Alzheimer’s disease is a neurodegenerative disorder which is the most common form of dementia in elderly people. The increase in average life expectancy during the 20th century causes an increase in frequency of Alzheimer’s disease. The onset of disease is insidious, takes more than thirty years. It becomes manifest with mild memory loss and then progress with severe cognitive impairment and functional decline. Patients lose their independence in performing daily activities and need a close caregiving. The caregiving is a stressful responsibility and problems such as sleeping difficulties, fatigue, anxiety and depression may frequently develop in caregivers. Socio-economic cost of Alzheimer’s disease is devastating. The cause of the disease is not fully understood yet and there is no effective curative treatment. Current medications for Alzheimer’s disease slow disease progression but cannot stop underlying degenerative process. This book is purposed to provide an overview for suggested pathological mechanisms, diagnosis and current management of Alzheimer’s disease as well as emerging therapeutic approaches.

Yildiz Dincer
Professor Of Medical, Biochemistry
About Editor

Prof. Yildiz Dincer (PhD) is senior scientist in Istanbul University Cerrahpasa Medical Faculty, Department of Medical Biochemistry, Istanbul TR. She received her master degree (1996) and PhD (2000) from the same department. Dr. Dincer has been in Imperial Research Fund-Clare Hall Laboratories, UK as a fellow in 1999, and has gained experience in the field of DNA repair by working in the team of Dr. Tomas Lindahl who shared the 2015 Nobel Prize in Chemistry for work on DNA repair. Dr. Dincer maintains an active research program studying on oxidative DNA damage, DNA repair/apoptosis, antioxidants and epigenetics. Dr. Dincer has published many articles and book chapters. She has served as the editor of various edited collections on topics such as iron deficiency, chemical carcinogens, chemotherapeutics and epigenetics. Dr. Dincer lives with her husband in Istanbul, Turkey.
I would like to thank Professor Aynur Özge for not only her contribution to this book as author but also for her efforts in participation of other authors.
Over the past few decades global prevalence of Alzheimer’s disease is increased and it became a major public health problem. Millions of elderly population have been suffering from Alzheimer’s disease worldwide. Many efforts have been made aiming to prevent Alzheimer’s disease due to its rising prevalence, the lack of a curative treatment and its high socio-economic cost. Although the study of Alzheimer’s disease is moving ahead rapidly, cause of the disease has not been fully clarified yet. Alzheimer’s disease is a slowly progressing brain disorder characterized by loss of synapses and neurons in cerebral cortex and in certain sub-cortical regions which leads to memory impairment, cognitive decline, and eventually death. The majority of Alzheimer’s disease cases are sporadic. This form of disease is known as late-onset Alzheimer’s disease, and is seen in cases older than 65 years. The rare and inherited form of disease is known as familial or early-onset Alzheimer’s disease. It is seen in cases younger than 65 years, sometimes as early as the mid-20s. The diagnosis of Alzheimer’s disease may be delayed or missed, because early symptoms develop gradually and are often associated with the normal aging process; the symptoms can mimic symptoms of various disorders such as vascular dementia, depression or brain tumor; there is no early diagnostic tools based on quantitative biochemical markers. Age, female gender, low education level, family history, major depression, head injury, diabetes mellitus, hyperlipidemia are potential risk factors for Alzheimer’s disease. The hallmarks of the disease are extracellular neuritic plaques composed of amyloid beta fibrils and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein. The pathophysiology of Alzheimer’s disease is highly complex and multifactorial. Oxidative stress, neuroinflammation, metal dyshomeostasis, mitochondrial dysfunction, insulin resistance and insulin deficiency in the brain are suggested as potential underlying mechanisms of Alzheimer’s disease. The current medications (acetylcholinesterase inhibitors, glutamate N-methyl D-aspartate antagonist) do not reverse disease but can slow disease progression. Investigations have focused on reducing the amyloid beta plaques, amyloid beta aggregation/toxicity and tau aggregation. Different therapeutic approaches including vaccination, anti-inflammatory agents, cholesterol-lowering agents, antioxidants and hormone therapy are under investigation. As the disease progresses patients become fully dependent on caregivers. Caregivers of Alzheimer’s patients are usually family members. Caring for someone with Alzheimer’s is a stressful life event and caregivers are under high level of emotional and physical stress. As the loved one’s cognitive, physical, and functional abilities diminish, nearly all caregivers experience sadness, anxiety, exhaustion, loneliness, social isolation, sleeping difficulties, problems with the family and at work which may lead health problems. The awareness about this issue, social and psychological support and caregiver education programs are helpful to alleviate caregivers stress.

The better understanding of Alzheimer’s disease provides a new perspective in AD management, I hope this book will be helpful for the clinicians, psychologists, medical and graduate students, health-care professionals, caregivers, researchers and other scientists pursuing the biological basis of Alzheimer disease.
<table>
<thead>
<tr>
<th>Sl no</th>
<th>Table of Content</th>
<th>Page no</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Clinical Aspect of Alzheimer’s Disease</td>
<td>1-22</td>
</tr>
<tr>
<td>2</td>
<td>Pathogenesis of Alzheimer's Disease</td>
<td>23-45</td>
</tr>
<tr>
<td>3</td>
<td>Current and Future Therapeutic Approaches and Management of Alzheimer’s Disease</td>
<td>46-60</td>
</tr>
<tr>
<td>4</td>
<td>Common Medical Problems in Patients with Alzheimer’s Disease</td>
<td>61-67</td>
</tr>
<tr>
<td>5</td>
<td>Nutritional Considerations in Patients with Alzheimer’s Disease</td>
<td>68-79</td>
</tr>
<tr>
<td>6</td>
<td>Caregiver Education and Support studies for Alzheimer’s Disease</td>
<td>80-88</td>
</tr>
<tr>
<td>7</td>
<td>Emerging Therapeutic Approaches</td>
<td>89-100</td>
</tr>
<tr>
<td>8</td>
<td>Future Perspective</td>
<td>101-106</td>
</tr>
</tbody>
</table>
Abstract

This chapter is about the giving some general information of Alzheimer’s Disease (AD). As a most common type of dementia, it is not only most known causes but also most important burden on our future. Epidemiological data shows us AD is the third most important health care problems in the budget of developing countries with a growing importance of bio-psycho-social aspect. We discussed definition of dementia disorders including AD with supported developing diagnostic criteria. This chapter has also included recent advances at biologic markers of AD brought new diagnostic sets. Mild cognitive impairment has been taken a specific subtitle in this chapter. The readers can also find some important hints for comparison of new sets of diagnostic criteria. This chapter has included a comprehensive summarized data about the known risk factors of AD. Changing clinical faces of AD has been given as a concept explanation. This chapter has been finalized a reference list for additional reading.

Keywords: Alzheimer’s Disease; Dementia; Diagnostic Criteria; Mild Cognitive Impairment

Clinical Aspect of Alzheimer’s Disease

Definition of Alzheimer’s Disease

Alzheimer’s Disease (AD) is a neurodegenerative brain disease of elderly and the most common known cause of dementia. It is characterized by a progressive decline in based on memory, language, thinking, behavior and other cognitive skills that affect to perform daily living activities. In Alzheimer’s disease, the brain cells themselves degenerate and die, causing a steady decline in mentioned cognitive, behavioral and daily living functions. AD is devastating not only for patients, but also for the caregivers, families and community [1].

Definition of dementia

Dementia is a brain disorder-usually in chronic or progressive nature- in which there is disturbance of multiple higher cortical functions, including first in memory, thinking,
language, visuospatial, and judgment. Cognitive impairment interferes with independency in daily living activities. Social behavioral, psychosocial impairment could proceed to dementia syndrome or could become a part of disease by course [2]. AD is the most common type of dementia; especially for older ages –more than half of the cases- and is not only a clinical phenomenon but is a definition of a distinct clinico-pathologic entity more than one century. The term of AD refers to a distinct ongoing pathologic process including preclinical, mild cognitive symptomatology and AD dementia phases [3]. In spite of well-defined unique pathological hallmarks of AD- beta-amyloid plaques and neurofibrillary tangles at specific localizations with a progressive nature- phenotypic presentation of disease could diverse individually. The diagnosis of dementia is mostly based on detailed history of patients’ and associates with clinical examination, laboratory and neuro-imaging investigations that are mostly suitable to rule out secondary causes. Current advanced biological markers (magnetic resonance and PET imaging techniques and Cerebrospinal Fluid (CSF) investigations) also could help to diagnose dementia and AD, but their role at daily clinical practice is still questionable. Although the term of dementia refers to impairment at multiple domains of cognition, isolated deficits are frequently present as early manifestations of ongoing degenerative process [4-6].

**Diagnosis of dementia**

Clinical examination of a patient referred to the neurologist for possible dementia should cover a broad range of possibilities. The spectrum of admitting complaints of patient could be various including: memory, behavior or personality alterations, alone or together with each other. The other part could present with neglect of symptoms by the patient and relatives may have noticed symptoms. Relatives or patients could describe impairment of daily living activities. A clinician should firstly differentiate mimics and reversible causes of dementia before final diagnosis of degenerative dementia (please refer to Table 1). This has significant importance from many aspects; first he/she should diagnose treatable conditions and second should differentiate static, non-progressive neurocognitive conditions. Common causes of dementia-like syndromes (sometimes defined as pseudo-dementia) are depression, delirium, drug side effects, thyroid problems, certain vitamin deficiencies and excessive use of alcohol and drugs [1-5]. Summarized list of potential secondary causes of dementia has been given at Table 1.

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<tbody>
<tr>
<td>1</td>
<td>Vascular dementia (multiinfarct dementia, subcortical ischemic vascular events, strategic infarct, CADASIL, etc)</td>
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<td>2</td>
<td>Normal Pressure Hydrosephalus</td>
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<td>3</td>
<td>Wernicke-Korsakoff Disease</td>
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<td>4</td>
<td>B12 vitamine deficiency</td>
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<td>5</td>
<td>Hypothroiditis</td>
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<td>6</td>
<td>Chronic hepatic disorders</td>
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<td>7</td>
<td>Toxic agents (organic solvents, drugs, etc)</td>
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<td>8</td>
<td>Herpes encephalitis</td>
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<td>9</td>
<td>Neurosyphilis</td>
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<td>10</td>
<td>Chronic meningitis</td>
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<td>11</td>
<td>Chronic subdural hematoma</td>
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<tr>
<td>12</td>
<td>Neoplastic and paraneoplastic disorders</td>
</tr>
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</table>

Table 1: Potential secondary causes of dementia.

Dementia diagnosis process includes a practical systematic approach at first step of examination:

1. Medical and neurological history
2. Neurocognitive/behavioral history
3. Toxic and nutritional risk factors
4. Vascular risk factors
5. Physical examination
We strongly propose **medical and neurological history** as first step of evaluation. Full medical history should be obtained. In the situation of cognitive complaints are present as a part of another systemic disease, if we do not diagnose underlying disease first, all consequent steps and investigations will only move away us from correct possibly treatable disorder. For example a patient with forgetfulness complaint could not associate his/her sleep apnea or snoring if clinician does not ask. Frequent apneas could cause objective cognitive deficits and impairment at daily performance as a result of sleep deprivation. The clinician should evaluate carefully other signs of systemic disorders, such as endocrine disorders, malignancy, and chronic infections [2,3].

**Neurocognitive/behavioral assessments** cover short mental examinations and detailed neuropsychological evaluations. This part of examination also should begin with detailed history obtaining. History of past disease should cover: cerebrovascular disease, epilepsy, repeated head trauma, past intracranial operations, current or past infectious disease history, psychiatric diseases, especially depression, psychosis, behavioral changes. But it should be remembered that depressive symptoms could occur at early stages of dementia [2,3].

**Toxic and nutritional risk factors** are also important to assess. Alcohol abuse, gastrointestinal surgery or malabsorption disorders, vitamin deficiencies, to be exposed to pesticides and heavy metals should be investigated. Vascular risk factors should be evaluated specifically; they have importance not only at diagnosis of dementia but also to determine dementia type (vascular dementia, AD differentiation etc.) [2,3].

**Physical examination** could provide systemic involvement signs for differential diagnosis of focused potential secondary causes of dementia. Neurologic examination could support focal neurologic involvement or movement disorders signs and could add important points to clinician. After the diagnosis of dementia one should decide final diagnosis of AD or other dementia syndromes. Although AD have characteristic clinical features, clinical variations are common. This heterogeneity complicates diagnostic accuracy, and correct diagnosis is critical to advancing research. Strengths and weakness of the major definitional approaches have been discussed and recommendations have been made to improve diagnostic precision [2,3]. Early detection of AD in its clinical course has proven to be an important goal since description of disease. Although we have advanced research and current biological and neuroimaging techniques; early diagnosis of disease is remaining challenging. AD must be distinguished from other dementia syndromes, including vascular dementia, fronto-temporal dementia and other dementia syndromes. The key features to differentiate AD from others are based to neuropsychological profile of patient examination, and the most important part of the diagnostic sets is still based on clinical examination. Optimal clinical criteria should allow for clinical variability in symptoms based on the patients’ socio-cultural background, language and intelligence. Although the newly proposed criteria include biomarker evidence and expected to enhance pathophysiological specificity of the diagnosis of AD, the core clinical criteria will continue to be the cornerstone of the diagnosis in clinical practice [2,3].

The most commonly used diagnostic tools of AD are DSM criteria and NINCDS-ADRDA criteria for several decades [2,7]. Recently International Working Group (IWG) and National Institute on Aging along with the Alzheimer’s Association (NIA-AA) developed new diagnostic criteria. And DSM-V published at 2013 and revised AD and dementia criteria. It has been summarized and compared IWG, NIA-AA and DSM-5 diagnostic criteria at below [7-11].

**IWG –Criteria**

Dubois and colleagues developed new criteria at the scheme of a clinic-biological disease. New criteria addressed several important aspects:

1) the diagnosis could be made at an living individual without biopsy confirmation,
2) there is no need to use ‘probable AD’ because other diseases could be excluded with biomarkers, and disease biology could be demonstrated with biological markers,
3) the same clinic-biological defining could be used at every stage of disease, even for non-demented individuals.
4) several biomarkers could suppose diagnosis and fulfill criteria
5) in the IWG concept of Mild Cognitive Impairment (MCI) is abandoned. The IWG-2
criteria published at 2014 and aimed to simplify approaches with recent advances.
Population-based studies are needed to assess reliability of new criteria at clinical
practice, but rapid progress in the field of AD has been brought necessity of new
criteria continuously.

| Workgroup proposed classification as; (1) Probable AD dementia, (2) Possible AD dementia, (3) Probable or possible AD dementia with evidence of the AD pathophysiology (intended for research purposes). Probable AD dementia. Meets criteria for dementia |
|---|---|
| 1 | Insidious onset (gradual onset over months to years) |
| 2 | History of worsening of cognition by report or observation |
| 3 | Initial and most prominent cognitive deficits. The most common syndrome feature is amnestic presentation, but non-amnestic presentation could be observed (language, visuospatial, executive domains) |
| 5 | Clinical features are not pointing another diagnosis. Working group also proposed ’Probable AD dementia with increased level of certainty’ subtitle and adding feature of documented cognitive decline or being a carrier of a causative AD genetic mutation (APP, PSEN1, or PSEN2) |
| 6 | Possible AD dementia Clinical features meet the core clinical criteria in the terms of the nature of the cognitive deficits for AD dementia |
| 7 | Atypical course. Sudden onset, or insufficient historical detail or insufficient objective documentation of progressive decline |
| 8 | Etiologically mixed presentation. Concomitant cerebrovascular disease or features of Dementia with Lewy Bodies or evidence for another neurological disease or a non-neurological medical comorbidity or medication use |
| 9 | Probable AD dementia with evidence of the AD pathophysiological process. Working group does not advocate the use of biomarkers for routine diagnostic purposes |
| 10 | The major AD biomarkers may be broken into two classes based on the biology |

Table 2: Diagnostic criteria of IWG for AD [2].

