# INITIAL FINDINGS AND EVALUATION OF ALZHEIMER'S DISEASE

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## 1. Introduction

Alzheimer's disease (AD) is the most ordinarily observed type of dementia and mercilessly mortifies the neurons. A woman named as Augusta Deter was diagnosed as AD for the first time by psychiatry and neuropathology specialist Dr. Alois Alzheimer on 25th of November, 1901. It seems a long time since beginning but neither the pathophysiology of the disease has been clearly understood nor a therapeutic approach has been improved to even halt the progression, let alone a complete cure. The patient's husband said that Augusta had progressive forgetfulness, difficulty in expressing herself, daydreaming, jealousy, and difficulty in carrying out activities of daily living and all those signs actually had started and progressed in the last a few years of duration.

As very well–known today, there are two main pathological hallmarks of the disease, as being extracellular β amyloid (Aβ) deposits and intracellular neurofibrillary tangles (NFTs). In this part, however, we discuss the very early sign and symptoms, instead of discussing pathological consequences of the diseases. Despite the fact that the disease is widely accepted as being associated with old age, it also could develop in early decades. The disease might abruptly come into view before the age of 65 which is known as Early Onset of Alzheimer's Disease and it also might ordinarily arise after the age of 65 which is known as Late Onset of Alzheimer's Disease and constitutes of more 90% of cases. Nowadays, the most common question arising about the disease is "What are the very early signs and symptoms preceding AD?".

## 2. Mild–Cognitive Impairment

When we ponder upon 'very early signs and symptoms' of AD, we should first go into some detail of the mild cognitive impairment (MCI). MCI is defined as a cognition status of an individual, which is impaired further than expected with a healthily aging, but impairment does not interfere with the daily activities yet (Petersen et al., 1997). Easily understood from this definition, there is also a healthily cognitive decline by aging.

There are accepted to be six domains of cognition which are learning and memory, language, social functioning, visuospatial function, executive functioning and complex attention. MCI (Fig. 1) is usually points out a cognition status in which an individual has difficulty in learning novel knowledge and recalling stored information. It is further divided into two types, as being amnestic and non–amnestic. Amnestic MCI is defined mainly as difficulty in recalling stored information, whereas in non–amnestic type, individual experiences a decline in one or more of those cognitive domains with a relatively preserved memory functioning. Amnestic type is known to be more common. Actually, the term "amnestic" precisely distinguishes the variety of MCI which includes an impairment in memory domain from the other which does not (Fig. 2).

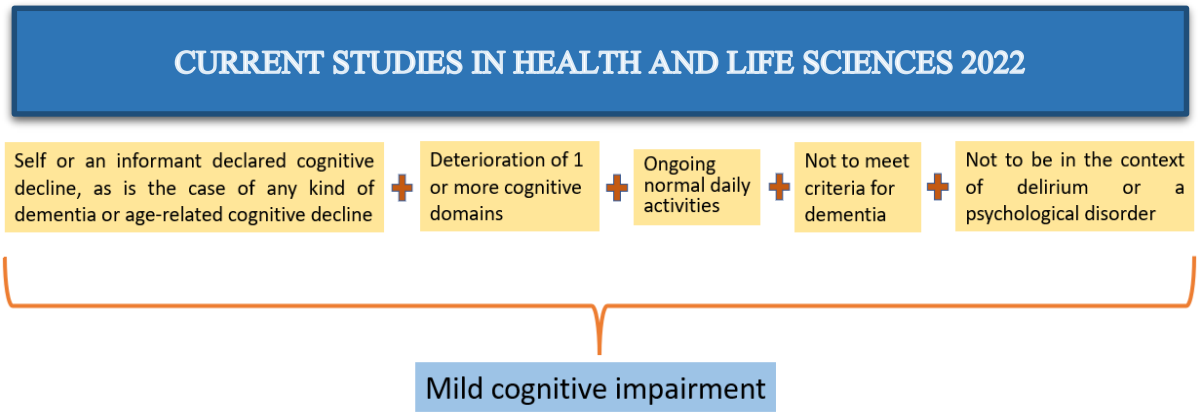


**Figure 1.** Mild cognitive impairment is actually diagnosed when you could not diagnose the case as dementia. Also, the case should not be in the context of delirium or a psychological disorder.

