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Alzheimer's Disease: A Clinical Perspective

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1. Introduction

Dementia is defined as a clinical syndrome characterized by progressive deterioration in multiple cognitive domains that are severe enough to interfere with daily functioning, including social and professional functioning. Alzheimer disease (AD) is the most common form of dementia often diagnosed in people over 65 years old, even though the early-onset AD can occur much earlier since 40 years of age. AD is a multifactorial disorder in which the causes and the progression are still not well-understood. Aging is the most common non-modifiable cause of dementia in the elderly, but it accounts only for approximately half of all cause. Research identified other potential causes among the interaction between modifiable environmental factors, such as vascular disease and genetic susceptibility. The recent genetic discoveries have shown that mutation of the β-amyloid precursor protein on chromosome 21, and the mutations of presenilin 1 and presenilin 2 on chromosome 14 and 1, were associated with increased susceptibility of AD. Finally, the presence of the ε4 allele of Apolipoprotein E (APOE) is considered as a risk factor for late-onset of AD. The Diagnostic and Statistical Manual on Mental Disorders, fourth edition text revised (DSM-IV-TR), defines dementia as an acquired disease characterized by decline in memory and at least one other cognitive function such as attention, visuo-spatial skills, language, or executive functions. Beside the cognition, the disease affects the emotional abilities and interferes significantly with work and daily-life activities. Dementia can be defined as either possible, or probable based on the recent published diagnostic criteria [1]. Since 1980s, numerous community-based prospective studies of aging and health have been implemented in the world; many of which have focused on dementia and its main subtypes of AD and vascular dementia (VaD). In this Chapter, we review the literature of clinical and epidemiological research in the dementias by focusing on most recent studies.

AD is an age-related phenomenon and is the most common cause of dementia, but increasing evidence from population-based neuropathological and neuroimaging studies shows that mixed brain pathology (neurodegenerative and vascular) account for a large number of dementia cases, especially in very old people [2]. According to the World Alzheimer Report, there were 35.6 million people living with dementia worldwide in 2010, a number that will increase to 65.7 million by 2030 and 115.4 million by 2050 unless effective means of reducing disease incidence are introduced. The total estimated worldwide costs of dementia were US $604 billion in 2010, including the costs of informal care, direct costs of social care, and the direct costs of medical care [3]. Increasing age is a well-established risk factor for dementia and AD. Both prevalence and incidence of AD increases exponentially with advancing age, and 70% of all dementia cases occur in people aged 75+ years [4]. Notwithstanding, despite the incidence rate of AD increases almost exponentially until 85 years of age, it remains uncertain whether the incidence continues to increase even at more advances ages or reaches a plateau [5]. In Europe, the age-adjusted prevalence is 6.4% for dementia in general, and 4.4% for AD among people 65 years and older [6]. In the US, has been estimated that the 9.7% of people aged 70+ years has AD [7]. More than 25 million people in the world are affected by dementia; most of them suffer from AD, with about 5 million new cases every year [8, 9]. The estimated global annual incidence is around 7.5 per 1000 people [8]. The incident rate increases from approximately one per 1000 person-year in people aged 60-64 to more than 70 per 1000 person-year in 90+ years-old. In Europe, the pooled incidence rate of AD in people aged 65 years and older was 19.4 per 1000 person-year. The incidence rates of AD across different regions are quite similar in the younger-old, but greater variations have been seen among the older ages, but this is probably because of differences in methodology such as study designs and case ascertainment [5]. In conclusion, the worldwide population aging explains the epidemic proportions for dementia making the disease an important issue for the public health.

2. Pathogenesis and mechanisms of AD

Alzheimer's disease has not a single cause but is the results of the interaction of multiple mechanisms that can be grouped into aging, genetic influence, vascular pathology, inflammation and environmental influence such as toxic exposure. However, currently, the precise pathogenesis of AD is not known. One of the most important pathologic features characterising AD is the brain atrophy which results by loss of neurons, synapses and dendritic arborization in the cerebral cortex and subcortical regions. Cerebral atrophy is associated with the presence of neurofibrillary tangles and amyloid plaques, two hallmarks over-expressed in AD brain [10]. Neurofibrillary tangles are insoluble aggregates of hyperphoshorylated microtubule-associated tau protein that become accumulate inside the cells themselves. Changes in tau protein lead to the disintegration of the brain microtubules, the main neuron's transport system [11]. Amyloid plaques are dense and insoluble extracellular deposits of β-amyloid peptide (Aβ). Aβ derived from APP protheolisis. This transmembrane protein is divided into smaller fragments by three different enzymes: α, β, and γ–secretases. The

cleavage of APP by β, and γ–secretases creates Aβ42 peptide, while the cleavage by α-secretase produce Aβ40. Aβ42 peptide aggregates more readily than Aβ 40, and the ratio of these two isoforms influence the formation of the senile plaques [12]. Genetic studies [13] have identified mutations in APP and presenilin 1 and 2 (components of the γ-secretase) that cause rare, dominantly inherited familial AD. These findings strongly supported the amyloid hypothesis [14], which posits that β-amyloid peptides play a pivotal role in AD pathogenesis. The amyloid cascade hypothesis suggests that deposition of Aβ triggers neuronal dysfunction and death in the brain. In the original hypothesis, this neuronal dysfunction and death was thought to be a toxic effect of the total amyloid load.

As knowledge of pathological changes in Alzheimer's disease increased, research identified Aβ oligomers as the principle players of the toxic effect [10]. Changes in tau phosphorylation status and consequent neurofibrillary tangles formation are also triggered by toxic concentrations of Aβ [14]. All the factors mentioned above (aging, genes, inflammation, and vascular pathology) can increase the production of Aβ. Despite genetic and cell biological evidence support the amyloid hypothesis [15], which is also the target of the new immunotherapies for AD, it is becoming clear that AD etiology is complex and that Aβ alone is unable to account for all the aspects of the disease. Others amyloid- independent hypothesis have been proposed [16]. The inflammatory hypothesis is based on the presence of activated microglia in AD brain. These cells, which have been shown to cluster around senile plaques, produce massive amounts of oxygen radicals and inflammatory mediators that are toxic to brain cells ultimately destroying them [17]. There is general agreement that the overproduction of free radicals generated from oxidative stress has a major role in neurodegeneration [18] and, as a reactive process, it may be involved in cell cycle regulation contributing to cell death [19]. In brain, a variety of stressants can induce oxidative stress as cerebral hypoperfusion, inflammation, aging, hypoxia, cigarette smoking, excess alcohol, or cardiovascular disease. There is also a vascular hypothesis that suggests that cerebral hypoperfusion in the presence of vascular risk factors can further lower cerebral blood flow to a critical level that threatens neuronal survival [20, 21]. Many other mechanisms have been suggested and can be involved in AD neurodegeneration, anyhow none hypothesis alone can explain the pathogenesis of AD [22].