**NIA-AA Diagnostic Criteria**

In the 1984, a group reported NINDS-ADRDA criteria and diagnostic criteria have been widely reliable for the diagnosis of probable AD [8]. Criteria have had a sensitivity of 81% and specificity of 70% and have been widely used in clinical trials and research. In 2007, the International Working Group (IWG) developed new criteria; subsequently at 2011 a new group (NIA-AA) revised criteria of NINDS-ADRDA in the light of accumulated evidence [9,10]. Both of them goaled to extend criteria to cover biologic markers and aimed to cover all stages of disease from the asymptomatic phase to advanced stage of AD. The NIA-AA classified AD at the three phases: preclinical phase, mild cognitive impairment due to AD, and dementia due to AD.

NIA-AA criteria first described dementia-core clinical criteria. Because there are many causes of dementia, they first outline all cause dementia:

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<td>1</td>
<td>Interfere with the ability to function at work or at usual activities; and</td>
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<td>2</td>
<td>Represent a decline from previous levels of functioning and performing; and</td>
</tr>
<tr>
<td>3</td>
<td>Are not explained by delirium or major psychiatric disorder;</td>
</tr>
<tr>
<td>4</td>
<td>Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a ‘bedside’ mental status examination or neuropsychological testing.</td>
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<tr>
<td>5</td>
<td>The cognitive or behavioral impairment involves a minimum of two domains (including memory, thinking, visuospatial abilities, language, behavioral).</td>
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Table 3: Dementia diagnostic criteria at NIA-AA.

MCI is separated from dementia with preserved daily living activities. MCI diagnosis is defined as a clinical judgment and defines daily complaints of the patient obtained from the patient and an informant.
DSM-5 Criteria

DSM-5 is the latest edition published at 2013. DSM-5, classifies dementia as neurocognitive disorder (NCD) [7]. Clinical diagnosis of dementia included minor NCD and major NCD. Minor NCD is another description of Mild Cognitive Impairment (MCI) defined by Peterson et al. To meet DSM-5 criteria for a mild NCD, an individual must have evidence of cognitive decline, but it does not interfere with daily living activities (DSM-5).

<table>
<thead>
<tr>
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<th>Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:</th>
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<td>2</td>
<td>Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and</td>
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<tr>
<td>3</td>
<td>A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment</td>
</tr>
<tr>
<td>4</td>
<td>The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications)</td>
</tr>
<tr>
<td>5</td>
<td>The cognitive deficits do not occur exclusively in the context of a delirium</td>
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The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia)

Table 4: Major and Mild Neurocognitive Disorders diagnostic criteria.

Mild Neurocognitive Disorders diagnostic criteria

A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:

1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

B. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).

C. The cognitive deficits do not occur exclusively in the context of a delirium.

D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Major or Mild Neurocognitive disorder Due to Alzheimer’s disease

Diagnostic Criteria

A. The criteria are met for major or mild neurocognitive disorder
B. There is insidious onset and gradual progression of impairment in one or more cognitive domains (for major neurocognitive disorder, at least two domains must be impaired).
C. Criteria are met either probable or possible Alzheimer’s disease as follows:

For major neurocognitive disorder:

Probable Alzheimer’s disease is diagnosed if either of the following is present; otherwise, possible Alzheimer’s disease should be diagnosed.

1. Evidence of a causative Alzheimer’s disease genetic mutation from family history or genetic testing
2. All three of the following are present:
   a. Clear evidence of decline in memory and learning and at least one other cognitive domain (based on detailed history or serial neuropsychological testing)
   b. Steadily progressive, gradual decline in cognition, without extended plateaus
   c. No evidence of mixed etiology (i.e., absence of other neurodegenerative or
cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline)

**For mild neurocognitive disorder:**

**Probable Alzheimer’s disease** is diagnosed if there is evidence of a causative Alzheimer’s disease genetic mutation from either genetic testing or family history.

**Possible Alzheimer’s disease** is diagnosed if there is no evidence of a causative Alzheimer’s disease genetic mutation from either genetic testing or family history, and all three of the following are present:

2. Steadily progressive, gradual decline in cognition, without extended plateaus.
3. No evidence of mixed etiology (i.e., absence of other neurodegenerative or cerebrovascular disease, or another neurological or systemic disease or condition likely contributing to cognitive decline).

D. The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another mental, neurological, or systemic disorder.

**Imaging of AD:** Definite AD diagnoses requires autopsy confirmation. It is difficult to say exact diagnose in early stages of AD. At this point neuroimaging studies and biomarkers make it easier. Current diagnosis of AD is made by clinical, neuropsychological and neuroimaging assessments. The MRI/CT in AD generally provides to measure volume changes in characteristic locations in brain which makes a diagnostic accuracy in late phases of the disease. Therefore there are developing new approaches to detect AD in early stages. In MRI/CT mesial temporal lobe atrophy including hippocampal and parahippocampal region, medial temporal atrophy and parietal atrophy especially in the interhemispheric surface of the parietal lobe is seen [11]. In CT diffuse cerebral atrophy with enlargement of the ventricles is seen. Also hippocampal atrophy in CT is associated with AD. But normal healthy individuals and some patients with dementia may have no cerebral atrophy. CT is not clinically useful in the primary diagnosis of the disease. The sensitivity and specificity of CT is 81% and 67% [12]. Dilatation of the perihippocampal fissure may be a useful radiologic marker for diagnosis of AD with CT, with a predictive accuracy of 91% [13].

The sensitivity and specificity are approximately 90% with MRI [14]. In MRI hippocampal atrophy (about 50%), enlargement of the temporal horns, third and lateral ventricles are seen [14,15]. Volume changes of the hippocampus, amygdala, cingulate gyrus, temporal horn, lateral ventricles and basal forebrain provides a prediction rate of 77%. Functional MRI (fMRI) techniques can be used to measure cerebral perfusion and structural imaging can be done. Activational fMRI studies have included Blood Oxygenation Level–Dependent (BOLD) imaging, and fMRI activation in the hippocampal and prefrontal regions is decreased in AD [16]. The MRI techniques are sensitive and specific in differentiating AD from normal aging and other dementias, and also can be used to detect asymptomatic or presymptomatic individuals. MRI findings of hippocampal atrophy are highly associated with AD but the specificity is not well established. Sensitivity is about 77%, and specificity is 80% [17].

SPECT is most commonly used for blood-flow measurement. SPECT isotopes have an average half-life of 6-12 hours and variable. This limits the use of SPECT. In AD SPECT is not used to assess AD, is used for diagnosing assessment of the disease.

SPECT studies of blood flow showed functional reductions in the posterior temporal and parietal cortex. Reductions of cerebral blood flow (CBF) and oxygen use is seen in the temporal and parietal neocortex region in AD. Reduction of glucose metabolism is seen in the posterior cingulate cortex [18, 19].

Regional CBF (rCBF) is lowest in the hippocampus, the highest in the striatum, thalamus, and cerebellum. A positive SPECT scan may show the probability of Alzheimer disease by 30%, and a negative scan may show the absence of Alzheimer disease by only 10%
SPECT scan studies have sensitivity and specificity of 80-90%. In one study, using quantitative SPECT scanning reported a 63% sensitivity and an 87% specificity. Using inhaled xenon-133 (133 Xe) and injected technetium-99m [99m Tc] hexamethylpropyleneamine oxime, researchers reported a sensitivity of 76% and a specificity of 73% [21].

PET scanning provides noninvasive measurement of cerebral blood flow, metabolism, and also receptor binding. Evaluation of pathogenesis, diagnosing and monitoring of the disease’s progression is possible with PET scanning [22]. Carbon-11 (11 C), fluorine-18 (18 F), or oxygen-15 (15 O) are generally used as tracers because of having short half-lives thus the subjects are not exposed to prolonged radiation [22]. The most common one used for PET scanning in AD is glucose with [18 F] FDG. FDG-PET is effective method for early diagnosing and differentiation of AD from other types of dementia. Also is used to detect individuals even before the onset of symptoms. In AD temporoparietal glucose hypometabolism is characteristic. In late phases of the disease frontal involvement may be seen [23]. Entorhinal cortex hypometabolism on FDG-PET has predictive value in the progression of disease. The identification of asymmetrical individuals by PET scanning will have a major role in the treatment of AD [24]. PET scanning with ligand PK11195 labeled with11 C, or (R)-[11 C] PK11195, showed increased binding in the entorhinal, temporoparietal, and cingulate cortices in AD. PET scan findings match the histopathological reports of Ab accumulation in brain areas [25].

PET scanning is more sensitive than SPECT scanning. In AD FDG-PET has a sensitivity of 94% and a specificity of 73% [26]. Developing a specific tracer for Ab plaques may increase the sensitivity of PET scanning in early stages of AD in the future. Florbetapir F 18 (AMYViD), flutemetamol F18 injection (Vizamyl) and florbetaben F 18 (Neuraceq) are also the new agents approved by FDA and studies of these agents have been going on [27]. Study of the dopamine transporter (DaTScan) is another technique used for differentiating AD from Lewy Body Dementia (LBD), not diagnosing AD.

**Biomarkers of AD:** Molecular mechanisms of AD and dementia are still completely unknown and biomarkers remain reserved to search. There are several studies have begun to target prevention of the disease at the early stages. There are no simple tests for AD or dementia. Complete clinical neuropsychological assessment is still the only way to make a correct diagnosis of preclinical stage of AD. On the other hand, neuroimaging techniques and research of biomarkers for diagnoses developed rapidly in the past decade. But consequently the value of biomarkers is not high enough and for now it is not possible to use them in screening. Biological determinants of AD appear more complex. It may remain less valuable in the next 10 years [2,3].

**CSF biomarkers:** In cerebrospinal fluid (CSF), total tau and Aβ levels are the most promising and informative biomarkers of AD. CSF tau level is increased because of its releasability from damaged and dying neurons. Aβ1-42 levels are reduce in CSF of AD because of its accumulation as insoluble plaques in the brain. The combination of increased CSF concentrations of t-tau and p-tau and decreased concentrations of Aβ1-42 can be used as a pathological CSF biomarker for AD. Detection of reduced Aβ1-42 level has the greatest sensitivity value 96.4% and the diagnostic specificity is 76.9%. On the other hand the specificity for t-tau is 92.3% with the sensitivity of 69.9-80.6%. But the ratio of t-tau/Aβ1-42, the sensitivity is 85.7% and specificity is 84.6%. Consensus reports have recommended that informative biomarkers of AD should have a sensitivity and specificity of more than 85% [28].

**Plasma biomarkers:** In some studies peripheral venous system of AD patients have been searched to identify diagnostic biomarkers. But it still remains a question if biomarkers will be found for AD. Serum α2 macroglobulin (α2-M), albumin, α1-antichymotrypsin, Complement Factor H (CFH) are previously shown to be potential biomarkers. Serum albumin and immunoglobulin levels showed different findings and also have been examined in CSF and the findings were controversial. Some of them showed a related increase of
immunglobulins and albumin in CSF and serum, and some of them not [29]. Both α2-M and its receptor LRP have been linked with Alzheimer’s disease, but there is not supportive study of an association. A proteinase inhibitor, α1-antichymotrypsin, has also been suggested as a blood-based biomarker of Alzheimer’s disease [30]. The CFH precursor was shown with a significant increase in AD but not in other neurodegenerative disorders. Also CFH is found to be in relation of severity of the disease. CFH was previously shown in plaques in AD without an increase in CSF. Elevated clusterin levels in plasma, but not in CSF is found in relation with cognitive decline. Elevated plasma clusterin levels is a risk for rapidly cognitive decline. Plasma clusterin levels may be usable prognostic marker for AD [31,32]. Exosomal miRNAs was searched in AD patients’ plasma. Subgroups of miRNAs especially miR-342-3p showed difference whereas the total amount of miRNAs did not differ. Integrating this data with other biomarkers of AD may provide information and can be used as a biomarker [33]. All these plasma biomarkers may help us to differentiate AD from other neurodegenerative disorders in the future. However, plasma based biomarkers are not feasible in AD because of not being specific for now.

<table>
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<tr>
<th>AD Mimics</th>
<th>Clues</th>
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<tr>
<td>Anxiety and depression</td>
<td>Neuropsychometric profile, Psychiatry consultation</td>
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<tr>
<td>Vascular cognitive impairment</td>
<td>MRI, CT</td>
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<tr>
<td>Transient epileptic amnesia</td>
<td>EEG and anamnesis</td>
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<tr>
<td>Transient global amnesia</td>
<td>Anamnesis and neuroimaging</td>
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<tr>
<td>Metabolic diseases</td>
<td>Laboratory investigations</td>
</tr>
<tr>
<td>Space-occupying lesions</td>
<td>MRI, CT</td>
</tr>
<tr>
<td>Infections</td>
<td>MRI, CT and Lumbar punctation</td>
</tr>
<tr>
<td>Korsakoff’s psychosis</td>
<td>Anamnesis, MRI, Laboratory investigations</td>
</tr>
</tbody>
</table>

**Table 5:** Important clues differentiate AD from other type of dementia syndromes. [34].

<table>
<thead>
<tr>
<th>DSM-V</th>
<th>NIA-AA</th>
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<td>Interfere with daily and occupational activities</td>
<td>+</td>
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<td>Instrumental living activities</td>
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<td>Cognitive decline is detected by objective assessment</td>
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<td>Cognitive decline is reported by a relative</td>
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<td>Non-amnestic presentation</td>
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<td>Gradual progression</td>
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<tr>
<td>Cerebrovascular disease temporally related with symptoms</td>
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<tr>
<td>Absence of clinical evidence of other dementia syndromes</td>
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<tr>
<td>Documented cognitive decline</td>
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<tr>
<td>Evidence of a causative genetic disorder (APP, PSEN1 or PSEN2)</td>
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<tr>
<td>Evidence of the AD pathophysiological process , Brain amyloid-beta (Aβ) protein deposition (low CSF Aβ and positive PET amyloid imaging)</td>
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<tr>
<td>Biomarkers of neuronal degeneration (CSF tau, decreased FDG uptake on PET in temporo-parietal cortex and disproportionate atrophy on structural MRI)</td>
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**Table 6:** Comparison of diagnostic criteria [34].
Epidemiology, Potential Causes and Risk Factors of AD

Alzheimer’s Disease prevalence term refers to the proportion of AD people in a population at a given point in time. Incidence refers to the number of new cases per year in a population. Since population aging has become a worldwide universal actuality, it’s expected to increase dementia people over years. United Nations Aging Program and the US Centers for Disease Control and Prevention reported that the number of older people will doubled and reach near 1 billion by 2030, and the proportion of older people being increased from %7 to %12 [35,36]. The largest increase is expected to occur at developing countries. Cost of dementia is estimated at 818 million dollars, and expected to rise at 2 trillion dollar level at 2030.