The risk factors for MCI display a high integrity and similarity with those of dementia. Vassilaki M. and colleagues declared that individuals with at least two of exceptionally four co–morbidities, hypertension (HT), hyperlipidemia (HL), coronary artery disease (CAD) and osteoarthritis carry the greatest risk of developing MCI (Vassilaki et al., 2015). Thus, inflammatory status of the individual seems to be one of the major determinants.

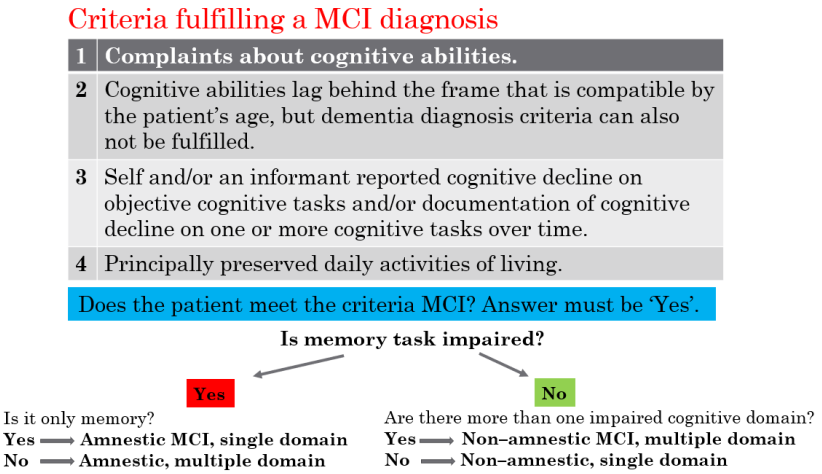


**Figure 2.** Subtypes of mild cognitive impairment (MCI) and distinguishing amnestic type from non–amnestic (Winblad et al., 2004).

The most plausible cause that's why MCI should be diagnosed is there are myriads of treatable reasons which can result in MCI and even be diagnosed as dementia clearly (Fig. 3).