3. Risk factors

The aetiology of dementia and AD has been extensively studied trying to find efficacious prevention and treatment strategies. As said, dementia is a multifactorial disorder caused by complex interaction between environmental and genetic factors. It has been estimated that 1-5% of AD cases are due to genetic mutations, while the most part are ascribable to modifiable environmental factors and their interaction with genetic susceptibility [10]. Age is the most powerful determinant of dementia, suggesting that aging-related biological process may be involved in the pathogenesis of AD [23]. In actuality, the association between age and AD is mediated by the cumulative effect of other risk and protective factors over the lifespan. The major risk and protective factors for AD can be summarized basing on the dif-

ferent etiological hypotheses including genetic susceptibility hypothesis, vascular pathway hypothesis, psychosocial hypothesis, nutrition and dietary hypothesis, and others (e.g., toxic or inflammatory factors). While the role of genetic, vascular and psychosocial factors in the AD onset is supported by strong to moderate epidemiological, neuroimaging and neuropathological researches, the evidences for the other factors are controversial and insufficient [5]. Following age, the presence of Apolipoprotein E ε4 allele (APOE ε4) is the most established genetic risk factor for developing late-onset AD. There are three forms of APOE alleles, ε2, ε3, and ε4, APOE ε4 increased the risk of AD by three times in heterozygote and more in homozygote, while ε2 decreases the risk [24, 25]. APOE allele ε4 is a susceptibility gene, being neither necessary nor sufficient for the development of AD.

In the last decade many others AD susceptibility genes have been identified, highlighting the importance of a genetic susceptibility for AD development [26]. Over the last decade, great attention has been paid to figure out which AD-related factors may be modified to decrease the risk of AD. Two groups of modifiable factors for late-life dementias have been identified as "vascular risk factors" that have been strongly associated with an increased risk of dementia; and the "psychosocial factors" that may contribute to the delay of dementia onset. Strong epidemiological evidences suggested that cardiovascular risk factors and vascular disease are associated with an increased risk of symptomatic AD [27].Thus, studies revealed age-dependents associations with AD for several aging-related conditions. The most important cardiovascular risk factors for subsequent AD include cigarette smoking [28, 29], heavy alcohol consumption [30], midlife high blood pressure [31], atrial fibrillation and heart failure [32], spontaneous cerebral emboli [33], midlife obesity or central adiposity as well as low BMI in late-life [34-36], midlife high cholesterol levels [37], diabetes mellitus and impaired glucose regulation [38-40], neuroinflammation [41, 42], and elevated plasma and total homocysteine levels [43].

Other risk factors for AD may include traumatic brain injury, late-life metabolic syndrome and depression, but their role is not clear and studies with long-term follow-up need to support the risk factors hypothesis [44, 45]. About psychological factors epidemiological research has been accumulating that some psychosocial factors and healthy lifestyle such as the social network and social engagement, weekly-to-daily physical activity, higher educational and socio-economic status and mentally stimulating activity, may postpone the onset of dementia by enhancing cognitive reserve [3, 46-48]. In addition, several studies reported a decreased risk of AD and dementia associated with a diet rich in both high polyunsaturated and fish-related fatty acids, such as the Mediterranean diet [49], and elevated levels of vitamin B_{12} and folate (50). Finally, controversy exists about the role of hormone replacement therapy with estrogens and progestin and subsequent development of AD. Several studies suggest that normal age-related depletion of estrogens in women and testosterone in men may represent potential risk factors for AD's onset [51], suggesting hormone replacement therapy (HRT) as method to reduce risk of late-life AD in postmenopausal women. Nevertheless, the therapeutic effects of HRT is not supported by the Cochrane's review, which found that HRT or estrogens for improving or maintaining cognition was not indicated for women with AD [52].

4. Clinical features

A peculiar feature of AD is the progressive and multi-focal cognitive deterioration characterized by the insidious onset, the absence of focal neurological signs, and memory disorders. It develops slowly and gets worse overtime. Progressing, the disease damages the most areas of the brain, and this is manifested through the gradually deterioration of memory, attention, executive functions, language, praxia, movement and personality. AD should be suspected when any individual, without alterations of awareness, refers generalized episodic memory disturbances with insidious onset that escalate up to interfere with daily living, social and/or occupational activities. In an attempt to help clinicians in recognizing the severity of disease, the Mayo Clinic group proposes three main stages in the natural history of AD, each characterized by distinctive symptoms and duration. The classification has been made based on clinical experience and generalization. It is not intended to be in an inflexible and taxonomic way, but it is important to realize that AD is the neurodegenerative process of the single person, and thus the duration and the type of symptoms may change from one patients to another. Considering that, it is helpful divide the AD progression into following stages: 1) "Early stage" characterized mainly by memory disorders; 2) "Moderate stage" where appears progressive cortical dysfunction (apraxia, aphasia, visuo-spatial disturbance) and disorders of instrumental functions; 3) "Advanced stage" with disorders of the "Control" functions and rise of neuropsychiatric disorders.

People may manifest mild symptoms long time before the clinical diagnosis of AD and often they are underestimated and mistakenly ascribe to either aging or stress. The early detection of symptoms is difficult because of the absence of a definite time of disease onset, so in the clinical practice patients with dementia are often first diagnosed when the disease is advanced to the early stage with the clear manifestation of cognitive and behavioural disorders [53]. The prodromal stage of the disease is known as "Mild cognitive impairment" (MCI) indicating those people likely to be in the earliest stage of dementia, but with so mild symptoms that cannot be formulate a formal diagnosis of dementia. Patients with MCI typically present forgetfulness due to the episodic memory impairment that leads to difficulties of recall and learning new information, but they do not have a clear deficit in daily functioning, being able to live independently with a minimal help [54]. Not all the subjects with MCI develop dementia, but all subjects affected by AD had first presented this mild stage. It is accepted that AD pathogenesis starts decades before clinical manifestation and that subjects decline slowly in cognition for years before meeting the diagnostic criteria for dementia [55, 56]. Longitudinal studies have shown that people with MCI have a high probability to develop dementia within 1-3 years after diagnosis [54]. When the progression of memory impairment and the decline in other cognitive domains (executive function, visuo-spatial, language, behaviour or personality) significantly interfere with the ability to function at work or at usual activities, the criteria for diagnosis of dementia are met [1]. The AD's "Mild stage" can last from 2 to 4 years. The typical scenario includes memory impairment for recent events with relative sparing for remote events (autobiographical memory), prospective memory disorders (remembering to perform a planned action or intention at the appropriate moment), difficulty with problem solving, complex task and sound judgment, difficulty

to organize and express thoughts, deficit in the ability to plan and execute actions in a correct sequence (executive function and apraxia), slowing in the ability to switch from one activity to another [54]. In addition, patients in the mild stage may start to present sporadic language disorders mainly characterized by decreased vocabulary and word fluency with a subsequent impoverishment of the speaking and writing [57].