Prevalence of AD

World Alzheimer Report published at 2015 and largely reviewed global impact of dementia by a consensus of authors. Living dementia objects are estimated to increase from 46 million at 2015 to 131.5 million at 2050. Economic impact of dementia will increase exponentially over years and this will occur for especially developing countries. These new estimates are 12-13% higher than those made at 2009. Despite several limitations, meta-analyses have yielded roughly similar age-specific prevalence of AD across regions. Much of the increase through to 2050 is attributed to occur at low and middle-income countries (Figure 1). The 58 per cent of world dementia sufferers is living at low and middle–income countries today and at 2050 this proportion is projected to reach %71. At 2015, the global prevalence of dementia was estimated to be 5.2% in people aged over 60 years, with the regional prevalence being 6.4% in America, 5.9% in Europe, 4.7% in Asia and 4.6% in Africa. The age-specific prevalence of AD almost doubles every 5 years at +65 years aged population. In developed countries, more than 1 in 10 older people (over 65 years old) is affected dementia related symptoms [37]. There is similar prevalence of Alzheimer’s disease across the world and covering %50-70 of all dementia patients [2]. Projections for growth in dementia population are attributed to low-middle income countries. Although developed nations started from a high prevalence but expected to experience only a moderate proportionate increase. This trend is driven mainly by growth rates of population [38].

Incidence of Alzheimer’s Disease

The pooled incidence rate of dementia among people 60+ years of age in the world was 17.3 per 1000 person-years [38]. The incidence rate of AD increases exponentially with age (Figure 1 State of Art Figure 2). There have been some geographic variations in the incidence of AD. Comparisons between European countries revealed geographical dissociation, and the higher incidence rates were found among southern countries [39]. The incidence rates of AD were reported highest at North America and Western Europe, and lower at Asia, Africa and Latin America. In Europe and America peak incidence is among those 80–89 years, in Asia it’s among those at aged 75-84, and in Africa among those aged 65-74 [38]. The organization estimated over 9.9 million new dementia case each year worldwide, implying
one new case every 3.2 seconds, and includes 4.9 million new cases (49% of total) in Asia, 2.5 million (25%) at Europe, 1.7 million (18%) at Americas, and 0.8 million (0.8%) in Africa. It’s important to follow incidence rates among countries, because it’s the most important demonstrator of secular trends and mostly affected by changes in population exposure to modifiable risk factors.

**Global impact of dementia and AD**

At the level of dementia sufferers, AD shortens life span and moreover it’s strongly associated with functional disability and dependence. In a follow-up study at Sweden people within over +75 years old people, more than half who developed functional dependence is attributed to dementia and AD over a three years period [40]. AD is also strongly associated with mortality. Helzner et al., [41], reported 3 to 6 years median survival time for newly diagnosed AD patients. Since rapid increase in the number of dementia subjects, AD will cause tremendous consequences for society. It was estimated that nearly half of AD patients require high level of care at home or institutions. At developed countries long-term institutional care will be the most main cost, whereas in developing countries home care by relatives of patients is expected to be major source of care. The global economic cost of dementia is estimated at 818 billion US dollars. This enormous sum is equivalent to Global Domestic Product (GDP) of some countries like Turkey, Netherlands [38].

**Potential Causes and Risk Factors of AD**

AD is a multifactorial disease as representative of neuro-degenerative diseases including Parkinson disease, Amyotrophic Lateral Sclerosis. There are genetic and environmental risk factors described. The pathophysiologic alterations may begin more than 20 years before clinical symptoms appear. Brain could compensate neuronal alterations for a long time and continue normal functions without any symptom. Because of the complexity of brain, an exact mechanism of symptomatology and threshold to symptoms occurs are still mystery. A healthy brain includes about 100 billion neuron, each neuron have branching extensions, accumulate nearly 100 trillion synapses. Synapses allow signals to travel through circuits and creating cellular basis of higher cortical and subcortical functions. The pathological hallmarks of AD are the accumulation of the protein Aβ at outside of neurons (beta amyloid plaques), and accumulation of an abnormal form of the protein tau inside of neurons (neurofibrillary tangles). Aβ accumulation is believed to disrupt synaptic transmission and tau tangles are believed to cause block transport at neuron. Both of them resulted with neuronal dysfunction, and eventually shared pathway is neuronal death, expansive cell loss and shrinkage of brain. Here one should note that MCI, specifically amnestic form is regarded as early clinical representation of AD but is not the beginning point of AD pathological disease process. It’s unclear whether some are conversing to AD with time and some of the living subjects are never showing dementia or MCI clinical picture although have pathological changes. Early diagnosis and intervention is very important to attenuate the course of AD and decrease the burden on patients, care-givers and also health systems. For the purpose of slowing the course of progress and preventing the disease, researchers have been studying to identify its causes and risk factors [2,38].

<table>
<thead>
<tr>
<th>Alzheimer's disease Genetic factors</th>
<th>Dominantly inherited AD: APP, PRES1, PRES2</th>
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</thead>
<tbody>
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<td>*Genetic mutations</td>
<td>APOE4, unknown genetic mutations or shared Environmental factors</td>
</tr>
<tr>
<td>*Family History</td>
<td>Diabetes Mellitus, Hypertension, Smoking, Hyperlipidemia, Obesity</td>
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<tr>
<td>*Cardiovascular disease</td>
<td>Lower education, social isolation, and mentally sedentary life</td>
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<td>*Psychosocial factors</td>
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<td>*Vitamin D deficiency</td>
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*Nutritional and dietary Folate, vitamin B12, and antioxidant deficiency

*Traumatic brain injury

**Table 7**: Summary of possible risk factors for Alzheimer’s disease.
Genetic Risk Factors: Genetically AD can be classified in two forms. (1) One of these forms is characterized with early onset of disease (<60 years) and the term “familial” is used to represent this form. (2) “sporadic” is used to identify late-onset AD (≤ 60 years) and less or no familial aggregation. Early-onset AD is dominantly inherited AD and is pathology is related to mutations in one of three genes including Amyloid Precursor Protein (APP), Presenilin 1 (PSEN1) or presenilin 2 (PSEN2). Amyloid hypothesis suggests that amyloid-beta (Aβ) is generated from APP. Mutations in APP and presenilins alter the ratio of Aβ species (increase Aβ_{42}, more toxic form) and unbalance the generation and clearance of Aβ. The accumulation of beta oligomer leads to the accumulation of neurofibrillar tangles which are responsible for synaptic dysfunction, axonal degeneration and neuronal loss. Increased cortical amyloid load was shown in almost all patients with AD. Moreover it was found in MCI patients and healthy elderly subject (over 70 years old) with the ratio respectively as 50% and 20-30%. Cortical amyloid load also increases the risk of converting MCI to AD. For example a study revealed a 93% risk for MCI patients to convert into AD over 3 years. On the other hand, the most important known genetic risk factor for AD (especially for sporadic form) is Apo lipoprotein E epsilon 4 (APOE ε4) alleles. APOE gene have three forms-ε2, ε3, and ε4. Everybody carries two of them constituting an allele and each from one parent. The most common form is ε3 form; having ε2 form could decrease risk of AD. The ε4 is related with increased risk of AD, those who inherit two ε4 genes have a higher risk. APOE ε4 is expressed in more than half of patients and shows vary effect on AD. Previous studies revealed that the presence APOE ε4 decreases the mean age and increases the risk for AD. In particular, one APOE ε4 allele may increase the risk for AD 2-3 fold, whereas two copies may increase the risk about 12 fold. Pet imaging studies showed that ApoE deposited in neuritic plaques and neurofibrillary tangles and is related to higher deposits of Aβ. Patients who carry APOE ε4 allele represented higher brain Aβ deposits when compared to other APOE allele carriers. This deposits increase the loss of dendritic spines. The possession of APOE ε4 allele is also associated with worse cognitive performance or cognitive decline in AD patients, MCI patients or non-demented participants. However, APOE ε4 allele does not guarantee the development of AD. Some patients have no copies of APOE ε4 whereas some APOE ε4 carriers may have intact cognitive functions.

Genome-wide association studies have demonstrated other susceptibility genes with lower impacts. Recent Genome-Wide Association Studies (GWASs) tested several genetic markers to determine the additional genotypes that may contribute to explanation of AD pathology. There are some studies show that there could be an association between AD pathology and some additional genetic variants including Clusterin (CLU), complement Component Receptor 1 (CR1), and phosphatidylinositol binding Clathrin Assembly Protein (PICALM). CR1 is a single chain type I transmembrane glycoprotein. CR1 plays an important role in regulation of complement Cb3 protein which is involved in complement system and important to protect against Aβ-induced neurotoxicity. CR1 risk allele has been associated with regulation of Aβ clearance in the brain and shown a mediated effect on cognitive decline. CLU, also known as apolipoprotein J, also plays a role in clearance of Aβ from the brain. There is some evidence showing an association between increased CLU level in cortex and hippocampus and AD risk. PICALM regulates the synaptic transmission and Aβ clearance, and in AD studies it was shown that there is a link between CLU, PICALM and lower memory performance.

Known Non-Genetic Risk Factors of AD

Age

Advanced age is the strongest risk factor for AD. Most of the patients are diagnosed at age 65 years and older. Although people younger than 65 can be diagnosed (early-onset of disease) these are rarer (less than 2% of subjects). Prevalence of AD shows an increase
with age and is doubled with every five year increase in age. Over the age of 85 years almost one-third of people have AD. A ten-year increase in age results the decrease in many cognitive performances such as memory, abstract thinking, set shifting and language [65]. However advanced age alone does not cause the disease.

**Family history** Individuals with first-degree relatives have AD are more likely to develop disease, both genetic and shared environmental factors could contribute to the familial aggregation. Several candidate genes have been studied, including vascular-related genes, cholesterol pathway and insulin degradation genes with inconsistent results.

However the mechanism of action of positive family history on AD pathogenesis is unclear. One explanation can be made by attributing the relationship between family history and APOE genotype. Approximately 45% of adult offspring of patients of AD carry ε4 allele and this possession increases the risk of developing AD [66]. Moreover, not only ε4 allele but also carrying ε3 allele substantially increases the risk of AD. Martinez et al., [67] found that risk of AD for first-degree relatives of a patient is 29.2% for those who carry of ε3/ ε3 genotype, 46.1% for carriers of ε3/ ε4, and 61.4% for carriers of ε4/ ε4. Family history may influence the effect of APOE 4. Johnson et al., [68] found less hippocampal activation in ε4 carriers with positive family history when compared with ε4 carriers with negative family history. Moreover this study showed that family history is a predictor of mesial temporal lobe (MLT) activation independent of APOE genotype. Family history is also associated with alterations in hippocampal region and white matter adjacent to hippocampus. This region is known as one of first regions affected by AD pathology [69].

**Mild Cognitive Impairment (MCI)** MCI is a definition of objective cognitive impairment with preserved daily living activities. MCI, particularly amnestic form is one of the major risk factor to develop AD. It’s estimated risk is 16% per year rate of progression to AD [70]. Findings of another study showed a progression rate 41% after 1 year and 64% after 2 years [71]. In a review, summarized result of the studies points that the most important part is clinical diagnostic criteria, different criteria could result with different rate [72]. This high rate of conversation of MCI to AD promoted researchers to determine the factors that contribute the progression of AD in MCI patients. Positron emission tomography studies revealed that identifying some biomarkers is a valuable technique with high sensitivity and specificity values for prediction of progression [73]. Especially 11C-Pittsburgh compound B (11C-ßBIP) that binds amyloid fibrillary, studies indicated high risk for MCI patients. In a meta-analysis 93% risk for conversation into AD over 1-3 years was estimated for MCI patients with a positive amyloid PET scan [46]. It also should be noted that studies included only amnestic form-MCI. Accumulated evidence also shows there are patients whom did not progressed to AD or restored. At 2011 proposed criteria, in particular cases, MCI is regarded as an early stage of AD.

**Cardiovascular Disease Risk Factors**

There is accumulated evidence suggesting that the health of cardiovascular and cerebral vascular structure is closely related with risk of developing AD. A healthy brain vascular territory is mandatory for neuronal health. However alterations in brain vascular system may cause neurodegenerative diseases such as AD. Cardiovascular dysfunctions have been linked in several ways to increase the likelihood of developing AD. For example, cerebral hypo perfusion reduces oxygen and glucose levels in brain tissue. As a result of impaired glucose level, reduced regional metabolic rate in temporal and parietal regions was found in AD patients. Reduced concentration of glucose transporter (GLUT) was showed by autopsy studies and supported previous findings. Toxic and metabolic disturbances are also partially responsible to develop AD. Vascular pathologies such as atherosclerosis, arteriosclerosis, cerebral amyloid angiopathy and, as well, Blood Brain Barrier (BBB) dysfunction were linked to AD pathology. Especially dysfunction and structural changes in BBB is associated with AD risk due to reduction in clearance of Aβ and increase in
neurotoxic molecules (as result of impaired energy supply) [74]. However, to control vascular modifiable risk factors including blood pressure, cholesterol, and obesity could decrease the risk of AD.

**Smoking and alcohol**

Although earlier studies reported lower prevalence rates of AD among smokers, this effect was due to selective survival bias. Following studies concluded that current smoking associated with a 1.8 fold increased risk of AD [75]. According to a recent review article, the cumulative body of research indicate that past and current smoking is associated with an increased risk for AD, and there is no evidence demonstrating that nicotine could provide any protection from AD [76]. The findings of a meta-analysis revealed that smokers have increased risk for AD when compared with non-smokers. Smokers also showed increased decline in their cognitive abilities [75]. Alcohol abuse can cause ‘alcoholic dementia’, and heavy drinkers have also increased risk of AD at late life, especially among the APOE ε4 allele carriers [77]. Contrast, light-moderate alcohol consumption was frequently related with a reduced incidence of AD [78-80]. However protective effect of mild-moderate alcohol consumption is also controversial due to information bias. The effect of healthy lifestyle, high socioeconomic status, and other dietary factors should be investigated. Indeed alcohol consumption could also protective effect at cardiovascular diseases and dose-dependent U-shaped relation of alcohol consumption and AD is seems mostly evident [81].

**Body mass index, obesity**

Obesity is assumed as a modifiable risk factor for dementia and AD, for a time. Body mass index (BMI) is defined as body mass (weight in kilograms) divided by the square of the body height (term of meters). A higher BMI at midlife is demonstrated with longitudinal studies as a risk factor for future [82,83]. Anstey et al., [84] showed that mid-life BMI may decline the onset age of AD. According to these results overweight and obesity groups all have increased risk for AD. It also should be noted that obesity is associated with other medical risk condition such as diabetes and hypertension. Thus as a risk factor obesity may show a comorbid effect for developing AD. Contrast late life, especially after age 65 BMI is reported inversely related with AD, thus, low BMI in late life was related to a higher risk for AD. Late life low BMI and weight loss should not be interpreted an individual’s general health and could be a result of some serious disorders including malignancy and dementia.