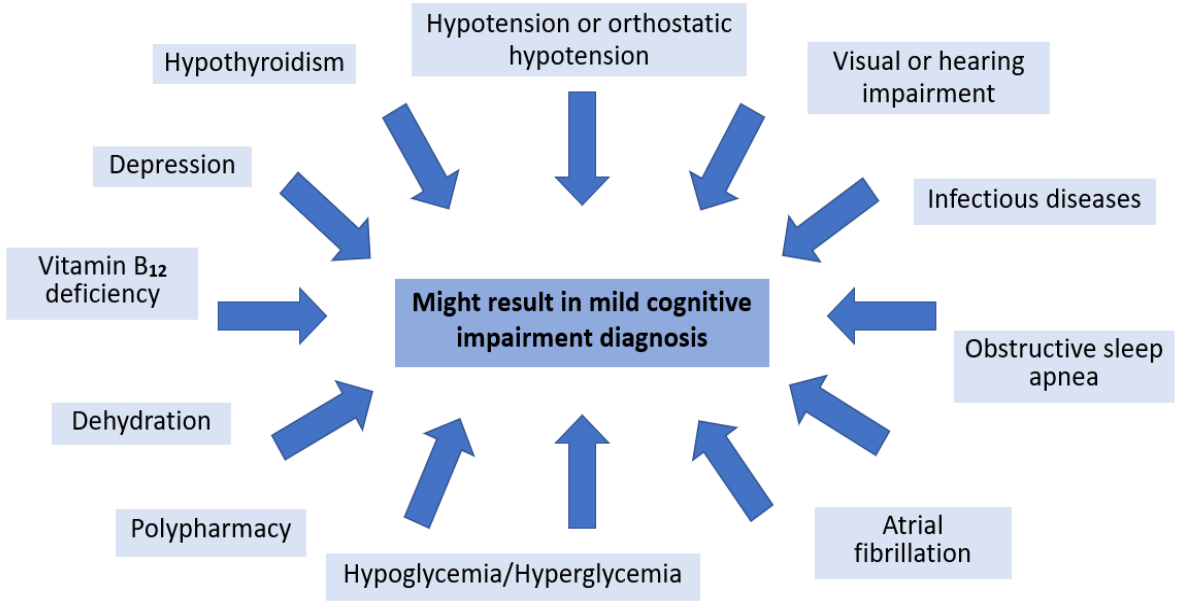


**Figure 3.** Main treatable reasons of mild cognitive impairment (Sanford, 2017).

Most of the treatable reasons might be easily neglected by the physicians. This may be because of mainly focusing on complaints about cognitive functions and partly due to existence of less than needed geriatric specialists and allied health staff. Despite the fact that a comprehensive geriatric assessment (Garrard et al., 2020) requires a devoted and steadfast educational discipline, which is the 'geriatrics', the circumstance is more complicated. Because cognitive complaints might arise in early decades, and this requires also well–equipped specialists from many others disciplines capable of managing cognitive complaints. So, leastways, differential diagnosis of cognitive complaints must be substantially placed in basic medical education. To start from scratch, depression is undoubtedly associated with cognitive decline and one of the most probably preventable reasons of the MCI. According to the one of the studies in which 6180 elderly aged 70 or more were observed in a collaborative observational type, patients with depression have an odds ratio of 2.7 compared to non–depressed ones for cognitive impairment (Scuteri et al., 2011). In another study, polypharmacy is associated with a significant decline in mini–mental state examination test (MMSE) (Oyarzun–Gonzalez et al., 2015). By conventional approach, a physician picks a therapeutic agent for his patient, according to the attributes of the patient, such as the age, gender, whether is there any chronical disease, existence of a pregnancy, malignancy etc. It seems that concept of selection of therapeutic agents is reshaped in the foreseeable future by taking into consideration novel approaches which predispose to select the best for cognition of the patient. It is well–known since recently that brain has its renin–angiotensin–aldosterone system (RAAS). Basically, pathways which are activated by angiotensin receptor type I (ATR–I) and angiotensin receptor type II (ATR–II) are found on poles exactly apart in brain. For instance, ATR–I chiefly heats up NADPH–oxidase system and generates pro–inflammatory and oxidative effects. In one of the studies, it is found that infarct bulk is scaled down in ATR–I knock–out mice after middle cerebral artery occlusion. On the other hand, an ATR–IV antagonist is found to weaken spatial memory abilities in rats (Royea

and Hamel, 2020; Wilson et al., 2009). So, angiotensin receptor blockers (ARBs) might attenuate co–existing cognitive impairment to a certain degree in patients with hypertension or stroke. These findings and hypothetical results show that, just as we are trying to choose the best blood pressure medication for a pregnant woman or a chronic kidney failure patient, approaches that will determine treatment options by considering cognitive functions will increase more and more in the near future.

The inter–relation between medical intervention and cognition is only one aspect to benefit maximum for cognitive status of individual. And as it is shown in Fig. 3, there are also many reasons other than medical therapeutics result in individual to display MCI or dementia like symptoms.

MCI, with its four major subtypes (Fig. 2), is believed to make the way for very early signs of dementing disorders which are AD, vascular dementia, Parkinson's disease dementia, Lewy body dementia and frontotemporal dementia. So, cognitive aging does not settle down in continuum of MCI and varieties of dementia (Tab. 1).

**Table 1.** Key features of normal cognitive decline with aging, mild cognitive impairment (MCI) and any type of dementia (Henderson, 2014).

| Type of cognitive decline | Do the symptoms interfere with the person's independence? | Are the symptoms caused by a pathology in the brain? |
|---|---|---|
| **Cognitive decline with normal aging** | No | No |
| **MCI** | No | Yes |
| **Dementia** | Yes | Yes |