Neurocognitive studies show that the episodic memory impairment is due to a deficit of storage newly acquired information in long-term memory [58] reflecting an early impairment of the "central executive" component of the working memory with relative sparing of the "slave systems". In this stage it is also likely that personality changes appear and the most prominent is apathy with symptoms of diminished interests and concerns and may be associated with depression. Social withdrawal, fluctuating mood, irritability or anxiety are less frequent. In some cases the non-cognitive symptoms may be more prominent than the cognitive impairment complicating the care of patients with AD. Despite that, they are not present in all patients and are not constantly progressive as the cognitive deficits. Decreased attention and motivation to complete task as well as dresses inappropriately are also common. Towards the end of the mild stage, patients may start to be confused especially in unfamiliar place, reflecting the onset of orientation defects. The "Moderate stage" of AD is the longest stage lasting from 2 to 10 years. The cognitive and behavioural symptoms increase in the severity, people get more confused and forgetful and the progressive deterioration interfere with individual independence, with person being unable to perform most common daily living activities and self-care. On cognition, the middle stage is characterized by a progressive cortical dysfunction with prominent language, praxis, visuo-spatial, executive function and abstract reasoning disorders. Progressive deterioration of oral and written communication includes anomias of aphasic lexico-semantic origin that progress into a fluent aphasia, speech planning defects and "empty speech" because of inability to recall vocabulary which leads to semantic paraphasias, progressive loss of reading and writing. Ideational and ideo-motor apraxia is responsible for difficulties in number processing and calculation. Memory impairment worsen may involve also the autobiographical memory.

Disturbance of visuo-perceptual contour processing and spatial processing evolve leading to deficit in recognizing familiar faces (prosopagnosia) and person, geographical and environmental disorientation, difficulty in coping figure, and visual imagery deficits. Patients become less able to succeed the more demanding tasks of daily living, such as manage finances and driving. The personality and behavioural changes worsen. Psychotic behaviour, paranoia, delusions, auditory or visual hallucinations are not unusual in this stage. Common manifestations are labile affect, irritability, wandering, aggression or resistance to caregiver. Sleep disorders including disruption in the sleep/wake cycle, sundowning, and urinary incontinence can develop. Patients lose awareness of their disease process and limitation (anosognosia). In the AD's "Severe stage" (1-3+ years), patients generally lose the ability to communicate coherently, and experience a great decline in physical abilities becoming mostly dependent on caregiver for feeding and hygiene. Language is reduced to single simple phrases or words. Despite the severity of communication problem, people can understand and return emotional signal. On the behavioural level, aggressiveness can be still present, but severe apathy and exhaustion are common symptoms. Neu-

rological disorders (tonic grasping, echolalia, oral grasping, Kluver-Bucy syndrome and bilateral apraxia), and motor abnormalities can develop. Muscle mass and mobility deteriorate until the patient is completely bedridden and not self-sufficient. People with AD typically die from medical complication as bronchitis, pneumonia, or pressure ulcers, and not because of disease itself [59, 60].

5. Alzheimer's disease diagnosis

The 1984 criteria made by the National Institute of Neurologic, Communicative Disorders and Stroke/Alzheimer's disease and Related Disorders Association (NINCDS-ADRDA) work group [61] were based on doctor's clinical judgment about the cause of patient's symptoms, taking into account reports from the patient and family members, and results of cognitive tests and general neurological assessment. These criteria have been quite successful and they have been widely used in clinical trials and clinical research, showing a sensitivity of 81% and specificity of 70% [62]. However, the increasing knowledge of the clinical manifestations and biology of AD determined the need of criteria revision. After 27 years, in 2011 the National Institute on Aging (NIA) and the Alzheimer's Association recommended new diagnostic criteria and guidelines for Alzheimer's disease [1,55,56]. The notable changes of the 2011 criteria are mainly due to the concept that the pathophysiological process of AD begins years, if not decades, before the diagnosis of clinical dementia, and to the incorporation of biomarkers that can indicate the presence or absence of AD pathology. The new criteria propose three different stages of Alzheimer's disease: preclinical AD, MCI due to AD, dementia due to AD. The preclinical stage occurs before symptoms development and indicates cognitive intact subjects with positive biomarkers of AD-related brain changes [55]. Table 1 shows diagnostic criteria of the different stages of preclinical AD phase. The investigation of the presence of this stage is strictly for research purposes only and usually used for individuals with high genetic risk of AD. Individuals with MCI have mild but measurable changes in cognition that are noticeable to the person affected and to family and friends but that do not affect the individual's ability to carry out everyday activities. Not all the subjects with MCI develop dementia, it is estimated that the rate of progression can be 10% per year. It is unclear why some individual progress into dementia and some others not, however it is believed that MCI can be an early stage of dementia. In the new criteria (Table 2) the use of biomarkers is suggested in order to investigate whether subjects have brain changes that put them at higher risk of developing AD. If biomarkers of AD-pathology result positive the diagnosis is MCI due to AD [56].

The new criteria proposed to classify people with AD dementia in the following groups after meet general criteria for dementia [1]: 1) Probable AD dementia, 2) Possible AD dementia, and 3) Probable or Possible AD dementia with evidence of the AD pathophysiological process. Table 3 shows the revised criteria for AD. The first two have been planned to use in a clinical setting and are very much similar to the previous NINCS-ADRDA criteria of possible and probable AD. The third group has been suggested only for research field.