**Blood pressure and hypertension**

High blood pressure is considered as a risk factor for AD in several ways. Several longitudinal studies revealed hypertension for long time, particularly uncontrolled high blood pressure is related with increased risk of late-life AD [85,86]. Variability of blood pressure is also related to cognitive dysfunction in AD patients. Lattanzi et al., [64] showed a link between systolic blood pressure (SBP) and faster cognitive decline in AD patients. Other studies also found a relation between SBP variability and white matter atrophy [87,88] In the light of this information, reduced cognitive functions might partially ascribable to structural changes in the brain stemming from white matter lesions. Hypertension history for a long time is clearly a major risk factor ischemic lesions, stroke and vascular dementia and effective treatment is protective not only against ischemic events, but also for late life dementia and even AD. However, results of the studies, which are investigating late life blood pressure and association of dementia are inconsistent, many studies found no association. Some studies also showed low blood pressure is related with higher dementia risk, but optimal blood pressure remains unknown. Lastly some studies suggest a protective effect of antihypertensive treatment against dementia [89]. Hoffman et al., [90] found significantly less Alzheimer pathological changes in medicated hypertensive than nonhypertensive persons.

Diabetes Mellitus (DM) is closely associated with cognitive decline in abilities such as working memory, mental flexibility, abstract reasoning, attention etc., in elderly. The mechanism underwent this process might partially ascribable to the relationship between
β-amyloid neurotoxicity, advanced glycosylation and altered insulin function [91]. Some animal models support this assumption. For example, Mooradian [92] showed reduced BBB choline transportation in diabetic rats. On the other hand, population-based large studies have shown consistently that type-2 diabetes increases the risk of AD with calculating relative risk varying from 1.5-1.9. In a longitudinal study with follow-up more than 5 years revealed that diabetes is strongest risk factor for AD and the risk is more prominent when other vascular risk factors are present [93]. Meta-analysis of diabetes and AD risk estimated relative risk of nearly 1.5 between type-2 diabetes and AD, and the risk increases by the presence of smoking, APOE4, and hypertension. Association could reflect a long-term effect of hyperglycemia or hyperinsulinemia on neurodegenerative changes in the brain.

**Hyperlipidemia**

Most cross-sectional studies have demonstrated that middle-aged hypercholesterolemia is an independent risk factor for AD. However results of studies investigated dyslipidemia in late life with AD have inconsistent results. A recent careful analysis of current literature has shown no or controversial association between late-life dyslipidemia and AD risk, and no beneficial effect of statin therapy [82].

**Hyperhomocysteinemia (HHcy)**

HHcy is a well-defined cardiovascular risk factor resulted from genetic and non-genetic mechanisms. Both of mutations of regulating genes or deficiencies of vitamin cofactors of homocysteine are potentially responsible from HHcy. Vitamin B12, folate and pyridoxine are some of the cofactors have role in homocysteine metabolism. Many studies have found association of plasma homocysteine with AD. In some studies HHcy at AD population are reported related with vitamin cofactor deficiency and reverted with vitamin supplements. In spite of this, epidemiologic studies have shown reversing of HHcy have not effect at dementia course [82,85].

**Vitamin D**

Recent studies confirm that the low serum vitamin D is associated with AD and dementia. Though vitamin D deficiency is common in older adults it’s important to establish effect of deficiency to AD. The serum level of vitamin D₃ is monitored by measuring 25-hydroxy vitamin D₃. The risk of cognitive decline reported markedly increases below a threshold between 25 and 50 nmol/L. In a recent prospective population-based large study, patients followed for up to 5.6 years. It was reported that vit-D deficient patients had about a 51% increased risk of dementia, whereas the increased risk for those who were severely deficient was about 122%. And they report AD markedly increases at 25(OH) D concentration below 50 nmol/L [71]. But there is no evidence-documented benefit of Vitamin D replacement at AD course. Well-conducted Randomized Clinical Trials (RCTs) to test the effectiveness of vitamin D supplements against placebo in patients with AD are essentially needed at this time [94,95].

**Traumatic brain injury**

Recent studies have shown that patients with Traumatic Brain Injury (TBI) have significantly more Aβ accumulation in gray matter and striatum when compared with control patients with no TBI history [96]. Similar results have also found in autopsy of patients who die within hours following TBI [97]. Moreover, the type of Aβ formed by TBI is Aβ₄₂ that is closely related to AD. Although there are several evidence about Aβ in TBI and AD patients, there are some doubt for the linkage between AD and TBI pathology. For example, plagues in AD are predominantly found in elderly and develop slowly whereas plagues in TBI patients develop in a short time after brain injury and can be found even in children [98]. Other factors such as age, sex and presence of APOE polymorphism also
contribute to this linkage and increase the risk of developing AD after TBI. For example it is known that ε4 allele causes poor recovery following TBI. Thus APOE ε4 carriers have higher risk after TBI when compared to non-carriers [99]. A recent review has summarized accumulated evidence in this subject. Retrospective studies report that history of traumatic brain injury is related with increased risk of dementia, particularly at men. While prospective studies have inconsistent results. There are also evidence suggesting extend of amyloid beta pathology and intraneuronal tau pathology after brain injury. In addition CSF amyloid beta levels are elevated after brain injury.

**Education, social and cognitive engagement**

People with fewer years of education have higher risk of AD than those with more educated. In recent meta-analysis results consistently and strongly shown that those with lower education had a higher risk for dementia, the pooled OR was 2.61% for prevalence and 1.88 for incidence studies [100]. The ‘cognitive reserve’ hypothesis has been proposed to explain this altitude [101]. Cognitive Reserve (CR) term refers to the ability to compensate the age-related changes and pathology in the brain without signs of disease. It has been supposed that brain networks are more efficient and have greater capacity with morphological changes at synaptic and neuronal levels. Early mental and physical stimulation, throughout for life course is thought to increase cognitive reserve and allowing to maintain functions in old age. Some animal models contributed this hypothesis. Petrosini et al., [102] showed that environmental enriched animal have changed brain chemistry, neural functioning and increased synaptic connectivity. Gray matter volumes can be vary to the degree of CR level. Increased gray matter volume of supramarginal gyrus and posterior cingulate cortex was presented in AD patients with higher CR [103]. In addition to education, extensive social networks, active engagement, and participation to intellectually stimulating activities could lower the risk of AD.

**Depression**

The relation between AD and depression is complicated with whether depression is a prodromal symptom of AD or a risk for later development of AD. In last meta-analyses it is supposed that depression is regarded as a risk factor to development of future AD. There is lack of evidence about why depression and AD may be linked. There is increasing evidence about possible role of vascular diseases, and also about shared genetic susceptibility. On the other hand, loneliness may contribute this link. It is known that feeling of loneliness increases the risk of AD and loneliness individuals tend to perform worse cognitive performance [104]. Long-term inflammatory process is another proposed link about togetherness. Even though there is no knowledge about shared pathophysiologic mechanisms, correct diagnosis of depression at patients and appropriate treatment could decrease the risk of future dementia [105]. Additionally, diagnosis of depression and management at MCI and AD subjects is critical to improve quality of life, and could have positive effect at the course of disease for all stages.

**Behavioral and Psychological Symptoms of AD**

Behavioral and psychological symptoms are recently defined shortly as neuropsychiatric symptoms (NPS) and being recognized more commonly as an important part of AD those are expressed throughout the course of disease. NPS have prominent impact on the Quality Of Life (QOL) for both patients and caregivers. Indeed recognizing of NPS provided new insight to pathophysiology of AD. Like we described depression as a risk factor of future AD, concurrently depression is also one of the major NPS at the course of AD. NPS of AD are thought to be indicator of more extensive neurodegeneration, functional dependence, and assumed as predictive of poorer outcome [105,106]. Prefrontal subcortical limbic involvement is an early feature of AD, thus could explain early and prominent behavioral symptoms, and NPS become more prominent and problematic as AD progresses. Depression and apathy
are the most common NPS observed more than half of the patients. At the last decades lots of measurement instrument have been developed to assess NPS at dementia subjects. Brief Psychiatric Rating Scale, Multidimensional Observation Scale for Elderly Subjects and Neuropsychiatric Inventory (NPI) are some of them. The NPI is the most commonly used questionnaire that evaluates 12 emotional behavior commonly observed in dementia, with the data collected from a relative or caregiver. Items evaluated at NPI include: delusions, hallucinations, agitation, depression, anxiety, apathy, irritability, euphoria, disinhibiting, aberrant motor behavior, nighttime behavior disturbances, appetite and eating problems [2,105].

**Depression and apathy**

Depression is commonly observed in the course of AD, with the prevalence of 25-75% and the most common NPS with apathy. Variability between studies results from methodology. A study showed 40% of AD patients showed depression symptoms during follow-up and moreover concurrence of depression is reported as related with poorer prognosis. Studies evaluating genetically shared mechanisms and pathophysiological processes related with depression have inconsistent results. The clear point is that depression at the course of AD is related with reduced cognitive capacity, QOL, and daily living activities. Treatment of depression is expected to benefit depressive and cognitive symptoms. Apathy is commonly exists with depression [106].

Apathy is defined as a loss of cognition, actions and emotions. Apathy is also could be defined as loss of motivational aspects of life and is a predictive of poorer outcome like other NPS of dementia. Apathy is the most common NPS occurred at the course of AD, together with depression. Whether depression and apathy are distinct syndromes remains controversial [107,108]. Reports at the European Alzheimer Disease Consortium Study showed that apathy is the most common NPS during the course of disease with the prevalence of 55.2%, followed with depression 36.7% prevalence [107].

**Agitation and aggression**

Agitation and aggression are generating significant danger to AD patients and caregivers. They are also correlated with poorer outcome and strongly associated with intensity of disease. Their prevalence increase with disease progression and more commonly reported at males. Aggression is frequently linked to frontal serotonergic dysfunction. There is a strong correlation between psychosis, delusions and aggression [107,108].

**Psychosis**

Psychotic symptoms are investigated at the items of hallucinations and delusions at NPI. They are rare NPS at early stages of AD but their frequency increases with disease progression. They are most disturbing and treatment resistant features of spectrum of NPS of AD. Like other NPS, their emergence represents more rapid progression. Aalten et al., reported presence of delusions at 19.4 % and hallucinations at 9.1% of their study population; although they are less frequent, authors conclude they are associated with the highest level of total NPS. Neuroimaging studies suggest these patients have greater cortical impairments and pathologic studies reveal that these patients have more prominent cortical impairment than without psychosis AD patients. Psychotic symptoms are reported more common at people with family history of AD, thus suggests the role of genetic susceptibility [107,108].

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AN ANALYSIS OF PROTECTIVE AND MODIFIABLE FACTORS. Alzheimer’s Disease International (ADI),
London, September 2014.


Alzheimer’s Disease (AD) is an age-related progressive neurodegenerative disorder characterized by progressive memory loss, cognitive impairment and functional decline. Many efforts have been directed to prevent AD due to its rising prevalence and the lack of an effective curative treatment. AD is a multifactorial disease and various mechanisms have been suggested to play key role in the pathogenesis. Increased understanding of the molecular mechanisms underlying AD pathogenesis provides a basis for development of new, effective therapeutic strategies to prevent onset and/or progression of AD. This chapter provides a brief overview about the pathologic mechanisms linked to AD.

**Keywords:** Alzheimer’s disease, oxidative stress, diabetes mellitus, neuroinflammation, epigenetics, sirtuins, microRNAs

**Hallmarks of Alzheimer’s Disease: Amyloid Plaques and Neurofibrillary Tangles**

The key neuropathological changes observed in AD brain are extracellular senile plaques that are mainly composed of amyloid-beta peptide (Aβ), intracellular Neurofibrillary Tangles (NFTs) composed of paired helical filaments of hyperphosphorylated tau protein and marked neuroinflammation. Two main proteins take play a major role in the pathogenesis of AD: Aβ and tau. Two primary hypotheses -amyloid cascade hypothesis and tau hypothesis- have been put forward on the basis of the various causative factors in order to explain which protein aggregate plays a more primal role in AD pathogenesis. Therefore two different lines of thought have evolved, one proposing that AD starts with the accumulation of Aβ and the other suggesting that AD starts with the accumulation of phosphorylated tau.

**Amyloid Cascade Hypothesis**

The amyloid-cascade hypothesis was first described in 1992 by Hardy and Higgins [1]. According to this hypothesis, Aβ and its aggregates trigger a cascade harming synapses and neurons which are responsible for the formation of pathological Aβ plaques, neurofibrillary tangles, synaptic loss, neurodegeneration and ultimately dementia in AD. Aβ peptides are natural products of brain metabolism, but the balance between production and clearance of
Aβ is disrupted in AD. Aβ is generated by proteolytic cleavage of Amyloid Precursor Protein (APP) which is synthesized in ribosomes on endoplasmic reticulum and then transported to the Golgi apparatus. APP is a transmembrane protein. It contains an Aβ-encoding region which is cleaved by a series of secretases: α then γ, or β then γ [2]. Proteolytic processing of APP occurs by one of two pathways, the non-amyloidogenic or the amyloidogenic (Figure 1).

For non-amyloidogenic cleavage of APP, α-secretase cleaves within the Aβ encoding region, releasing a soluble fragment, sAPPα, into the extracellular space. After this first cleavage the remaining C-terminal fragment which includes 83 amino acid residues (C-83) is subsequently cleaved by γ-secretase within the transmembrane region, generating p3 (Aβ17-40) and APP intracellular domain (AICD). AICD and p3 (3 kDa) peptide are released into the cytosol and extracellular space, respectively. AICD can potentially translocate to the nucleus and function as a transcription factor [3]. Aβ species are formed by cleavage with β- and then γ-secretases of APP in the amyloidogenic pathway. β-secretases include β-site APP-cleaving enzyme 1 (BACE1) and 2 (BACE2). Cleavage by β-secretases releases a soluble N-terminus fragment, APPβ (sAPPβ), into the extracellular space and the remaining C-terminal fragment of 99 amino acid residues (C-99) is still membrane bound. C99 is further processed by γ-secretase at the C-terminal region of the Aβ sequence, generating AICD and an insoluble fragment, Aβ, which contains 38–43 amino acid residues. Aβ is released into the extracellular space where it accumulates and contributes to amyloid plaque formation [4]. Particularly Aβ42 is more predominant toxic form of Aβ species found in plaques due to its high hydrophobicity, aggregation and fibrillarization potential [2]. It readily forms insoluble aggregates. Aβ accumulation in the brain induces oxidative stress and inflammatory response thus leads to neurotoxicity which contributes to impairment of cognitive functions.

