genetic component or by certain risk factors in adulthood, but by the result of a complex interaction between genetic and environmental factors throughout our entire life.

In the next decades, an increase in the prevalence of Alzheimer's disease in particular and cognitive impairment in general is expected. Advances in clinical research will make the management of this disease more sophisticated. In the near future, there will be new tests to identify both people at risk of developing Alzheimer's disease and those having early symptoms of cognitive impairment. At the same time, there will be more medicines available and possibly the progression of the disease may be delayed for years. With the improvement in diagnosis and early detection of Alzheimer's disease, more people will be diagnosed at the early stages of the disease. The role of the family will be more and more crucial, as together

with early diagnosis and pharmacological treatment there will be coordination of care and support functions both for patients and for carers of people with dementia. Many of these individuals will have the added value of still being there for their families, to look after children, for example, or being an important part in the ageing of the parents themselves. To improve care and support to these people, the public and private sectors have to work together to eliminate age-related barriers that reduce access to help and support services and to improve the comprehension of the unique needs of the people diagnosed with Alzheimer's disease and their environment.

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