	Aβ (PET or CSF)	Markers of neuronal injury (tau CZ-F, PET-FDG, MRI)	Evidence of subtle cognitive change
Asymptomatic cerebral amyloidosis	Positive	Negative	Negative
Asymptomatic cerebral amyloidosis + neurodegeneration	Positive	Positive	Negative
Amyloidosis+ neuronal injury+ subtle cognitive/ behavioral decline	Positive	Positive	Positive

(Sperling RA et al. 2011) [55]

Table 1. Pre-clinical Alzheimer´s Disease stages: National Institute on Aging (NIA) and the Alzheimer's Association diagnostic criteria 2011.

MCI- core clinical criteria

• Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)

• Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)

• Preservation of independence in functional abilities

• Not demented

Examine etiology of MCI consistent with AD pathophysiological process

• Rule out vascular, traumatic, medical causes of cognitive decline, where possible

• Provide evidence of longitudinal decline in cognition, when feasible

• Report history consistent with AD genetic factors, where relevant

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MCI due to AD:

Intermediate likelihood

Clinical criteria + positive Aβ biomarkers and untested neuronal injury biomarkers

Clinical criteria + untested Aβ biomarkers and positive neuronal injury biomarkers

High likelihood

Clinical criteria+ positive Aβ and neuronal injury biomarkers

MCI- unlikely due to AD

Clinical criteria + negative Aβ and neuronal injury biomarkers

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(Albert SA et al. 2011) [56]

Table 2. Mild Cognitive Impairment due to AD: National Institute on Aging (NIA) and the Alzheimer's Association diagnostic criteria 2011.

Probable AD	A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days
	B. Clear-cut history of worsening of cognition by report or observation; and
	C. The initial and most prominent cognitive deficit are evident on history and examination in one of the following categories
	a. Amnestic presentation is the most common syndromic presentation of AD dementia. The deficits should include impairment in lerning and recall of recently learned information. There should also be evidence of cognitve dysfunction in at least one other cognitive domain
	b. Nonamnestic presentations:
	• Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present
	• Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultagnosia, and alexia. Deficits in other cognitive domains should be present
	• Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present
Possible AD	Atypical course
	A. Atypical course meets the core clinical criteria in terms of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline
	or
	Etiologically mixed presentation
	B. Etiologically mixed presentation meets all core clinical criteria for AD dementia but has evidence as the following:
	a. Concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or
	b. Features of Dementia with Lewy bodies other than the dementia itself;
	or
	c. Evidence for another neurological diseases or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition
Probable AD with three levels of evidence of AD pathophysiology	Intermediate
	Aβ unavailable or indeterminate
	Neuronal injury positive
	Intermediate
	Aβ positive
	Neuronal injury unavailable or indeterminate
	High
	Aβ positive
	Neuronal injury positive
Possible AD (atypical presentation) with evidence of AD pathophysiology	High but does not rule out second etiology
	Aβ positive
	Neuronal injury positive

Dementia-unlikely due to AD	1. Does not meet clinical criteria for AD dementia.
	2. a. Regardless of meeting clinical criteria for probable or possible AD dementia, there is sufficient evidence for an alternative diagnosis such as HIV dementia, dementia of Huntington's disease, or others that rarely, if ever, overlap with AD.
	b. Regardless of meeting clinical criteria for possible AD dementia, both Aβ and neuronal injury biomarkers are negative

(McKhann GM et al. 2011) [1].

Table 3. Dementia due to AD: National Institute on Aging (NIA) and the Alzheimer's Association diagnostic criteria

The diagnostic procedure in clinical setting is usual divided into two phases. Screening is used to formulate the diagnostic hypothesis and is followed by the diagnostic confirmation. During the screening phase, the main point is to collect detailed information on history not only from the patient itself, but also from the people who take care of patients such as familial or other type of caregiver. Information about history includes medical history (presence of severe medical disease that may cause encephalopathy, psychiatric disease, traumatic brain injury or other neurological disease), medications, family history of dementia, and changes in both basic activities of daily living (such as self-feeding, dressing and bathing, ambulation) and instrumental activities of daily living (such as grooming, homework, manage finances, driving, and leisure). To obtain information on activities daily living could be particularly helpful to use standardized evaluation instruments such as Katz ADL scale [63] Lawton-Brody IADL scale [64], and the Bristol Activities of Daily Living Scale [65]. In addition to the history, a systematic assessment of general cognitive functioning is required through instruments designed for this purpose. There are no screening tools that can quickly assess different levels of cognitive impairment. The American Academy of Neurology guidelines suggested to use the Mini-Mental Status Examination [66], and the Memory Impairment Screen (MIS) [67]. In recent times, the Montreal Cognitive Assessment (MoCA) was developed as a tool to screen patients in who has been hypothesized a mild cognitive decline and usually performed in the normal range on the MMSE [68, 69]. Studies have shown that MoCa is sensitive for the mild stages of AD dementia, whereas MMSE is superior for more advanced stages with the functional impairment. A complete summary of neuropsychological tests has been proposed [70].

After the screening, the second phase consists of a neurological examination, a neuropsychological assessment, and a behavioural disease evaluation. A complete general neurological examination has been recommended as well as accurate neuropsychological evaluation in order to test possible differential diagnosis. The presence of Parkinsonism can suggest a Lewy Body's dementia, while asymmetric tendon reflex or other lateralizing signs can suggest a vascular component. Other neurological signs, for example peripheral neuropathy may indicate toxic or metabolic problems. There is no evidence-based data to support the usefulness of specific routine blood tests for evaluation of those with dementia but these are useful in excluding co-morbidities. Most expert opinion advises to screen for vitamin B12, folate, thyroid stimulating hormone, calcium, glucose, complete blood cell count, renal and liver function abnormalities. Serological tests for syphilis, Borrelia and HIV should be con-

sidered in individuals at high risk [71]. Structural neuroimaging, computed tomography (CT) or magnetic resonance imaging (MRI) is recommended as level B in the Dementia Guideline [71] at least once in each patient in order to exclude other condition as neoplasms, subdural hematomas. The lumbar puncture is not recommended unless the suspicion of prion disease or viral encephalitis.

6. Biomarkers

A biomarker is any characteristic that is objectively measured and evaluated as an indicator of biologic or pathogenic process and it should also be reliable, non-invasive and simple to perform [72]. Regarding AD, biomarkers included in the new diagnostic criteria are a measurement of the underline pathology and can be divided in markers of amyloid accumulation (CSF Aβ level, PET with amyloid-tracers) and markers of neuronal injury (atrophy of MTL at MRI, tau level in CSF, metabolic PET) [55]. Table 4 shows all the biomarkers.