The balance between different secretase activities is very important in the maintenance of the physiologic Aβ levels. It has been thought that increased production of Aβ and/or decreased degradation by Aβ-degrading enzymes, or reduced clearance across the blood-brain barrier may cause aggregation and accumulation of Aβ in the brain. Proteolytic degradation by the proteases, neprilysin and Insulin Degrading Enzyme (IDE), uptake by astrocytes and microglia and passive flow into the cerebrospinal fluid and sequestration into the vascular compartment by soluble form of the low-density Lipoprotein Receptor Related Protein 1 (LRP1) are the major pathways to remove Aβ peptides from the brain [5,6]. The degradation and clearance of Aβ from the brain have been suggested to be impaired in patients with AD [7,8]. Aβ aggregates may lead to a cascade of pathological events ranging from excitotoxicity, endoplasmic reticulum stress,
oxidative stress, synaptic dysfunction, mitochondrial dysfunction, loss of calcium homeostasis and inflammation. However, amyloid-cascade hypothesis alone is not sufficient to explain AD pathogenesis as removal of Aβ did not halt AD pathology [9].

**Tau Hypothesis**

Tau is an intracellular protein. It belongs to a family of microtubule-associated proteins that promotes microtubule assembly and stabilization. Stabilization of microtubules is essential for normal configuration of neuronal extensions, polarization of cells and also for axonal transport. Tau has neurotoxic effects when hyperphosphorylated due to loss of its normal function. Hyperphosphorylation impairs its ability to bind and stabilize microtubules, and hyperphosphorylated tau has an increased tendency of self-aggregation forming insoluble fibrils. Hyperphosphorylation of tau promotes the formation of paired helical filaments which would eventually evolved into NFTs, dystrophic neurites, and neuropil threads [10]. Abnormal hyperphosphorylation of tau is the key player of AD neurodegeneration as the major component of neurofibrillary tangles in AD. Abnormally hyperphosphorylated tau has been isolated from AD brain in 1990s [11].

In vitro studies have shown that tau phosphorylation at different sites may cause different effects in its biological function as well in pathogenic role. Phosphorylation of tau at Ser262, Thr231, and Ser235 has been shown to inhibit its binding to microtubules by 35%, 25%, and 10%, respectively [12]. Phosphorylation of tau is catalyzed by enzymes known as protein kinases. An inappropriate activation of tau kinases such as glycogen synthase kinase-3β (GSK-3β), cyclin-dependent kinase 5 (cdk-5) and c-Abl has been thought to cause of tau hyperphosphorylation and subsequent NFT formation [13].

A sizeable body of evidence has demonstrated that tau has additional roles including regulation of synaptic function and neuronal signaling which may be involved in AD pathogenesis. Tau has been thought to play an important role in regulation of synaptic function by interacting with synaptic proteins (e.g post synaptic density protein PSD-95) which is involved in regulation of synaptic plasticity. The abnormal tau phosphorylation has been suggested to disrupt the interaction between tau and -95/NMDA receptor complex [14].

Tau protein may also be involved in regulation of mitochondrial dynamics. Abnormal phosphorylation of tau may directly influence mitochondrial function by decreasing ATP production and increasing susceptibility to oxidative stress [15]. The mislocalization and accumulation of tau proteins in dentrites and dendritic spines may disrupt neuronal cell communication which leads to neurodegeneration and loss of memory [16].

Although both hypotheses suggest primal roles of Aβ and tau protein in AD pathogenesis, increasing evidence suggests that there may be a crosstalk between two pathologies. Aβ can facilitate NFT formation [2] and tau pathology can affect the formation of amyloid plaques [17]. Aβ interacts with tau pathology via three pathways leading to tau hyperphosphorylation and tau axonal transport deficits which result in NFT formation; (i) Aβ activates tau kinase, GSK-3β, and induces GSK-3β-mediated phosphorylation of the Kinesin Light Chain (KLC) leading to altered deposition of tau and subsequent NFT formation, (ii) Aβ may induce proteasome dysfunction leading to decreased tau degradation and increased tau aggregation, (iii) Aβ activates caspase-3 which is responsible for tau truncation and tau aggregation [18]. On the other hand, tau-related pathways affect APP processing and Aβ formation. Tau kinases may phosphorylate APP and activate y-secretase leading to formation and aggregation of Aβ oligomers. In addition, APP axonal transport deficits and altered APP production may occur depending on the inhibition of tau degradation [19]. However, the mechanisms linking Aβ toxicity and tau hyperphosphorylation have not been exactly clarified yet.

**Pathogenic Mechanisms in Alzheimer’s Disease**

**Oxidative Stress**

Oxygen metabolism generates free radicals such as Reactive Nitrogen Species (RNS)
and Reactive Oxygen Species (ROS) including superoxide anion and hydroxyl radical. Free radicals have unpaired electrons in separate orbitals in their outer shell and exhibit a high reactivity. They readily interfere with biomolecules such as lipids, proteins and nucleic acids in organelles and subsequently alter their structure and function. Free radicals produced by oxygen metabolism play important role in cell signaling and homeostasis. However, an imbalance between their production and clearance from the body results in oxidative stress. Environmental factors such as UV, ionizing radiation, certain drugs and chemicals can enhance free radical production causing oxidative stress. Oxidative stress on polyunsaturated membrane lipids results in alteration of the membrane properties such as fluidity, ion transport, enzyme activities and eventually leads to cell death. Protein oxidation causes to impaired cellular metabolism whereas DNA oxidation leads to formation of DNA strand breaks and mutation. Transition metal ions such as iron and cupper promote free radical production due to their pro-oxidant property. In the presence of these metal ions, free radical production increases via Fenton and Haber-Weiss reactions. Harmful effects of free radicals can be prevented by antioxidant defence system that contains small antioxidant molecules and antioxidant enzymes such as Superoxide Dismutase (SOD), Catalase (CAT), glutathione peroxidase and glutathione reductase. Impaired antioxidant defence is the most important factor for development of oxidative stress.

Increased oxidative damage is an early change in AD patients. The levels of protein carbonyls and 3-nitrotyrosine (protein oxidation markers), 8-hydroxydeoxyguanosine (8-OHdG) and 8-hydroxyguanosine (DNA and RNA oxidation markers), malondialdehyde (MDA), 4-hydroxynonenal, and F2-isoprostanes (lipid peroxidation markers) have been found to be elevated in AD brains [20,21]. Increased oxidative stress in AD is attributed the pro-oxidant role of Aβ. Aβ possesses pro-oxidant properties that can influence oxidative processes. At high micromolar and nanomolar concentrations, Aβ aggregates form fibrils and induce free radical formation, lipid and protein oxidation, DNA damage and subsequently cause neuronal death. Transition metal ions including iron and copper are required for pro-oxidant activity of Aβ. Direct interaction between Aβ and transition metal ions may result in increased free radical formation [22]. Aβ treatment has been shown to increase the levels of hydrogen peroxide and lipid peroxides in both cell and animal models [23,24]. On the other hand, as a closed circuit, oxidative stress also promotes Aβ production by decreasing α-secretase activity while promoting β- and γ-secretase expression and activity [25]. Although data is highly limited, oxidative stress may also influence hyperphosphorylation and polymerization of tau protein. It has been suggested that the elevated amounts of fatty acid oxidation that is determined in AD patients, can facilitate the polymerization of tau [26]. Antioxidant defence capacity is the main determinant in development of oxidative stress. Neurons are vulnerable to free radical attacks since their glutathione content, a powerful antioxidant, is relatively low and their membranes contain a high amount of polyunsaturated fatty acids. Defective antioxidant defense, increased oxidative stress and enhanced Aβ deposition have been shown in APP overexpressing transgenic mice [27]. Dumont et al. have demonstrated that facilitation of the mitochondrial antioxidant defence improves resistance to Aβ, decreases plaque formation or increases plaque degradation in a transgenic AD mouse model [28]. Recently, the possible role of SOD in AD pathogenesis has been demonstrated in Tg2576 APP-overexpressing AD mouse model. In this model a cytoplasmic copper/zinc superoxide dismutase deletion has been found to be associated with increased Aβ oligomerization, accelerated loss of memory and spatial learning [29]. On the other hand, aging is a natural and inevitable process and is associated with a prolonged free radical production. Due to the decline in antioxidant defence capacity during aging, human body becomes insufficient to counteract the free radicals. Since AD is generally seen in elderly individuals, increased oxidative stress in AD patients may be partially attributed to advanced age. As a matter of fact, activity of antioxidant enzymes including SOD, catalase, glutathione peroxidase and glutathione reductase have been reported to be decreased in brains of patients with AD [30]. Inflammation is a free radical-producing state. Neuroinflammation is a contributory factor
in AD pathogenesis that will be described below. Production of free radicals by glial cells due to inflammation may exacerbate the oxidative stress in AD patients. Taken together, oxidative stress is a key player in AD but it is still controversial whether it plays a causative role in the disease or secondary to the pathological changes seen in AD.

**Neuroinflammation**

Neuroinflammation is a process including activation of innate immunity in the brain. Neuroinflammation functions in protecting central nervous system from infectious insults, injury or diseases. Microglia is key players in neuroinflammation. Neuroinflammation is an early event in the pathogenesis of AD. Transgenic animal models of AD have demonstrated that neuroinflammation is enhanced around amyloid plaques [31]. Microglial activation have dual effects on AD progression: (i) activation of microglia results in production of cytokines and chemokines which in turn initiate phagocytic activity and thus help Aβ clearance and degradation [31], (ii) prolonged microglia activation initiates a pro-inflammatory cascade and disease proceeds to chronic state that synaptic dysfunction, mitochondrial damage, further activation of microglia, and eventually neuronal death occur [32].

Microglial activation results in production and release of pro-inflammatory cytokines such as interleukin IL-1β, IL-6, IL-8, tumor necrosis factor-α (TNF-α), chemokines, ROS and RNS that lead neuronal and vascular degeneration in AD brains [33]. In addition, these cytokines stimulate the nearby astrocyte–neuron to produce further amounts of Aβ42 [34]. Not only synthesis of pro-inflammatory cytokines but also their cognate receptors are upregulated in AD patients [35]. In vitro studies have demonstrated that blood–brain barrier is disrupted in AD. Blood–brain barrier dysfunction has been attributed to (i) Aβ42 that is able to modify the expression of tight junction proteins and alter barrier properties [36], (ii) pro-inflammatory cytokines that cause the loss of tight juctions and breaching the blood–brain barrier [37].

Oxidative stress is a driving force for neuroinflammation. Free radicals in the terms of ROS and RNS can mediate redox signaling leading to activation of transcription factors which control the expression of pro-inflammatory cytokines, chemokines and other ROS/RNS-generating enzymes. As a closed circuit, ROS and RNS production increase due to neuroinflammation. The link between neuroinflammation and Aβ deposition is BACE1 that is involved in amyloidogenic processing of APP. BACE1 gene expression is controlled by NF-κB signaling that is activated by inflammation [38]. BACE1 expression is upregulated upon inflammatory stimuli leading to increased production of Aβ [39]. On the other hand, Aβ induces the expression of inflammatory cytokines and enzymes by stimulating NF-κB and MAPK signaling pathways. As a closed circuit, Aβ accumulation in senile plaques may produce sequential inflammatory events and excitotoxicity which in turn cause neurodegeneration and cognitive impairment [40].

Bellucci et al., [41] have suggested that inflammation may play a significant role in the events leading to neurodegeneration in the tauopathies. They have found that production of pro-inflammatory cytokines (IL-1β) and enzymes (COX-2) are increased in tau-positive nerve cells in brainstem and spinal cord. According to these findings NFTs may trigger neuroinflammation by activating microglia. It has been shown that suppression of neuroinflammation is concordant with reduction in Aβ plaques and hyperphosphorylated tau in brain, and is associated with improvements in cognitive and behavioral deficts in AD mouse models [42-44]. Treatment with antitumor necrosis factor-α (anti-TNF-α) or interleukin-1β (IL-1β) antibodies is efficient in reducing the pathology in animal models of AD [45,46]. Nonsteroidal anti-inflammatory drugs (NSAIDs) and peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists have been shown to reduce the expression and activity of β-secretase and lower Aβ secretion [47]. Suppression of neuroinflammation with NSAIDs has been suggested to rescue memory and cognitive decline. However, retrospective epidemiological studies have demonstrated that prolonged treatment with NSAIDs delays onset of AD when initiated early stage or before disease initiation [48], but its efficiency has not been shown in neither mild nor moderate forms of AD [49].
**Metal Toxicity**

Trace elements such as iron, zinc and copper are crucial for neuronal function. However, these metal ions accumulate in brain during the aging and contribute to neurodegeneration. Metal homeostasis is disrupted in AD brain. Zinc, copper and iron have been found to be accumulated within the core and periphery of senile plaques and these metals have been suggested to be involved in Aβ aggregation and oxidative damage [50]. In the presence of Fe^{2+} or Cu^{2+}, hydrogen peroxide yield the hydroxyl radical via Fenton and Haber-Weiss reactions. Therefore both iron and copper accumulation lead to an increase in oxidative stress.

Aβ contributes to oxidative stress indirectly by damaging mitochondria and directly by regulating the redox activity of several metals such as iron and copper [51]. APP and its Aβ fragments have specific binding sites for Cu^{2+} and Fe^{3+}ions [52]. In vitro studies have demonstrated that Aβ-copper complexes catalytically produce hydrogen peroxide and hydroxyl radical and eventually induce oxidative damage [53]. There is growing evidence that copper can facilitate Aβ aggregation by binding to Aβ which results in Aβ plaque burden [54]. On the other hand, there is evidence that APP has potential beneficial effect on reducing ROS generation. APP contains an Iron Responsive Element (IRE) on the 5’ untranslated region of its mRNA [55]. APP translation is thus responsive to cytoplasmic free iron levels. When cellular iron levels are high, translation of APP is increased. Ferroxidases prevent oxidative stress caused by Fenton and Haber-Weiss reactions by oxidizing Fe^{2+} to Fe^{3+}. APP possesses ferroxidase activity which is demonstrated in primary neuron cultures. It catalytically oxidizes Fe^{2+}, loads Fe^{3+} into transferrin which in turn causes to neuronal iron export and a decrease in ROS production. Due to its ferroxidase activity APP may be upregulated in response to increased iron stores in AD brain [56].

Zinc may accelerate the precipitation of Aβ and produce protease-resistant “non-structured” aggregates [57]. It has been suggested that compounds affecting zinc homeostasis can decrease Aβ deposition in the brain [58]. Deregulation of neuronal Zn^{2+} homeostasis is believed to be strictly connected to oxidative stress. Zn^{2+} can trigger free radical production by interfering with the activity of the electron transport chain (inhibits complex I and III) [59]. In addition, Zn^{2+} may contribute to iron accumulation and free radical production by inhibiting the ferroxidase activity of APP [56]. On the other hand, zinc and iron promote tau phosphorylation and aggregation by binding to tau [60].