Despite the fact that MCI is considered to be produced by certain types of brain pathology, it might display each of three possible aftermaths, progress to dementia, follow a stable course or symptoms might regress. Then, if it would progress to dementia, the patient is expected to display pre–dementia symptoms. Those of the patients with MCI who will complete the steps of pathological course of AD are believed to show symptoms mostly related to episodic memory (difficulty in learning and retaining new information) at the very early stages. Albert and colleagues (Albert et al., 2011) proposed a new concept to differentiate MCI prone to transform into AD from other types of MCI, 'MCI due to AD'. This new concept primarily depends on detecting very early signs of episodic memory impairment. This determination is so difficult that the earliest signs of episodic memory impairment should also not have a negative impact on the flow of one's occupational and social life. We should get the evidences of episodic memory impairment, but still it should be clearly established that the individual has been able to take care of himself and carry on daily activities. So only in this way, we can exclude a

diagnosis of dementia for the patient's condition. Although memory is the principal cognitive domain to be impaired involved in MCI patients who destinably progress into AD, other cognitive domains, such as executive functioning, language, visuospatial skills and attentional control should also be examined.

### 3. Challenges in Early Diagnosis of AD

All around the world, two third of all dementia cases are consisted of AD patients. Forecasts also show plausibly that the frequency of AD will increase gradually worldwide in the coming years. This seems a foregone conclusion principally due to taking into account increased life expectancy, population and incidence of cardiovascular disease. Arguments that will enable us to intervene in this whole process can be put forward easily relatively. For instance, what can be done to reduce the prevalence of cardiovascular diseases, which is an important risk factor for both AD and vascular dementia, could be ruminated on. High cholesterol level in middle age increases the risk of AD (Kivipelto et al., 2002; Whitmet et al., 2005). Whereas body mass index (BMI) populously negatively correlates with dementia after age of 65, obesity in middle ages clearly increases the risk of dementia seen in later ages (Fitzpatrick et al., 2009). Physical activity makes the individual less prone to develop dementia or AD (Larson et al., 2006). Findings about blood pressure level are controversial. While higher than normal blood pressure levels in the middle ages have been accused of increasing the risk of dementia, some other researches propose that low blood pressure level in old ages as a risk factor of developing dementia (Qiu et al., 2005; Ruitenberg et al., 2005). All these remarkable findings, actually a small part of those considered to be associated with AD, can be defined as modifiable risk factors for AD. Ensuring the control of modifiable risk factors will undoubtedly contribute to the reduction of the prevalence of dementia and AD. Hence, certain studies indicate a slightly decreased or still stable incidence of dementia in high–income countries (Roehr et al., 2018). This may be because of a more qualified control of modifiable factors in high–income and high–educated regions of the world. Early diagnosis of AD also provides a chance for control of those risk factors, because very early symptoms or diagnosis of MCI and AD make the clinician and the patient even more alarmed about controlling the risk factors to be able to halt the progression of the disease. So, MCI or early symptoms of AD should be made more recognizable or well–known.

According to the one of the previous studies, first symptom of MCI patients is a decline in memory, with 80%, in compliance with the anamnesis acquired from the informants. Depression like symptoms is the first sign in 9% of those patients. Following these two, decline in language abilities, weakening of high–order social or functional daily activities, disorientation and personality and behavioral changes are also seen as first symptoms, respectively and with a decreasing percentage. In that study, informants reported that a second symptom had currently been besides first symptom at the time of first/baseline evaluation of the patient. In those of patients whom MCI turns into AD, second symptoms appended to decline in memory as first symptom are mostly weakening of high–order social or functional daily activities and disorientation (Devier et al., 2010). It is very famously known that a neuropathologic examination is the gold standard to diagnose AD. Since this is unlikely, one of

the best ways to early diagnose the disease seems to provide a depiction of early signs and symptoms and place them in a proper continuum.