6.1. Medial temporal lobe atrophy

Bilateral atrophy of medial temporal lobe structures, including hippocampus, has been found in patients with AD (Figure 1). Moreover it has been reported that the brain atrophy detected with neuroimaging reflects the typical pattern of progression of neuropathology, spreading from entorhinal cortex and hippocampus to the association cortices, as describe by Braak and Braak [73, 74]. In a meta-analysis of studies using visual and linear measurements of medial temporal lobe atrophy (MTA) on MRI, the overall sensitivity and specificity for detection of AD compared with controls was estimated to be 85% and 88%, respectively [75]. A yearly decline in hippocampal volume is approximately 2.5 times greater in patients with AD than in normal aged subjects. In clinical practice simple visual rating scales estimating hippocampal atrophy has proven to be useful to support the diagnosis in the first stage of the disease [74]. Although MTL is a biomarker of neurodegeneration and a good surrogate of disease progression, it has low sensitivity and specificity (51-70% and 68-69%, respectively) in identifying prodromal AD stage [76].
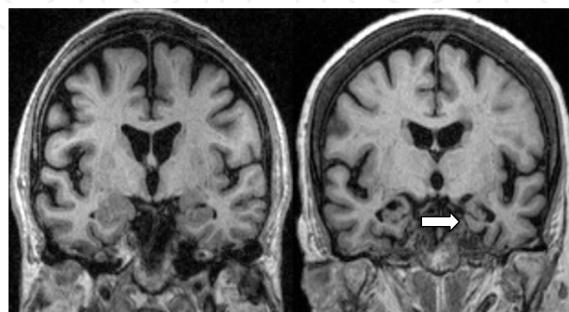
Figure 1. Coronal T1-weighted MRI scans of control (left) and patient with AD (right). The patient with AD shows atrophy of the hippocampus (arrow) [74].

6.2. Metabolic PET

PET with traced glucose (FDG-PET) shows brain metabolism and reflects pattern of neuro-degeneration. Metabolic reduction in bilateral temporal- parietal regions and in posterior cingulate is the most commonly described diagnostic criterion for AD [77].This specific pattern significantly predicts decline to AD with an average overall accuracy of 86%, and with sensitivity and specificity about 75-80%. Moreover some studies on pre-symptomatic carriers of genetic mutations for AD revealed FDG-PET hypometabolism many years before the clinical onset of the disease [78,79].

6.3. PET with amyloid-tracers

Interestingly recently has been developed a technique to detect amyloid in vivo using PET. [18F]-FDDNP and [11C] Pittsburgh compound-B (PIB) were the first amyloid PET tracers developed. Both tracers bind with nanomolar affinity to amyloid and enter the brain in amounts sufficient for imaging with PET. Retention of the tracers in neocortical and subcortical brain regions was significantly higher in AD patients than in controls. In subjects with MCI and positive retention the rate of progression to AD is estimated 25% per year [80]. A recent meta-analysis estimated a sensitivity of 93% and specificity of 56.2% [78]. Similarly, genetic at-risk cohorts demonstrate evidence of Aβ accumulation many years before detectable cognitive impairment [79]. This method could be used to follow the therapeutic efficacy of the new AD immunotherapies.

6.4. CSF Aβ and tau

Many reports have demonstrated a decline in CSF Aβ and elevation of total tau, phospho-tau, and tau/Aβ ratio in AD subjects. The reduction of Aβ could be by about 50% in subjects with AD compared with age-matched controls [81] and this phenomenon is thought to result from deposition of Aβ into plaques, leaving less Aβ being available to diffuse into the CSF. CSF total tau reflects the intensity of the neuronal and axonal damage, and it is increased in AD subjects by 2-3 folds compare with controls. However, tau, as a marker of neuronal injury, can be transiently increased after any acute brain injury (such as stroke or trauma) [82]. A comprehensive review [83] reports that Aβ shows a sensitivity and specificity of 86% and 90%, respectively, in differentiating AD from controls. For tau, the sensitivity is 81% and the specificity 90%, and p-tau has a mean sensitivity of 80% when specificity is set at 92%. By use of a combination of concentrations of Aβ42 and t-tau for AD versus controls, high sensitivities (85–94%) and specificities (83–100%) can be reached. The reliability of CSF biomarker has been tested by the comparison with autopsy results, showing high sensitivity and specificity in discriminating AD from both the cognitively normal elderly and from patients with other dementias. These CSF markers have also been shown to predict AD in patients with MCI [84], and to precede symptoms in familial AD [85]. However CSF biomarkers are not related with dementia severity.

Biomarkers, despite their great potential especially in the research field, are not recommended for the routine use in clinical diagnostic setting. Clinical criteria provide very good accu-

racy, there is limited standardization of the biomarkers and the access is limited to university hospitals.

	Specificity	Sensitivity
Biomarkers of Aβ deposition		
CSF Aβ [83]	90%	86%
PET amyloid imaging [78]	56.2%	93.5%
Biomarkers of neuronal injury		
CSF tau [83]	90%	81%
Medial temporal lobe atrophy on MRI [75]	88%	85%
FDG-PET imaging [78]	74%	78.7%

Table 4. Alzheimer´s disease biomarkers: diagnostic accuracy

7. Others biomarkers

7.1. CSF BACE1 and sAPP

APP, amyloid precursor protein, is sequentially cleaved by α-or β-secretase (BACE1), followed by γ-secretase enzyme. The cleavage by BACE1 and γ-secretase generates Aβ peptide, likely to aggregate in plaques, and the N-terminal secreted fragment of APPβ (sAPPβ). In contrast, APP cleavage by α-and γ-secretase generates non-amyloidogenic fragments and secreted fragment of APPα (sAPPα). Thus, CSF BACE1 activity and sAPPβ and sAPPα proteins have been testing to provide information about amyloidogenic vs. nonamyloidogenic processing in the brain. Although some reports have shown higher levels of CSF BACE1 activity in AD compared with healthy controls and higher levels in subjects with MCI who progress to AD, others have not observed these, or have shown a decline of BACE1 activity in AD [86]. It is possible that CSF BACE activity is elevated in incipient AD and subsequently decline with disease progression. Several groups have measured CSF sAPPβ and sAPPα levels from AD and control subjects to understand brain APP metabolism better. Some studies reported higher levels of sAPPβ and a reduction in sAPPα levels in AD, however, these results need further confirmation [86].