Aluminium (Al) is a known neurotoxin which may have various adverse effects on central nervous system. Al can access to the brain via blood-brain barrier and it accumulates in a region-specific manner. There is some evidence, although it is controversial, that Al may trigger all major histopathological events associated with AD. Independent studies have shown that Al strongly promotes amyloid aggregation and accumulation at physiological concentrations [61,62]. After chronic oral exposure, Al elevates APP expression, promotes Aβ deposition and amyloidosis in hippocampal and cortical pyramidal neurons in rats and mice [63,64]. Al binds the amyloidogenic Aβ peptide resulting in the formation of neurotoxic Aβ-sheet conformation [65]. While the role of Al on tau-related pathology has been shown in vitro, in vivo studies are limited. Al catalyzes a covalent transfer of entire triphosphate from ATP to tau in vitro. Therefore it promotes the phosphorylation of tau non-enzymatically [66]. It may cause neurofibrillary abnormalities, synaptic loss and disrupt axonal transport mechanisms. It has been reported that Al-induced NFTs are made up of normal neurofilaments instead of abnormal tau proteins [67]. Al may affect neuroinflammatory signaling by promoting NF-κB expression which is upregulated in AD [68]. In addition, Al may contribute to AD via causing oxidative damage to neurons through Fe [69]. Al stabilizes ferrous (Fe^{2+}) ion which catalyzes the Fenton reaction, thus leads the enhanced oxidative damage that may exacerbate events associated with AD. Metal chelation therapy based on
binding and removing to these metal ions can provide a beneficial effect against oxidative stress in AD. Treatment with metal chelators such as clioquinol and desferrioxamine have provided some success in altering the progression of AD [70,71]. Therapeutic approaches targeted to restore metal balance are an active area of current investigations in the field of AD.

**Mitochondrial Dysfunction**

Hypometabolism is a hallmark of AD. Mitochondrial dysfunction plays important role in both brain aging and AD. For the first time, Swerdlow and Kan have proposed mitochondrial cascade hypothesis for sporadic form of AD in 2004 [72]. According to this hypothesis, mitochondrial dysfunction occurs early in disease pathogenesis and causes Aβ deposition, synaptic loss and NFT formation that are seen in AD [73]. The mitochondria is the major source of ROS in the central nervous system, and is also particularly vulnerable to oxidative stress due to lack of DNA repair activity. Oxidation of mitochondrial DNA renders it vulnerable to somatic mutations which augments mitochondrial dysfunction. In addition to ATP production, mitochondria carry out significant cellular processes including maintainece of Ca\(^{2+}\) homeostasis, regulation of cellular metabolism and apoptosis [74]. Impaired Ca\(^{2+}\) homeostasis leads to excessive Ca\(^{2+}\) uptake into mitochondria which in turn initiates apoptosis [73]. Mitochondrial dysfunction has been suggested to trigger onset of neuronal degeneration in AD. Mitochondrial abnormalities in their number and size, deficient energy production, increased mitochondrial degradation by autophagy, decreased cytochrome oxidase activity (complex IV) activity, and a decrease in activity of certain tricarboxylic acid cycle enzymes (especially pyruvate dehydrogenase and α-ketoglutarate dehydrogenase ) have been determined in AD brains [75,76]. Mutations in mitochondrial DNA arising from impaired mitochondrial bioenergetic have been detected in AD patients. These mutations are associated with decreased cytochrome oxidase activity. It has been suggested that since decreased cytochrome oxidase activity is accompanied by the decline in mitochondrial respiratory function, it eventually proceeds to neuronal damage and cognitive decline in AD [77].

Aβ has been shown to accumulate in mitochondria from AD patients. Intracellular and mitochondrial accumulation of Aβ likely precedes extracellular Aβ deposition. Aβ deposits can increase mitochondrial damage directly and indirectly. In direct manner, Aβ deposits can disrupt lipid polarity and protein mobility in mitochondrial membranes, break membrane potential, inhibit key enzymes of the mitochondrial respiratory chain and decrease ATP production [78,79]. The indirect effect of Aβ deposits on mitochondrial dysfunction occurs in synaps. Synaptic loss is one of the major characteristics of AD. In neurons mitochondria are significantly more likely to be localized at synapses and are essential for the formation and maintenance of synapses. Abnormalities in mitochondrial functions contribute to synaptic dysfunction and eventually synaptic loss.

After the synthesis, APP is targeted to both mitochondria and plasma membrane by virtue of N-terminal chimeric signals. Aβ is transported into the mitochondria by mitochondrial import channels. APP has been shown to accumulate exclusively in the protein import channels of mitochondria of human AD brains but not in age-matched controls. It has been determined that decreased function of mitochondrial import channels due to the overproduction of APP leads to decreased translocation of nuclear-encoded cytochrome c oxidase subunits IV and V proteins that are essential for mitochondrial function [80].

Tau protein may also be involved in mitochondrial dysfunction in synaps, indirectly. There are several studies indicating that hyperphosphorylated tau may contribute to worsening of AD progression by effecting complex I, mitochondrial transport and mitochondrial dynamics [81]. Tau can bind kinesin, a motor protein which transports mitochondria along axons
to synapses with other transport proteins. Under conditions of elevated tau, transport of mitochondria along axons to synapses is impaired. Phosphorylated tau prevents transport proteins to attach which results in improper synaptic activity and synaptic degeneration [82, 83].

**Brain Insulin Resistance and Insulin Deficiency**

Type 2 diabetes mellitus is a risk factor for AD, and AD risk is increased in patients with type 2 diabetes. AD and type2 diabetes share many common pathological processes. The features of both disorders are influenced by abnormal systemic and/or brain glucose metabolism and insulin signaling pathways. Impaired glucose metabolism is associated with increased oxidative stress and accumulated advanced glycation end products that both create a viscous cycle involving oxidative stress and mitochondrial dysfunction.

Pancreatic insulin is transported by cerebrospinal fluid into the brain and crosses the blood–brain barrier by an active and saturable process [84]. Insulin is even produced in brain tissue itself [85]. Insulin receptors are mostly located in the cerebral cortex, olfactory bulb, hippocampus, cerebellum, and hypothalamus where are the cognition pertinent areas of the brain. They are largely localized in neurons, being less abundant in glia. Insulin can also bind to insulin like-growth factor 1 (IGF-1) receptors on the neurons. By binding neuronal insulin and/or IGF-1 receptors, insulin regulates physiological functions such as food intake, inhibition of hepatic gluconeogenesis, counter-regulation of hypoglycemia, reproduction, modulation of tau protein phosphorylation, APP metabolism, Aβ clearance, neuronal survival, neurotransmission, learning and memory [84,86]. In addition, insulin acts as a growth factor for neurons. It promotes neurite outgrowth and axonal regeneration. Insulin also functions by controlling neurotransmitter release processes at the synapses and activating signaling pathways associated with learning and long-term memory. Concordantly, defective insulin signalling in the brain has been demonstrated to be an important factor contributing AD pathology [87]. Recent studies have demonstrated that brain glucose utilization and insulin signalling are impaired in AD. AD is associated with a decrease in the levels of insulin in the cerebrospinal fluid, in the ratio of cerebrospinal fluid insulin/plasma insulin, a decline in the expression of insulin receptors and an increase in fasting plasma insulin levels [85,88]. Impaired insulin signalling in the AD brain is attributed to increased oxidative stress. Oxidation of membrane receptors, signaling proteins, transcription factors, and epigenetic regulators may lead disrupted insulin signalling and glucose utilization. Impaired insulin signaling may affect AD pathogenesis via tau hyperphosphorylation, Aβ metabolism and acetylcholine signalling. Decreased insulin function leads to the over-activation of GSK3β, which results in hyperphosphorylation of tau, followed by formation of NFTs [89,90]. Insulin and IGF-1 signaling have beneficial effects on Aβ homeostasis. They promote tissue clearance of Aβ and non-amyloidogenic pathway of APP processing; consequently protect neurons from Aβ toxicity [91]. On the other hand, insulin stimulates the expression of choline acetyltransferase, the enzyme responsible for acetylcholine synthesis. Therefore, decreased insulin levels as well as insulin resistance can ultimately contribute to a decrease in acetylcholine in AD brains [92].

**Genetic Aspect of AD**

Generally, AD is classified as familial and sporadic. Late-onset sporadic form constitutes the vast majority of AD cases (95 % of cases). Autosomal dominant early-onset familial form represents only about a small fraction of all AD cases (5% of cases) but progresses much faster than sporadic form of AD. Familial form of AD is associated with mutations in genes encoding APP on chromosome 21, and the subunits of the APP cleaving enzyme, γ-Secretase, termed Presenilin-1 (PSEN-1), on chromosome 14 and presenilin-2 (PSEN-2) on chromosome 1 [93,94]. Although missense mutations in the APP gene are first to be identified in familial AD, they only account for a small fraction (~0.1%) of all familial AD mutations.
Mutations in PSEN-1 and PSEN-2 are account for the vast majority of familial AD mutations with over 150 currently identified mutations [96]. PSEN-1 and PSEN-2 mutations are associated with changes in APP processing that favor overproduction of toxic Aβ_{42} or an increase in the proportion of Aβ_{1-42} to Aβ_{1-40} (it is generally believed that Aβ_{1-40} peptides are non-amyloidogenic while Aβ_{1-42} are amyloidogenic). Although the exact causes of sporadic AD are not yet determined, multiple genes and acquired mutations due to environmental factors (aging, diet, smoking) may increase an individual’s susceptibility or predisposition to AD. Genome-wide association studies have led to discovery of susceptibility genes that may be involved in AD pathogenesis. These genes are APOE, bridging integrator 1 (BIN1), clusterin (CLU), ABCA7 (ATP-binding cassette transporter), Complement Receptor 1 (CR1), Phosphatidyl Inositol-Binding Clathrin Assembly Protein (PICALM), Membrane Spanning 4-Domains Subfamily (MS4A6A), CD33, MS4A4E and CD2-Associated Protein (CD2AP) [97].

Among these genes, the gene encoding APOE on chromosome 19 contributes the greatest risk. APOE in humans consists of three major isoforms-APOε2, APOε3, and APOε4- which are encoded by different alleles (epsilon [ε] 2, 3, and 4). APOE is synthesized and secreted mainly by astrocytes. Its main function is lipid transport in the brain. In addition, APOE plays important role in regulation of brain Aβ peptide levels by binding Aβ peptides and facilitating their proteolytic degradation. Aβ peptides are proteolytically degraded within the brain by neprilysin and insulin degrading enzyme. The degradation of Aβ peptides within microglia by neprilysin and extracellular Aβ degradation by insulin-degrading enzyme are facilitated by APOE. It has been suggested that Aβ clearance with the Apoε4 isoform is less effective than other isoforms in facilitating degradation of these peptides [98]. Although the APOε4 allele is represented in approximately %25 of population, it has been postulated to be a risk factor for sporadic AD in older adulthood [99]. Cross-sectional studies in patients with AD have shown that the APOε4 allele is associated with impaired memory function, more severe atrophic changes and hypometabolism in the medial temporal lobe structures [100-102]. Autopsy studies on AD have indicated the APOε4 allele to be associated with greater densities of Aβ deposition, senile plaques and neurofibrillary tangles, especially in the hippocampus [103]. Besides this, the APOε2 allele may have a protective effect against AD. APOε2 carriers are associated with less Aβ plaques and neurofibrillary tangles than both APOε4 carriers and APOε3 homozygotes [104]. However, the influence of APOε4-allele on development, progression, clinical presentation of AD and rate of cognitive decline have not been fully described yet.

BIN1 has been suggested to be the second most important risk locus which is responsible for late onset AD. BIN1 is a member of the (BAR) family of genes that are involved in various cellular processes, including endocytosis, actin dynamics and membrane trafficking/tubulation. A BIN1 variant (rs59335482; an insertion of three C bases) which is associated with increased AD risk has been identified in three independent AD case–control cohorts. Insertion has found to led overexpression of BIN1 in cell cultures [105]. Although BIN1 is related with calcium homeostasis, inflammation and apoptosis, it is likely involved in AD pathogenesis by modulating tau pathology. It has been reported that knocking down the BIN1 significantly suppresses tau-derived neurotoxicity [105]. The BIN1 expression has been reported to be increased at onset and in shorter disease duration in AD patients [106].

CLU is a multifunctional glycoprotein that is also termed as apolipoprotein J. It is involved in regulation of brain lipid metabolism, prevention of inflammation and reduction of oxidative stress and apoptosis. It prevents fibril formation by binding Aβ peptides and facilitating their transport into the bloodstream. CLU concentration in peripheral blood has been found to be clearly increased in AD. However, it is still need to be clarified how CLU variants influence the development of AD [107,108].
Another susceptibility gene for sporadic AD risk is ABCA7. Gene product, ABCA7, is a member of the ATP-binding cassette superfamily of transporters. It is a multispan transmembrane protein, and is most abundantly expressed in the microglial cells in the brain. ABCA7 may contribute to the pathophysiology of AD via various pathways including Aβ accumulation, lipid metabolism and phagocytosis. The levels of ABCA7 have been found to be increased in the AD brain, and are positively correlated with amyloid plaque burden and disease severity. Several studies have identified different SNPs in ABCA7 related to sporadic AD [109].

Complement signaling pathways which are required for proper microglial function may be altered in AD, leading to reduced ability to phagocytose apoptotic cells and clear Aβ. CR1 is involved in the clearance of amyloid plaques. Genetic variations in CR1 have been reported to be associated with global cognitive decline, higher burden of AD brain pathology and increased risk for AD [110, 111]. In summary, many susceptibility genes have been suggested to be associated with sporadic AD risk [112]. Although the association between sporadic AD risk and some genes has been confirmed by several recent genome wide association studies, genetic case-control studies and meta-analyses which provide better understanding on their precise roles in sporadic AD are still far from complete.

**Epigenetic Aspect of AD**

Epigenetic mechanisms are defined as acquired and heritable modifications on DNA that regulate the gene expression without affecting the DNA base sequence. They act on genes through reversible changes leading to their activation, repression or silencing. Thus, epigenetically regulated or dysregulated transcription states can cause to development of healthy or pathological states. Epigenetic modifications are classified in three types: DNA methylation, histone modifications and non-coding RNAs. Epigenetic modifications are dynamic and unlike genetic mutations, they can be reversed by environmental factors and therapeutics. Physical and behavioral factors, nutrition, physical and mental exercise, environmental pollutants, pesticides, chemicals and certain metal ions affect the epigenetic mechanisms. Especially, nutrition is one of the main epigenetic regulators. Folate, vitamin B12, betain, choline and methionine play a pivotal role in DNA methylation as well in maintenance of genomic stability. In addition to their antioxidant properties, dietary polyphenols modify epigenetic mechanisms.

There is an overwhelming scientific consensus that epigenetic changes contribute to aging and aging-associated diseases. Genetic mutations are involved in the pathogenesis of familial AD, but epigenetic mechanisms are likely to be important in the etiology of sporadic form of AD. Epigenetic mechanisms involved in the AD pathology has become increasingly clear with novel researchs. Recently, the diet containing nutrients that are able to modify epigenetic mechanisms has been suggested as a preventive approach for AD [113].