The preclinical phase is defined as a period in which the person is asymptomatic but neuropathological changes might have been present for a long time (Fig. 4). So, the most

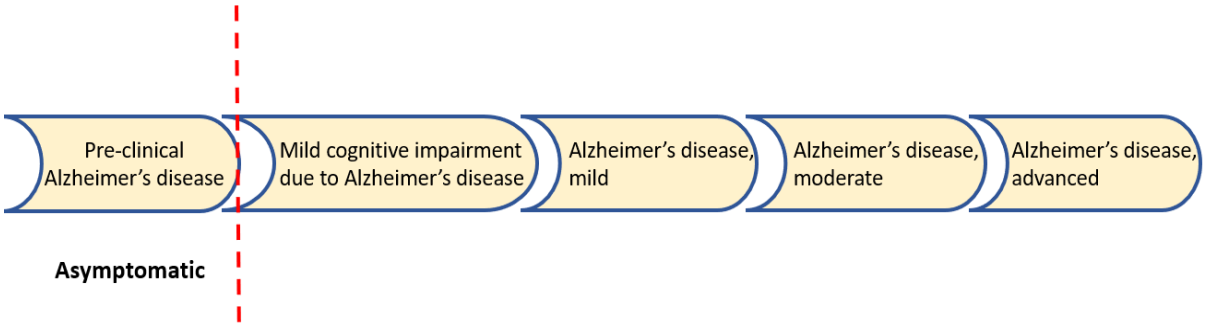


**Figure 4.** Alzheimer's disease continuum based on the 2011 National Institute on Aging and Alzheimer's Association (NIA-AA) guideline.

challenging issue seems pre–clinical phase. Because any sign or symptom cannot be readily observed, but devastating process of the disease has already started in this phase.

In the very early stages, the most critical determinant in revealing the signs and symptoms related to cognitive decline is the person himself or the person's closest family members, friends or caregivers. Whereas all these people may sometimes positively contribute to the diagnostic process, they also may behave in such a way that fail the early diagnosis. For instance, the patient himself may avoid to reveal or tell symptoms of certain kind of decline in his cognitive abilities due to fear of stigmatization (Dubois et al., 2016). And, relatives may misinterpret the signs, considering them as a natural consequence of advanced age (Galvin et al., 2012). Physicians' initial assessment has also a great importance for detection of signs and symptoms associated with MCI/AD. A comprehensive medical history; including recent and chronic illnesses; any medications that could cause memory loss or might adversely affect cognition; traumas; usage of illicit drugs or drug abuse; history of epilepsy or seizures should be questioned. In addition to an extensive neurological examination including history of any falls recently and notice of any gait disturbances, cognitive abilities of the patient should be examined in all aspects, including episodic memory, executive function, attention, language, and visuospatial skills. Under the heading of risk factors, whether there is a dementia patient in the family and the person's history of cardiovascular disease, obesity and smoking should be questioned in detail. Cognitive and behavioral changes should be questioned. In general, it should be questioned what a day means to the person, whether he has been forgetful recently or lost his belongings, whether he has recently felt depressed, hopeless, and whether he has been able to manage his financial affairs. As can be seen, in this evaluation process, which actually starts with the anamnesis, it is aimed at first to eliminate the causes that can be diagnosed and treated. Satndard laboratory tests and screening tests are also added if needed. Various algorithms have been developed for an initial assessment (Cordell et al., 2013; Porsteinsson et al., 2021).

In the first evaluation and afterwards, we can say that the things to be done to reach the diagnosis of Alzheimer's and to give the necessary up–to–date treatment are more or less clear. However, if we are going to talk about the difficulties of early diagnosis and treatment, we should also mention what studies on MCI have taught us. When the MCI period before AD is diagnosed correctly, it undoubtedly provides an important opportunity for the implementation of approaches that will prevent or delay the emergence of AD. Therefore, it may even be reasonable for any clinician to place more emphasis on diagnosing MCI or performing community screening for MCI than on diagnosing AD or conducting population screening for AD. Nevertheless, diagnostic criteria for MCI used in clinical trials seem to have insufficient preciseness (Visser et al., 2005; Jelic et al., 2006). A series of randomized controlled trials examined effects of non–steroidal anti–inflammatory drugs and acetylcholine esterase inhibitors on MCI patients, to detect whether those drugs prolong the period between the moment when the MCI is diagnosed and when MCI turns into a clear or probable AD. These studies gave us information about the effects of drugs on the transformation period of MCI to AD. However, it is extremely surprising to see that even small differences in criteria for identifying patients with MCI changed the results drastically (Visser et al., 2005; Jelic et al., 2006; Petersen et al., 2005; Thal et al., 2005). In one of those studies (Thal et al., 2005), less patient receiving placebo turns into AD than in group receiving rofecoxib. Cognitive function scales (MMSE test, auditory verbal learning test, cognitive scale of AD assessment scale, selective reminding test, clinical dementia rating, etc) are frequently used for the diagnosis of both AD and MCI. However, considering that the inclusion criteria have such an impact on the results of those trials and the importance of MCI progressing to AD, it is indisputable that the inclusion criteria should be very delineative. For instance, being positive with apolipoprotein ε4 allele is a definite risk factor for AD. Does apolipoprotein ε4 allele positivity deserve to be a heading in MCI inclusion criteria? Is it worth the cost? Positron emission tomography (PET) with fluorodeoxyglucose (FDG) has been approved for use in early diagnosis of AD (Silverman et al., 2002). Should it come into routine use for early detection of MCI and AD or be one of inclusion criteria? Cerebrospinal biomarkers like Tau (τ) and Aβ and in vivo imaging of Pittsburgh compound B (C–PiB), a carbon–11 labelled thioflavin–T derivative (C–PiB) might also extend the accuracy of early diagnosis (Jelic et al., 2006; Yamin et al., 2017). Novel randomized clinical trials are needed to be conducted to develop inclusion criteria of MCI and AD.