7.2. Plasma Aβ

Several studies investigated plasma level of Aβ in AD. One group of researchers reported that in patients with newly acquired Alzheimer's disease, the plasma Aβ levels decline significantly compared with controls or participants with prevalent Alzheimer's disease during an average follow-up period of 3 years [87]. Another study reported that higher baseline plasma Aβ concentrations and greater reductions in plasma Aβ concentrations were associated with cognitive decline in non-demented elderly people over 4 years follow-up [88].

This study indicated that plasma Aβ level is elevated during the pre-symptomatic stage in at-risk individuals, but subsequently start falling with the development of Alzheimer's disease/MCI. Anyhow most groups have not found any significant differences between patients and controls. Wu and colleagues [86] recently tried to measure, through specific antibody, plasma level of BACE1, sAPPβ and sAPPα. They reported significant increase in plasma BACE activity, sAPPβ, and sAPPα in a small sample of AD patients (n=20) compared with age-matched controls (n=30).

7.3. Clinical variants of Alzheimer's disease

The common conception of Alzheimer's disease (AD) is a disorder that initially affects memory function, associated with early pathological changes in medial temporal lobes, and progresses to involve language, visuospatial skills and other cognitive abilities, reflecting progressive involvement of association neocortices [61]. It is recognised, however, that the clinical presentation of AD is variable and in some cases the presenting dominant symptom is not memory [89-91]. Non-amnestic presentations are frequently referred to as "focal" presentations of AD. It is well established that most patients with a progressive disturbance of aspects of visuo-perceptual and spatial abilities, often referred to as posterior cortical atrophy, have underlying AD pathology. In addition, it is now clear that a proportion of patients with progressive aphasia, both fluent and non-fluent type, can have AD as the primary pathology. Recently, cases of corticobasal syndrome (CBS) secondary to AD pathology have also been reported [90]. The existence of a frontal presentation is more controversial. Patients with familial AD secondary to presenilin 1 mutations may have a behavioural onset [92, 93] and there are isolated reports of sporadic AD resembling fronto-temporal dementia (FTD) [91, 94].

7.4. Progressive aphasia

Primary progressive aphasia (PPA) is a clinical syndrome in which cognitive decline is limited to one or more components of the language system. Since Mesulam's first description of the phenomenon [95] clinical, neuropsychological and imaging studies have converged on the existence of three distinct clinical subtypes: semantic dementia (SD), characterized by fluent but empty speech, impaired comprehension and high incidence of dyslexic errors, in association with selective atrophy in anterior temporal regions; non fluent/agrammatic aphasia (PNFA) with phonologically and/or grammatically distorted speech output, preserved single word comprehension, and atrophy focused on the left inferior frontal and insular regions; logopenic variant (LPA), characterized by a slow production rate, long word finding pauses, sparse phonological paraphasias and difficulty with sentence (but not single word) repetition. MRI reveals abnormalities in more posterior brain regions [96]. Pathologically, PNFA and SD are more likely to present an FTD pattern, although in some cases they can be the clinical presentation of atypical AD pathology. In contrast, biochemical, amyloid imaging and post mortem findings in LPA support the idea that the syndrome is a clinical marker of AD pathology [97]. Clinical evolution of that variant leads to mutism and memory impairment.

7.5. Visual variant

Posterior cortical atrophy (PCA) or visual variant of AD is characterized by early impairment of visuo-spatial skills with less prominent memory loss and is associated with atrophy in parieto-occipital and posterior temporal cortices with right predominance [98]. Clinical presentation includes difficulties in reading lines of text, in judging distances, in identifying static objects within the visual field, alexia, and features of Balint's syndrome (simultanagnosia, oculomotor apraxia, optic ataxia, environmental agnosia) and Gerstmann's syndrome (acalculia, agraphia, finger agnosia, left–right disorientation) [99]. Deficits in working memory and limb apraxia have also been noted [100]. By the time PCA has run its course, many patients develop also memory and language deficits. Findings of pathological studies all show that Alzheimer's disease is the most common underlying cause of PCA [101]. Some studies have shown that PCA cases have the greatest density of both plaques and neurofibrillary tangles in visual and visual-association cortices and fewer tangles and senile plaques in the hippocampus and subiculum [101]. CSF biomarkers (Aβ, tau, and P-tau) show similar pattern in patients with PCA compared with AD subjects, supporting the hypothesis that PCA is associated typically with underlying Alzheimer's disease pathology. However, some cases are attributable to other causes, such as corticobasal degeneration, dementia with Lewy bodies, or prion disease [98].

7.6. Progressive apraxic syndrome

Autopsy proven AD cases can be related to an apraxis clinical syndrome. Patients with these phenotype present progressive loss of use of the limbs which compromises performance on manual tasks such as dressing, handling a knife or a fork and writing. Cognitive assessment reveals apraxia and in less extends deficits in spatial function, with initially preserved memory [102]. The clinical spectrum of that phenotype may also include others symptoms of the corticobasal syndrome (CBS), as asymmetric parkinsonism, ideomotor apraxia and alien limb phenomena. CBS is an unusual clinical manifestation of various neurodegenerative pathologies, AD, FTD, corticobasal degeneration (CBD). The one related to AD presents a temporo-parietal atrophy prevalent on the left side and hypoperfusion of parietal lobe, with less involvement of pre-frontal regions compare with FTD and CBD [103].

7.7. Frontal variant

Sometimes AD patients presents a prevalent impairment of the executive function in the early stages of the disease, but there is also a multidomain deficit [90, 102]. Two reports, [91, 94] have claimed that a behavioural onset of cognitive dysfunction, with disinhibition, apathy and personality change could be also an atypical presentation of AD pathology. Alladi and colleagues [90] after the examination of 28 cases of behavioral variant - FTD found AD pathology in two cases. None of the two patients had amnesia at the onset of the disease, but in both cases diffuse cognitive dysfunction developed early in the course of the disease. Authors concluded that a behavioural variant of AD exists, but in contrast to patients with non-AD pathology, the disease does not appear to remain restricted to the frontal lobes for very long.

8. Treatment and management

Regarding the therapeutic management of a disease generally there are at least three possibilities: (i) prevention strategy, (ii) symptomatic treatment, and (iii) disease modifying therapies. Currently, a long list of factors that can reduce or delay the risk of AD onset has been reported, but so far there is no certain evidence supporting the prevention efficacy in AD. In Europe, there are three ongoing multidomain interventional random clinical trials (RTCs) that focus on the optimal management of vascular risk factors and vascular diseases and include also medical and lifestyle interventions. The results of the RTCs might help in improving strategies of dementia prevention [3]. This indicates the principle type of AD treatment is based on symptomatic drugs. There is no cure for AD, but new types of disease modifying treatments are under investigation. Non-pharmacological interventions have been also recently added in AD patient management.