**Aberrant DNA methylation in AD**

DNA methylation is the most widely studied epigenetic mechanism. DNA methyltransferases (DNMT1, DNMT2, DNMT3A and DNMT3B) catalyze the transfer of a methyl group to the carbon atom in position 5 of a cytosine moiety in the presence of the methyl donor S-adenosyl methionine (SAM). DNA methylation occurs at the CpG rich regions, called CpG islands, in gene promoters. Methylation at this site disrupts the binding of transcription factors and repress the transcription. Therefore, hypermethylation results in gene silencing whereas hypomethylation is associated with active chromatin. Vitamin B12, B6 and folic acid influence DNA methylation patterns altering SAM availability via metabolites of the SAM cycle (Figure 2).
Numerous studies have shown that there is a consistent decrease in global DNA methylation in both normal aging and AD [114,115]. Aberrant DNA methylation profiles have been detected in AD patients even if they are in the preclinical stage [116]. Although AD is associated with global DNA hypomethylation in middle frontal gyrus and middle temporal gyrus [117], specific gene regions and loci such as APP, PSEN1 have been reported to be hypo- or hypermethylated. An enormous research effort has been directed towards understanding the causative role of DNA methylation status of AD-related gene promoters in the pathogenesis of disease. However findings of different studies are inconsistent and the role of DNA methylation in AD pathogenesis still remains unexplained. For example, hypomethylation-associated overexpression of the APP gene has been demonstrated in the brain of an Alzheimer's patient [118]. However in another study, no significant difference has been found in the methylation level of APP gene in AD patients as compared with controls [119]. There is evidence that Aβ can modulate DNA methylation. In murine cerebral endothelial cell cultures Aβ_{1–40} treatment has been shown to reduce the status of global DNA methylation whereas increase the DNA methylation on the promoter region of neprilysin that is an enzyme involved in Aβ degradation [120]. DNA methylation change in promoter of PSEN-1 gene has been examined in AD. According to data of human postmortem brain tissue studies, PSEN-1 gene promoter has a very low level of methylation and reduced DNA methylation is associated with increased PSEN-1 gene expression [121,122]. However, most recently, the methylation status of PSEN-1, BACE1, DNMT1, DNMT3A and DNMT3B promoters in blood DNA obtained from AD patients and controls have been analysed and it has been reported that none of the studied regions is differently methylated between AD and controls [123]. Some other genes that are thought to be involved in AD pathogenesis have also been investigated in respect with the promoter methylation status. The promoters for cAMP-responsive element that is associated with synaptic plasticity have been found to be hypermethylated in AD [124]. GSK3β is the major kinase that phosphorylates tau protein in the brain. It has been reported that GSK3β activity and expression levels are increased in AD brains which may be due to hypomethylation of its promoter region [125]. Promoter methylation of neuronal protein phosphatase 2A has been found to be downregulated in affected brain regions of AD patients, causing the accumulation of both phosphorylated tau and APP isoforms, and increased secretion of Aβ peptides [126,127]. Promoters of cyclooxygenase-2,
brain-derived neurotrophic factor and NF-κB have been reported to be hypomethylated, whereas promoters of cAMP response element-binding protein and synaptophysin have been reported to be hypermethylated in the frontal cortex of postmortem AD brain [124].

Taken together, although DNA methylation changes have been determined in AD brains the causative role of DNA methylation on amyloidopathy and taupathy have not been fully understood. However, it is clear that DNA methylation is strictly linked to folate, methionine, homocysteine metabolism (see figure 2). An experimental study with APP-overexpressing transgenic mice fed with a folate/B12/B6-deficient diet has resulted in increased S-Adenosylhomocysteine (SAH)/SAM ratio, upregulated PSEN-1 and BACE, and enhanced Aβ accumulation [128]. The lower availability of SAM may be related to the altered expression of genes involved in APP metabolism and Aβ accumulation. As a matter of fact, SAM level has been demonstrated to be decreased in postmortem AD brain [129]; plasma homocysteine levels have been found to be increased whereas serum folate levels are decreased in late-onset AD patients with respect to controls [130]. Therefore, the global hypomethylation determined in AD brain may be due to abnormal levels of the intermediates producing through folate/methionine/homocysteine metabolism.

In light of these considerations, it has been concluded that folate, vitamin B12 and vitamin B6 are not only required for growth and neurotransmitter synthesis but also essential for maintenance of physiological DNA methylation patterns in the brain. Their deficiency may result in aberrant DNA methylation profiles which have been detected in AD patients.

**Histone modifications in AD**

The reversible post-translational histone modifications and subsequent chromatin remodeling play important roles in regulation of memory and learning. Histone proteins undergo various post-translational modifications including acetylation, methylation, phosphorylation, ubiquitination, sumoylation and adenosine diphosphate (ADP)-ribosylation. Among these modifications, acetylation/deacetylation is the most extensively studied type of histone modification due to its regulating function on gene expression. Acetylation status of histones is maintained by the opposing actions of Histone Acetyltransferases (HATs) and Histone Deacetylases (HDACs). HATs catalyze the transfer of an acetyl group from acetyl-coenzyme A to lysine residues on the N-termini of histone proteins. HDACs remove acetyl groups from acetylated histone proteins. In general, histone acetylation is linked to chromatin decompaction and transcriptional activation. In contrast, deacetylation leads to more condensed chromatin state and transcriptional repression or silencing. HDACs are classified into four classes as I, II, III and IV according to their sequence homology.

After the discovery of the fact that histone acetylation is associated with cognitive functions, role of histone modifications in AD has been investigated with experimental studies. Treatment with HDAC inhibitors have provided some benefits in memory and learning in transgenic mice models of AD [131]. Su et al., [132] have reported that valproic acid, a HDAC1 inhibitor, decreases Aβ production and reduces plaque formation in the brains of APP (V717F) transgenic mice. Also, daily given phenylbutyrate, HDAC inhibitor, have been reported to reverse spatial memory loss and maintain normal phosphorylated tau levels in the hippocampus of transgenic Tg2576 mouse model of AD, but it has no effect on Aβ levels [133].

Sirtuins are NAD+-dependend class III HDACs. Seven sirtuins (SIRT1-7) have been identified in mammals, with varied roles in chromatin integrity, metabolic regulation, oxidative stress, DNA repair and apoptosis. In early 2000s, epidemiological studies have revealed that individuals who maintain a low calorie diet have a reduced risk of developing
AD. The influence of calorie restriction on AD pathology has been examined in AD mouse models, and it has been shown that calorie restriction reduces amyloid plaques by activating SIRT1 [134,135]. This neuroprotective effect has been attributed to an increase in NAD+/NADH ratio and subsequent activation of SIRT1 during the calorie restriction. SIRT1 is the most frequently studied HDAC in AD. According to results of studies with cell culture models and transgenic mouse models, SIRT1 overexpression increases α-secretase activity, reduces Aβ formation, promotes neuronal survival [136] and inhibits neuroinflammation [137]. Furthermore SIRT1 deacetylates the acetylated tau and promotes its degredation and clearance. SIRT1 downregulation has been shown to inhibit tau polyubiquitination and tau turnover, thus results in accumulation of phospho-tau [138]. It has been reported that cortical SIRT1 expression is decreased in autopsy specimens of AD patients but not in the individuals with mild cognitive impairment; SIRT1 mRNA and protein levels are negatively correlated with the duration of symptoms and the accumulation of tau, but are weakly correlated with the Aβ₄₂ [139]. In accordance with these data, a significant decline in serum SIRT1 level has been determined in patients with both AD and mild cognitive impairment in comparison to healthy elderly individuals [140].

In light of these data, SIRT1 activation seems as an useful approach to prevent onset and progression of AD. Resveratrol is a naturally occurring polyphenol found in red grapes and red wine. It is known with its antioxidant, anti-carcinogenic and anti-inflammatory activities. In addition to these properties it is a powerful activator of SIRT1 [141]. SIRT1 activation by resveratrol has been shown to protect against amyloid plaque formation in AD models. Resveratrol is undergoing evaluation in clinical trials (www.clinicaltrials.gov). SIRT3 regulates mitochondrial energy metabolism and mitochondrial dynamics. SIRT3 has been thought to be involved in neuroprotection by decreasing ROS production. However the number of SIRT3 studies is highly limited in the field of AD.

**MicroRNAs in AD**

miRNAs are small (approximately 22 nucleotide length) non-coding RNAs that play a significant role in the regulation of gene expression in a post-transcriptional manner. miRNAs bind specific target mRNAs in the 3'-untranslated region and supress their translation and/or promote their degradation. More than 30,000 miRNAs have been identified in humans. miRNAs play an important role in various processes such as proliferation, differentiation and apoptosis in both healthy and pathological states. miRNAs are highly expressed in different compartments of the brain and many of them are brain-specific or brain-enriched. miRNAs have a selective distribution within neurons and synapses. They have been found to regulate translation of proteins needed for neurite outgrowth, synaptogenesis and activity-driven synaptic plasticity [142]. They may also control expression of genes related with learning, memory and cognitive performance in general. Enourmous studies have been conducted to understand the role of miRNAs in the pathogenesis of neurodegenerative disorders including AD [143-145]. Although there are some inconsistent data, several miRNA profiling studies have independently validated specific miRNAs which are dysregulated in the AD brain (Table 1). These specific miRNAs may affect the AD-related pathology either directly (by modulating expression of key genes such as APP and BACE1), or indirectly (by affecting expression of genes related with neurogenesis and immune response). It has been revealed that expression of APP gene is modulated by miRNAs and, as a closed circuit, Aβ treatment also causes to down-regulation of substantial proportion of miRNAs [146]. Therefore Aβ seems as a powerful regulator of miRNA levels. miRNAs can be used as potential diagnostic tools due to their stability and convenience of detection in serum. Examination of miRNA profile may be benefical for early detection of AD (may also be helpful for determination of AD risk in the first degree relatives of the patients). In addition, modulation of mRNAs may be a novel therapeutic strategy in AD. However, miRNAs is a relatively novel topic in the field of AD researches. There are inconsistent findigs probably due to non-homogeneous experimental conditions. Further studies are needed to better understand miRNA-mediated gene silencing which contributes to AD pathogenesis.
<table>
<thead>
<tr>
<th>miRNA</th>
<th>Role in AD pathogenesis</th>
<th>Affected tissue/expression in AD patients</th>
<th>Referens</th>
</tr>
</thead>
<tbody>
<tr>
<td>miR-9</td>
<td>Downregulated in primary neuronal cell cultures after treatment with Aβ peptides; involved in inflammatory and oxidative stress pathways in the AD; targets include BACE1, SIRT1 and NFκB</td>
<td>Upregulated in the hippocampus and temporal lobe neocortex of AD brains; downregulated in the patient serum</td>
<td>147-149</td>
</tr>
<tr>
<td>miR-107</td>
<td>Negative correlated with neuritic plaque density; increases BACE1 mRNA levels; targets include BACE1, CDK5 and ADAM10</td>
<td>Downregulated in AD patients</td>
<td>150-152</td>
</tr>
<tr>
<td>miR-15</td>
<td>Involved in the regulation of pro-apoptotic markers in AD brain; participates in neuronal tau hyperphosphorylation in vivo</td>
<td>Downregulated in AD brains</td>
<td>144, 153, 154</td>
</tr>
<tr>
<td>miR-29</td>
<td>Inversely correlated with the density of amyloid plaques and BACE1; increases amyloid production in neuronal cellular models, in vitro</td>
<td>Downregulated in human AD temporal cortex, cerebellum and patient serum</td>
<td>155, 144</td>
</tr>
<tr>
<td>miR-34</td>
<td>Related with amyloid plaque density, neuritic plaque counts and neurofibrillary tangle counts; negative correlated with BACE1 level</td>
<td>Downregulated in temporal cortex of AD patients</td>
<td>150, 151, 155</td>
</tr>
<tr>
<td>miR-181c</td>
<td>Downregulated in primary neurons treated with exogenous Aβ42 peptides; regulates SIRT1 expression</td>
<td>Downregulated in the AD cortex and cerebrospinal fluid</td>
<td>156, 146</td>
</tr>
<tr>
<td>miR-106</td>
<td>Directly binds to APP; repress the expression of the transporter ABCA1 that results in an increase of Aβ levels</td>
<td>Downregulated in the temporal cortex of AD brain</td>
<td>157</td>
</tr>
<tr>
<td>miR-146a</td>
<td>Involved in inflammatory and oxidative stress pathways as a regulator</td>
<td>Upregulated in the temporal cortices of AD patients</td>
<td>147, 158</td>
</tr>
<tr>
<td>miR-155</td>
<td>Downregulates complement factor H in neurodegenerative brain</td>
<td>Upregulated in Down's syndrome, a neurological disorder which shows AD-like neuropathology with age</td>
<td>159</td>
</tr>
<tr>
<td>miR-125b</td>
<td>Positive correlated with gray matter neurofibrillary tangles; upregulated by NF-kB in response to IL-1β and Aβ42-induced stress in human neuronal glial cell; increased miR-125b expression disturbs the balance of phosphatase and kinase activity in cultured neurons; targets include synapsin II and complemeneter factor-H</td>
<td>Upregulated in the hippocampus, medial frontal gyrus, cerebellum and temporal lobe neocortex of AD patients</td>
<td>156, 147, 148, 158, 159, 162</td>
</tr>
<tr>
<td>miR-153</td>
<td>Reduces expression of APP in human fetal brain cultures</td>
<td>Decreased levels in brain of AD patients</td>
<td>163</td>
</tr>
<tr>
<td>miR-195</td>
<td>Downregulates the level of Aβ by inhibiting the translation of BACE1.</td>
<td>Decreased levels in cerebrospinal fluid of AD patients</td>
<td>156, 164</td>
</tr>
<tr>
<td>miR-132</td>
<td>Activates neuronal processes and regulates brain-derived neurotrophic factor and methyl CpG binding factor MeCP2 expressions; accelerates tau hyperphosphorylation</td>
<td>Decreased expression in hippocampus and medial frontal gyrus of AD patients</td>
<td>156, 165</td>
</tr>
</tbody>
</table>

| Table 1: miRNAs associated with Alzheimer's Disease. |

References


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Abstract

Alzheimer’s Disease [AD] is one of the most challenging threats to the healthcare system in society. It is believed that this ultimately leads to dysfunction and death of cholinergic neurons, and compensation for this loss had been the primary focus of first generation therapeutic agents. The amyloid and tau hypotheses have lead to a focus on amyloid and tau as therapeutic targets. The current therapeutic goals are to reduce amyloid levels, prevention of amyloid aggregation/toxicity and tau phosphorylation/aggregation. There is also a significant advancement in understanding the function of cholinesterase [ChE] in the brain and the use of ChE inhibitors in AD. The mechanism of a new generation of acetyl- and butyryl ChE inhibitors is being studied and tested in human clinical trials for AD. Other strategies, such as vaccination, anti-inflammatory agents, cholesterol-lowering agents, antioxidants and hormone therapy, are also being studied for treating or slowing the progression of AD. Although several anti-amyloid β compounds have been examined in clinical trials as potentially useful drugs, all of them have failed to show significant benefits so far. In contrast, tau-targeted drugs have been developed and have entered clinical trials. We expect strongly a therapeutic drug for dementia to be released in the near future. Developments of early diagnostic tools based on quantitative biochemical markers will be useful to better follow the course of the disease and to evaluate different therapeutic strategies.