### 4. Very Early Manifestations of Alzheimer’s Disease

It is absolutely agreed upon by scientists that brain damage is starting even a few decades before deterioration of memory and cognition explicitly appears in AD. So, before signs and symptoms arise, there should be a silent period with ongoing damage in brain. Memory loss, forgetfulness, difficulties in completing daily tasks, indigent judgement and wrongful decisions, decrease in ability of taking action instinctively, loss of sense of initiative, repeating questions heard very recently, trouble in management of financial issues, being on the loose, getting lost, losing things, misplacing the objects and mood and personality changes are the notable symptoms of the AD. But, when and how these symptoms begin is questionable. For instance, do difficulties in remembering memories, names, people etc. always indicate the disease?

Undoubtedly, some memory changes are encountered by old age (National Institute on Aging, An Official Website of the United States Government). Especially, slimming of episodic memory is a foregone conclusion with age progression (Shing et al., 2010). All people understand that as they age, there are changes in their cognitive abilities. The most common question they ask themselves or the doctor they are examined is "Are these changes in my cognitive abilities normal or a sign of dementia?". One of the first of the changes that are considered normal with advancing age is a decrease in cognitive speed. For example, it may take longer time to remember a word or a person's name. Decline in complex attention also occur naturally with advancing age. For example, you may need to turn down the volume of your radio while setting up the medications you use daily. Working memory also weakens with advancing age. For example, it becomes difficult to remember the address you asked while listening to instructions on how to get there. When getting ready to go to a wedding, things like shaving first, taking a shower, getting dressed, and being able to do it all on time or when a friend starts acting cold towards you, things like noticing the situation, thinking over the possible causes, trying to understand his point of view and taking action to solve the problem might get more difficult by older age. This indicates a decline in mental flexibility. Visual or hearing impairments can also cause cognitive decline to be felt more prominent than it actually is. However, this changes never affect the individual's daily day functioning. These findings are also unlikely to cause significant changes in pen and paper cognitive tests. MCI cognitive impairment is a period in continuum where the physician realizes significant changes in those tests. And the patient begins to have more difficulty in bill paying, setting up the pill box, remembering taking their medications and even carrying on household chores, in such a way that still does not affect the daily basis functioning to diagnose the patient as dementia. In amnestic MCI, scores of cognitive tests are prone to poorer than those of individuals with normal cognition and better than those of individuals with AD, mostly ranging in the normal limits. The same range could be seen when the individuals are put to verbal and visual memory tests.