8.1. Symptomatic treatments: acetylcholinesterase inhibitors

The neuropathology of Alzheimer's disease is characterized by early loss of basal forebrain cholinergic neurons, leading to decreased cholinergic transmission which is involved in many aspects of cognition, including memory and attention. Inhibitors of the acetylcholinesterase enzyme (AChEIs) increase acetylcoline level in brain, which leads to memory improvement. Since the introduction of the first ChEI in 1997, these agents are considered first-line pharmacotherapy for mild to moderate AD stages [71]. Four ChEIs are currently available: tacrine, donepezil, rivastigmine and galantamine. Tacrine (Cognex), the first approved, is not commonly used because of a poor tolerability profile and low oral bioavailability [104]. The Cochrane's Review [105] of placebo controlled trials of ChEIs demonstrated that the treatment determine an improvement of 1.4- to 3.9-point in the ADAS-Cog scale at 6 months and 1 year. In clinical trials, a change of 4 points is considered clinically significant for patients with mild to moderate dementia. In addition to their effects on cognition, these agents also have demonstrated beneficial effects on measures of behavior, activities of daily living (ADLs), and global patient function as reported in a recent meta-analysis [106]. Donepezil (Aricept) was approved in the mid-1990s. The starting dose is 5 mg once daily which can be increased after 4 weeks to 10 mg, if well tolerated. The common side effects are nausea, vomiting, gastritis and diarrhea. The length of the response has been documented up to 52 weeks. When donepezil is discontinued, performance of the subject returns to the same as in the untreated state. Rivastigmine (Exelon) is a pseudo-irreversible inhibitor as it dissociates from the enzyme slowly. Two type of administration are available: oral and transdermal patch. The oral starting dose is 1,5 mg twice daily that can be weekly increase of 1,5 mg until a total amount of 12 mg per day (6 mg twice daily). The transdermal patch last 24 hours and has two dosages: 4,6 mg and 9,5 mg. The target dose, 9,5 mg/24 h, can be reached after 4 weeks if the low dosage is well tolerated. Side effects of oral Rivastigmine are approximately the same as donepezil, while gastrointestinal symptoms are at least three times less prominent with the patch [104]. Rivastigmine is also an inhibitor of butyrylcholinesterase that facilitate cholinergic neurotransmission by slowing the degradation of acetylcholine released by functionally intact cholinergic neurons. The therapy with Galantamine (Remin-

yl) starts with 4 mg twice daily and increases in increments of 4 mg per dose twice a day to a maximum of 12 mg twice daily if tolerated. Currently it is also available in an extended-release formulation that can be taken once daily. Galantamine has some nicotinic receptor activity. All AChEIs can influence cardiac rhytm, but is not common unless a person has an underlying disturbance in cardiac conduction. An electrocardiogram prior to initiating the treatment is recommended. AChEIs may also have an effect on respiratory conditions, such as chronic obstructive pulmonary disease or asthma, or gastrointestinal disease, such as gastric ulcer. The absorption of AChEI is not influenced by food intake. These agents are recommended for the treatment for patient only in the mild and moderate stages [71].

8.2. Memantine

Memantine is an NMDA (N-methyl-D-aspartate) receptor antagonist that reduces glutamatergic excitotoxicity. Based on the glutammatergic hypothesis of AD, Memantine has been claimed to be a disease modifying therapy. Clinical trial with Memantine reports a mild efficacy in maintaning functional level in patients with severe dementia [107]. Memantine is licensed for the treatment of people with moderate-to-severe AD. The starting dose is 5 mg that can be increased of 5 mg every week up to the dose of 20 mg. Side effects are very unusual and include restlessness, hyperexitation and fatigue. There are good evidence of clinical benefit in patients moving into severe stages of AD from a combination therapy with Memantine and an acetylcholinesterase inhibitor [108-110].

8.3. Disease-modifying treatments

Since the role of beta amyloid (Aβ) is considered to be paramount in the development of AD, several research strategies have been undertaken to alter the biochemistry of Aβ in the brain through interference of either the formation or the deposition of Aβ. The amyloid precursor protein can be processed in two different pathways, non-amyloidogenic by α-secretase and amyloidogenic ones by β-secretase followed by γ-secretase [12]. Thus, the inhibition of β or γ-secretase is the target of therapies that aim to reduce the production of Aβ, while new immunotherapeutic strategies promote removal of Aβ from the brain. Drugs that can act as β-secretase inhibitors belong to a group of type 2 diabetes therapies, thiazolidinediones (rosiglitazone and pioglitazone). Despite the promising biological plausibility of these compounds, the results of randomized clinical trials (RCTs) have been disappointing [111-112]. A number of γ-secretase modulators (semagacestat and tarenflurbil) have also failed to provide benefits in the treatment of AD [113,114]. Immunotherapies or "vaccines" are based on both active and passive immunization. Initial approaches based on immunization with Aβ fragments performed extremely well in transgenic mouse models but showed less promise in humans [51]. The most promising of these, AN-1792 (QS-21) resulted in significant Aβ-antibody titers in patients with mild-to-moderate AD in Phase II trials. Postmortem analysis on long-term follow-up also confirmed that the therapy had resulted in a significant reduction in Aβ burden in the brain. However, there was no evidence of any clinical benefit and the trial was halted owing to patients developing aseptic meningoencephalitis, thought to have been induced by cytotoxic T-cell activation. Immunotherapies have

since been designed using shorter peptides designed to mimic immunoreactive sections of Aβ, in an effort to avoid severe inflammatory response. There are various immunotherapies taking these approaches. For example, CAD-106, which targets Aβ1–6, resulted in Aβ clearance without collateral immunoreactivity in Phase I trials, and is now in a Phase II RCT. Passive immunotherapy for AD has met with some criticism owing to the challenge of designing an approach that can achieve significant antibody concentrations in the brain. Although some of the data from animal studies do suggest a possible impact on oligomer formation and brain amyloid load. Currently, monoclonal antibody therapies include bapineuzumab (AAB-001) and solanezumab (LY-2062430) that are now in a phase III RCT [115]. The results of these trials are eagerly awaited, but experts' consensus is not anticipating positive outcomes. Despite the facts that vaccines can remove Aβ from the brain, a fundamental debate continues around the clinical benefit of Aβ clearance. Neurofibrillary tangles are another hallmark of AD pathology, however treatments to target tauopathy have received far less attention than amyloid therapies. Very preliminary results in animal models have shown that a tau immunotherapy might be a valuable approach [116].