Although there is no sign of cognitive decline in very early stages, certain biomarkers of which handling has been becoming more and more indispensable for detection of early disease should be mentioned. With the forecast made according to a hypothetical situation; early diagnosis is so important that even if we could not prevent progression of the disease, it has been revealed that when we delay its manifestations by 5 years to grow on, the number of AD patients would decrease by 57%, and the medicare costs reduce by almost half (Alzheimer's Assocation). Although we refer to MCI as the preclinical stage, it should not be forgotten that AD exhibits a continuum of pathology and there should be still periods before MCI. Since signs and symptoms can also be detected in MCI, but do not meet the criteria for diagnosing AD in MCI; the preclinical phase can be defined as the period in which the individual does not have any clinical signs and symptoms at all, but biomarkers related to AD pathology can be detected (Fig. 5).

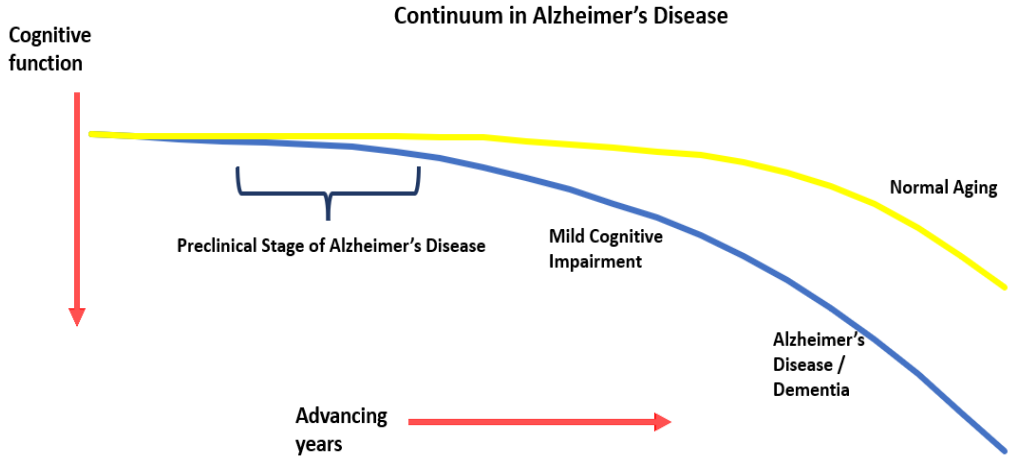


**Figure 5.** Clinical continuum model of AD. Conceptual preclinical AD precedes MCI. The definition of preclinical AD includes presymptomatic individuals who carries autosomal dominant mutations, asymptomatic biomarker–positive elderly individuals with the potential to develop MCI due to AD, and individuals who exhibit an insidious decline in cognitive abilities in a degree that exceeds the decline in normal aging but does not yet meet the criteria for the diagnosis of MCI. This diagram stands for a hypothetical model for the pathological–clinical continuity of AD. However, not all individuals with biomarker evidence of AD–pathophysiological process progress to clinical phases of the disease (Budson and Solomon, 2012).

So, according to this clinical continuum model (Fig. 5), there must also be a pathophysiological continuum. It is known that there is a deterioration in the processing of Aβ proteins without any measurable decline in cognitive abilities. However, if a presymptomatic individual with underlying AD pathology lives long enough, he will one day become symptomatic. Both screening findings and quantifiable chemicals/biospecimens are considered to be biomarkers which provide information regarding the stage and characteristic changes in AD. In this content, five major biomarkers are identified, which are in mostly order of development decreased 42–amino acid form of amyloid–β ($A\beta_{42}$) in cerebrospinal fluid (CSF), increased τ protein in CSF, decreased FDG uptake on PET (FDG–PET), PET amyloid imaging and structural changes, i.e. cerebral atrophy on MRI (Jack et al., 2010). Either CSF $A\beta_{42}$ or PET amyloid imaging are substantial biomarkers indicating brain amyloid plaque deposits. C–PiB is currently one of the leading trackers for imaging amyloid accumulations in vivo with PET amyloid imaging. In vivo C–PiB uptake imaging noteworthily congrues with regional quantitative analysis of Aβ accumulation in post–mortem studies (In patients subjected to ante–mortem PiB–PET imaging and autopsy). On the other hand, lower than normal level of $A\beta_{42}$ in CSF might display an association with clinical AD diagnosis, and is harbinger of well–known pathological findings at autopsy (Schoonenboom et al., 2008). Another important association seen in almost all patients is that unusually low $A\beta_{42}$ levels in CSF match with PiB–PET findings.

Although high levels of τ protein in CSF is not entirely specific for AD, elevated levels of τ correlate positively with clinical severity of disease, with phosphorylated τ being more

important for AD. This means that the greater τ concentration is encountered, the more intensified cognitive impairment takes place in the MCI–AD continuum. Briefly, increased CSF τ concentration is a well–known indicator of neuronal injury and also associated with ischemic or traumatic brain injury, but a more detailed delineation of that issue is out of the intended scope of this chapter. Higher than normal level of τ in CSF is forerunner of NFTs pathology findings at autopsy. Cerebral glucose consumption as assessed by FDG–PET is an effective biomarker for local neuronal network integrity. Cerebral glucose consumption measured by FDG–PET positively correlates with synaptophysin protein level which is considered to be an indicator of well–being of synaptic density (Rocher et al., 2003). In the framework of Alzheimer's disease, decreased FDG uptake on PET imaging means that functional synaptic capability is impaired. So much so that even if the atrophy caused by AD is rectified hypothetically, the use of glucose per gram tissue has been found to decrease in the AD neuropathology–specific topography of the brain (Ibáñez et al., 1998). Lastly, although the atrophy seen on MRI is not specific to AD, it is known to correlate with disease severity and cognitive decline. When these biomarkers are put on in a temporal order, Aβ deposits are mentioned in the first place, while signs and symptoms of cognitive impairment are not yet seen (Fig. 6). As for signs and symptoms of cognitive decline become evident mainly with the emergence of biomarkers of neurodegeneration. Thus, in the early stages of the disease, we can although detect decreased FDG uptake with PET and obtain images confirming Aβ deposition, encounter reduced Aβ levels in the CSF, but not yet detect signs of atrophy in advanced conformity with age on MRI. In case of NFTs, the formation and increase of NFTs does not entirely precede cognitive impairment, as we mentioned for Aβ plaques. Either of individuals with NFTs or those with Aβ plaque deposits can display normal cognitive abilities. However, NFTs seen in asymptomatic individuals are more specific to the entorhinal cortex and these individuals tend to be in Braak stages I and II (Braak and Braak et al., 1997). NFTs are much more common in symptomatic individuals and are not unique to the entorhinal cortex, instead more widely distributed in brain. However, even individuals with extensive Aβ plaque deposits can be asymptomatic.

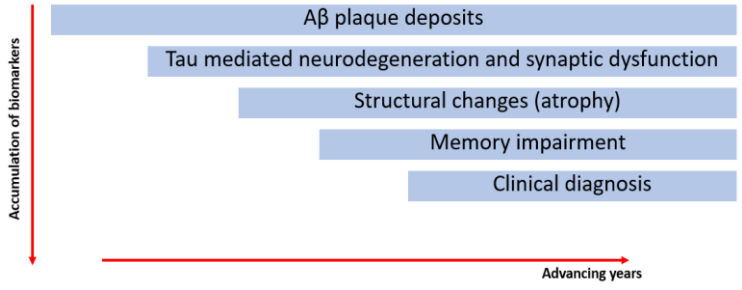


**Figure 6.** Aβ accumulation is determined by measurement of $A\beta_{42}$ in CSF or by PiB–PET. Tau measurement in CSF, or FDG–PET reveal the neurodegeneration and synaptic dysfunction. The degree of atrophy is determined by MRI (Jack et al., 2010).

## 5. Conclusion

Understanding that Alzheimer's disease is a continuous process may present us with different options for intervention. For example, the view that decreased FDG uptake detected in PET leads to neurodegeneration brings to mind possible vascular or metabolic interventions. In this case, we may find ourselves focused on treating AD by looking for ways to protect the vascular health of our central nervous system, rather than trying to find drugs that inhibit neurodegeneration. On the other hand, conditions such as MCI are becoming almost as important as AD. The diagnosis of MCI gives the person a chance to both regulate his present and future and adapt lifestyle modifications to his daily life. We should not forget that the question of "will I have AD?" is being asked more and more each day by growing elderly population has been covering a greater place in the practice of clinicians.

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