8.4. Non-pharmacological treatment

In the last ten years there has been a great public interest in possible non-pharmacological therapies to delay disease progression and functional decline. The psychosocial interventions fitted to this goal and they were developed based on the concept of "cognitive reserve". Evidence from meta-analyses and systematic reviews has shown that a higher cognitive reserve is associated with a significantly reduced risk to develop dementia [117]. Generally "cognitive reserve" describes the mind's resistance to damage of the brain. There has been proposed two models to explore the reserve, a passive model called "brain reserve" and an active model knows as "cognitive reserve" [118]. There are several different approaches to neuropsychological and training interventions focusing on cognition with different evidence for efficacy in people with AD. In large part, the psychosocial interventions have shown significant, but modest effect-size when used alone. The American Association for Gertiatric Psychiatry (AAGP) proposed a care/treatment model that combines pharmacological therapies with psychosocial intervention for people with AD [119]. To date, the literature about psychosocial intervention is wide [120-123]. For this reason we decide to illustrate briefly the most important intervention below. The psychosocial interventions can be classified according to the treatment goal and include behaviour, emotion-oriented and stimulation-oriented treatment, and cognitive training [124].

Behaviour-oriented therapy is used to modify dysfunctional behaviour employing behaviour change techniques which increase or decrease the frequency of behaviour through the use of reinforcement, punishment, and extinction following the Experimental Analysis of Behaviour (B.F. Skinner). Behaviour therapy is helpful to reduce typical behaviour's problems such as incontinence and wondering [125-127]. Stimulation-oriented interventions include recreational activities such as creative arts (such as craft, music, dance, andtheatre) and leisure education, art therapy, music therapy, pet therapy, and other formal activities aim to maximize pleasurable activities for the patients. Stimulation improves modestly be-

Drug	Suggested Dosage	Approved indication
Cholinesterase inhibitors		
Donepezil (Aricept)	5 mg once daily, which can be increased to 10 mg/day after 4 weeks	Mild to moderate AD Sever AD in add-on with Memantine
Rivastigmine (Exelon)	Oral: Twice daily starting with 1.5 mg which can be increased up to 6 mg twice daily in 6 weeks Transdermal patch: once daily, 4,6 mg/24 h, or 9,5 mg/24 h.	Mild to moderae AD
Galantamine (Remynil)	Twice daily, beginning with 4 mg and increase after 4 weeks to 8 mg twice daily. A dosage of 12 mg twice daily can also be reached after a medical examination Availabe a new extended-release formulation that can be taken once daily	Mild to moderate AD
NMDA atagonist		
Mematine (Ebixa)	Twice daily beginning with 5 mg increase up to 10 mg twice daily in 4 weeks Available a dosage of 20 mg that can be taken once daily	Moderate to severe AD
Immunotherapies		
Active immunization CAD-106 Passive immunization Bapineuzumab (AAB-001) Solanezumab (LY-2062430)		Pashe II RCT* Phase III RCT* Phase III RCT*

*RCT= randomize clinical trial

Table 5. Alzheimer's disease pharmacological treatments

haviours and mood, but the main effect is to change the daily-life routine [124]. Emotion-oriented approaches include supportive psychotherapy, reminiscence therapy, validation therapy, sensory integration (snoezelen), and simulated presence therapy (SPT). Supportive psychotherapy has not received formal scientific studies, but can be used to address issue of loss in the early stage of AD and help mildly impaired patients to adapt themselves to a new lifestyle imposed by the disease. Reminiscence therapy remains controversial, individually or in group, on past life events of the patient helped by using external aids such as photographs, household items, music and sound recordings, or other familiar items from the past. The final goal is to improve the psychological well-being, mood, and coping skills of patients with AD [128]. Researches have shown that reminiscence is useful to improve directly emotions in overall mood, thus can improve cognitive functioning [129-132]. Validation therapy [133] is based on the empathic relationship between the patient and the therapist.

Through listening, the therapist examines the reality's perception of the patient in order to create significant emotional and relational contacts. The objectives are to stimulate the patient to take social role, stimulate verbal communication, and encourage social interaction. Validation is intended for patients with severe to moderate dementia. Cognitive training involves guided practice on a set of standard tasks designed to stimulate specific cognitive functions (memory, attention, or problem-solving). The underlying assumption is that practice may improve or maintain functioning in a given domain, generalizing the effects of practice beyond the clinical context to everyday life [121]. The aim is to reduce cognitive deficits. The Reality Orientation Therapy (ROT) is a technique widely used in treatment of AD [134-136]. The objective is to stimulate the personal, time, and space orientation in the patient through repeated multimodal stimulation (verbal, visual, and musical), strengthen the basic information with respect to space and time coordinates, and his personal history. The level of stimulation is modulated agree with residual cognitive resource of patient. Other types of cognitive training include skills training and cognitive retraining focusing on cognitive deficits. There has been demonstrated that cognitive training improve cognitive functioning, but effects were transient and often accompanied by negative effects linked to frustration [137]. Finally, the caregivers are also part of the treatment and should be carefully managed overtime.

9. Conclusions

Alzheimer´s disease is a common disorder of aging, and a major cause of dependence and mortality among elderly. Substantial progress has been made over the past few decades in understanding AD. Nevertheless, our knowledge of this disease is still profoundly imperfect, as demonstrated by the failure of all but symptomatic treatments for clinically diagnosed AD. We know that in people aged >85 years, dementia and cognitive impairment are common, reaching a combined prevalence >50% in the oldest old, and that the incidence of dementia continues to rise in the oldest age groups. Thus, screening is essential to identify cognitively normal individuals in midlife or old age who have a high risk of developing MCI and AD, so that interventions, when available, can be administered to stop the development of specific disease-related pathologies. Although the exact pathogenetic mechanism of AD is still unclear, thanks to new technologies, we are now able to detect in vivo subjects with AD-related brain pathological changes. Many studies have provided evidence that AD pathology begins as many as 20 years before symptoms appear. These findings determined a new concept of AD, where the symptom of dementia represents the final part of the "continuum" of AD. Recently, based on the new knowledge about AD, some disease modifying therapies have been developed and their results are eagerly awaited.

Acknowledgements

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