Keywords: Alzheimer Disease; Anti-Amyloid Managements; Cholinesterase Inhibitors; Disease Modifying Agents; Memantine

Management of Alzheimer’s Disease

The first step in AD management is accurate recognition and diagnosis of the disorder, and then disclosing that diagnosis in a sensitive and timely way to the patient and others as appropriate. Disclosure of diagnosis is not harmful, and actually decreases depression and anxiety in patients and their care-givers [1]. The vast majority of patients with mild dementia wish to be fully informed and 75% of caregivers wish their relative to be informed...
Differences among ethnic, cultural, and religious groups may influence how and what disclosure occurs. It offers the patient opportunity to pursue desired activities and maximizes individual autonomy and choice by providing information necessary for decision making and advance planning, including the decision to give informed consent to research projects and autopsy. At time of diagnosis several issues need to be addressed, including the provision of high quality understandable information about the illness and its course to patient and caregiver, a careful assessment for any co-morbidities and consideration given to other services that may be required including social services, mental stimulation, occupational therapy, physiotherapy, speech and language therapy. Occupational therapy can benefit patients daily functioning and reduce the need for informal care [3]. Medico-legal issues need to be addressed, with driving often needing prompt attention and action taken according to the legal framework operating in that particular country. Care-giver support should consist of education about AD, and attending peer support groups may be helpful. Care-giver stress and depression are common and, if present, more intensive care-giver support and counselling and/or specific treatment for depression may be needed. The provision of a standard education and support package to caregivers has been shown in Randomized Controlled Trials [RCT] to decrease psychiatric symptoms in caregivers and lead to delays in institutionalisation for patient [4,5]. Management should include clear arrangements for follow-up, as regular monitoring of medication response and adverse effects as well as changes in the severity of dementia [using scales like the Mini-Mental State Examination [MMSE]] should be undertaken. Reassessment for development of co-morbidity [including carer stress] should be an integral part of management.

Primary Prevention of AD

This refers to the prevention of subsequent dementia in cognitively normal subjects and is the ultimate goal for AD management. Several risk factors have been well established for AD, though some [such as age, sex and genotype] are not modifiable. Potentially modifiable risk factors which have been established through several epidemiological studies include vascular risk factors [hypertension, smoking, diabetes, atrial fibrillation and obesity] and head injury while protective factors that are described include use of antihypertensives, non-steroidal anti-inflammatories, statins and hormone replacement therapy, high education, diet, physical activity and engagement in social and intellectual activities. However, whether modifying these factors will reduce risk of dementia is not yet known. A meta-analysis concluded that there is no good evidence to recommend statins for reducing the risk of AD while results of the large, prospective, placebo-controlled Women’s Health Initiative Memory Study showed that the use of estrogen plus progesterin in post-menopausal women was actually associated with a significantly increased risk of dementia [6,7]. Treatment of hypertension for prevention of dementia, including AD, has been the best studied risk factor to date. However, most RCTs have been stopped early because cardiovascular endpoints were reached, meaning they were underpowered to detect differences in rates of dementia. A study of treating hypertension in the very old cases reached similar conclusions, and contained a meta-analysis of all studies supporting a significant risk reduction [8]. However, the period over which treatment needs to be given is not known, nor has it been established whether treating vascular risk factors, including hypertension, in those with established AD affects disease progression. Currently, no clear recommendations about dementia prevention can be made.

Secondary Prevention of AD

This refers to the prevention of development of AD in non-demented subjects with some evidences of cognitive impairment. The groups most often studied in this regard are those with Mild Cognitive Impairment (MCI), and several RCTs of ChEIs have been undertaken in MCI, most targeting conversion to dementia as the primary outcome. A meta-analysis included eight studies involving all three ChEIs, with duration of treatment ranging from
16 weeks to 3 years [9]. There were no differences in rate of conversion to AD between active and placebo groups, and most secondary outcomes were also negative. There have also been negative studies of aspirin in primary prevention of cognitive decline and of anti-inflammatories and vitamin E in MCI. A large study showed no effect of Gingko on preventing AD [10]. Therefore, no treatments have demonstrated efficacy for preventing or delaying development of AD in MCI subjects until now, while evidence exists that ChEIs, Vitamin E, Gingko Biloba and anti-inflammatories are not substantively helpful.

**Treatment of Established AD**

There are currently no means of reversing the pathologic processes of AD. Currently available medications do not halt the underlying degenerative process but can slow disease progression and therefore delay symptomatic decline [11]. The specific goals of therapy are to preserve cognitive and functional ability, minimize behavioral disturbances, and slow disease progression with maintenance of patients and caregivers [12]. Nevertheless, realistic expectations of treatment outcomes are needed because the impact for most patients is likely to be modest and temporary, with not every patient responding to treatment. The main benefit of pharmacotherapy is an attenuation of decline over time rather than an improvement in cognitive or behavioral symptoms. It is important to discuss this point with patients and their families, who may expect improvement rather than relative stability [13]. Failure to do so often will result in patient and family dissatisfaction with prescribed therapies and the risk of discontinuation. Beneficial response to a ChEI (ie, delayed deterioration of cognitive or behavioral problems) can be determined from the physician’s global assessment of the patient, the primary caregiver’s report, a neuropsychologic assessment or mental status questionnaire, or evidence of behavioral or functional changes [14].

Four drugs are commonly used for treating AD: Three ChEIs approved for mild to moderate disease, one of which also is approved for severe AD, and a glutamate N-methyl D-aspartate [NMDA] antagonist approved for moderate to severe disease.

**Cholinesterase Inhibitors**

Cholinesterase inhibitors increase cholinergic transmission at the synaptic cleft, potentially benefiting patients with cholinergic deficits as in AD. Three such drugs are currently available in the US: donepezil, rivastigmine, and galantamine. There has been several well conducted placebo-controlled, large scale RCTs with this three ChEIs, which have shown efficacy on cognitive function, global outcome and Activities of Daily Living (ADL) in patients with mild to moderate AD, usually defined as MMSE between 16 and 26. Mean global improvement over placebo is 3–4 points on the ADAS-Cog, a level of improvement roughly equivalent to the naturalistic decline expected over a 6 month period. Most studies have been over relatively short duration [6 months], though 1 and 3 year studies have been reported with donepezil which suggest the benefits of ChEIs continue in the longer long. Retrospective analysis and some long term open studies suggest a possible effect of ChEI on disease modification, but more data are needed before this can be confirmed. RCTs of ChEIs in more severe AD [MMSE < 10] have also shown positive results and a Cochrane review concluded that trials supported evidence of benefit in mild, moderate and severe AD [15-17]. In light of current evidence, limiting prescribing of ChEIs to only some AD subjects according to certain cut-offs on a measure such as the MMSE, as operated in many countries, does not seem justified. Although a point will be reached in severe AD when ChEI are unlikely to continue to have benefit, it is currently unclear at what point in the disease process ChEI should be withdrawn.

Rivastigmine is also approved for dementia in Parkinson’s disease. A large double-blind placebo-controlled trial of rivastigmine showed meaningful improvements in cognition and everyday functioning [18].
While there is expert consensus that cholinesterase inhibitors are more effective in Dementia with Lewy Bodies (DLB) than in AD, for both cognitive and behavioral effects, evidence from large controlled trials is lacking [19].

In vascular dementia, evidence is mixed for the cholinesterase inhibitors. They are often prescribed in vascular dementia because of the frequent co-occurrence of cerebrovascular and neurodegenerative disease [19].

In frontotemporal dementia, there is no convincing evidence of benefits from these drugs, and there are reports that they worsen behavior symptoms [20].

There is inadequate evidence on the use of cholinesterase inhibitors in other neurocognitive disorders. ChEIs are generally well tolerated, although common gastrointestinal adverse effects such as nausea, diarrhea, and vomiting may sometimes lead to discontinuation of treatment in some patients.

There have been few direct comparisons between ChEIs, and those which have been undertaken have been small in size and not produced consistent evidence of better efficacy of one drug over another. There is some evidence from open-label studies that patients who do not tolerate or do not seem to benefit from one ChEI may tolerate or draw benefit from the other. One of the ChEIs, rivastigmine, is now available in a transdermal [patch] formulation which appears to have lower incidence of side effects than oral administration but equal efficacy [21].

A disease modifying effect of ChEIs has been proposed, and has some basic scientific support, but no convincing clinical data either from trials of clinical endpoints or of those using biomarkers, has yet been forthcoming to support these claims.

Effects on non-cognitive Behavioural and Psychological Symptoms Of Dementia (BPSD) have also been shown; despite cognition effect sizes are modest. There remains uncertainty as to which particular non-cognitive symptoms may respond best, though effects on psychosis and apathy are consistently reported. Effects on agitation are less clear, and a large placebo-controlled RCT in moderate to severe AD failed to show an effect of donepezil on patients with clinically significant agitation [22].

**Memantine**

Memantine, a non-competitive N-methyl-D-aspartate receptor antagonist, also has been subject to several RCTs in AD. It is believed to be neuroprotective against excitotoxicity in the cortex and hippocampus. Studies in moderate to severe AD have been more consistently positive than those in mild to moderate AD, previous reviews of the literature have concluded that while there is a significant effect in cognition at all severities, but effects on global outcome, ADL and behaviour were only apparent in the moderate to severe studies [23]. Once daily dosing has been shown to be as effective as the original recommendation of administration twice daily [24]. Modest effects on behaviour were also found in a pooled analysis of six studies which included all those with MMSE < 20, with delusions, agitation/aggression and irritability being the most responsive symptoms, though studies of subjects primarily selected for the presence of these behavioural features have not yet been reported [25].

A systematic review showed that memantine had a small beneficial effect on cognition at six months in moderate to severe AD, marginal effect on mild to moderate AD, and a small but clinically undetectable effect in mild to moderate vascular dementia [26].

In frontotemporal dementia, memantine has shown mixed results. There is preliminary evidence of benefits in DLB and Dementia in Parkinson’s disease; however, there have been reports of worsening delusions and hallucinations in DLB.
Combination therapy of a ChEI and memantine is rational from a pharmacologic perspective because the agents have different mechanisms of action. In a randomized controlled trial, patients with moderate to severe AD who were already receiving donepezil derived significant benefit from the addition of memantine in terms of cognition, ADLs, global outcome, and behavior [27]. There are also economic benefits associated with the addition of memantine to donepezil treatment for patients with advanced AD. A recent study demonstrated improvement in clinical outcomes plus cost savings associated with the use of memantine [28]. In a study by Tariot et al., the incidence of nausea was substantially lower in patients receiving memantine add-on therapy compared with those receiving donepezil monotherapy [27]. The safety and tolerability of combining rivastigmine capsule and memantine also has been studied in a 26-week, prospective, open-label study of patients with moderate AD [29]. The combination was found to be both tolerable and safe, with a reduced incidence of gastrointestinal- related AEs compared with those documented in the US prescribing information for rivastigmine, suggesting that this beneficial effect of memantine may be applicable across ChEIs [29].

Management of Mild to Moderate Disease

Since the introduction of the first ChEI in 1997, most clinicians would consider these agents to be first-line pharmacotherapy for mild to moderate AD [30]. Four ChEIs are currently available: tacrine, donepezil, rivastigmine, and galantamine. Tacrine is not commonly used because of a poor tolerability profile and low oral bioavailability, and it is, therefore, excluded from this discussion [21]. ChEIs raise acetylcholine levels in the brain by inhibiting acetylcholinesterase [31]. Despite minor variations in their mode of action there is no evidence to suggest any difference in efficacy between the 3 commonly used ChEIs [30]. Likewise, the tolerability profile is similar between the ChEIs for the oral formulations. However, the 10-cm2 rivastigmine patch has shown efficacy similar to oral rivastigmine formulations, but with approximately two-thirds fewer reports of nausea and vomiting, with Adverse Event [AE] rates similar to those of placebo [32]. AD is often accompanied and worsened by malnutrition, and weight loss is a frequent complication of AD, occurring in approximately 40% of patients at all stages [33]. Donepezil, rivastigmine, and galantamine cause a broad spectrum of AEs, of which nausea, vomiting, diarrhea, and weight loss are the most common [34, 35].

There continues to be debate regarding the extent of the benefits achieved with ChEIs. Although some assert that the most that can be achieved with ChEIs is symptom modification, others consider these agents to have disease-modifying effects [30,36]. In one study, after discontinuation of therapy, rivastigmine treated patients showed less deterioration in cognitive function compared with placebo treated patients, suggesting an effect on disease progression [37]. In another study, donepezil treatment slowed progression of hippocampal atrophy compared with untreated patients, suggesting a neuroprotective effect of donepezil in AD [38]. However, these early observations require confirmation, and, at present, the ChEIs generally are considered symptomatic medications.

A systematic analysis of double-blind, placebo controlled trials of ChEIs demonstrated treatment effects ranging from a 1.4- to 3.9-point improvement at 6 months and 1 year, in the midrange of the 70-point ADAS-Cog scale [30]. In clinical trials, a change of 4 points is considered clinically significant for patients with mild to moderate dementia [39,40]. As such, the symptomatic improvements observed are modest and of debatable clinical significance, despite being statistically significant [35]. In a meta-analysis of 16 double-blind, placebo-controlled trials of ChEIs composed of almost 8000 patients, the numbers needed to treat for one additional patient to benefit were 7 for stabilization or better, 12 for minimal improvement or better, and 42 for marked improvement [41]. Although the numbers needed to treat seem favorable, uncertainty remains regarding the clinical relevance of these outcomes and the duration of the apparent benefit because the majority of trials reviewed were of less than 26 weeks’ duration.
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. A recent meta-analysis that analyzed clinical results from 29 randomized, placebo-controlled trials of patients with mild to moderate AD found that ChEI therapy was associated with significant modest benefits in terms of neuropsychiatric and functional outcomes [42]. Current guidelines acknowledge that preventing or delaying further loss of ADL function is an important goal of AD therapy and that the benefits of ChEIs may be diminished when treatment is delayed [11,43]. Significant preservation of ADL function has been observed with donepezil, galantamine, and rivastigmine compared with placebo [12].

ChEIs also have been shown to reduce AD caregiver burden: in patients with moderate to severe AD, donepezil treatment for 24 weeks significantly reduced caregiver time spent assisting patients with basic and instrumental ADLs (<52 minutes/day; \(P < .005\)) [44]. A small study has demonstrated that rivastigmine treatment reduces caregiver time spent assisting with ADLs (up to 690 hours over 2 years) [45]. Longer periods of treatment with ChEIs also decrease the risk for nursing home placement [46,47]. A retrospective analysis of a large US medical claims database showed that over a 27 months follow-up period, more patients who were not treated with ChEIs were placed in nursing homes (11.0%) than were those who received either rivastigmine (3.7%) or donepezil (4.4%) [47]. These studies suggest that ChEIs enable patients to live longer in community settings with associated personal, social, and economic benefits [12].

Memantine is sometimes used to treat patients with less severe disease, despite its use in early AD not being supported by the FDA. Although memantine has been reported to improve cognition, global status, and behavior in patients with mild to moderate AD, its mechanism of action would suggest that it does not have a place in early AD [48]. Memantine is not a ChEI; it is a low- to moderate affinity, noncompetitive [channel blocking], NMDA receptor antagonist that seems to block pathologic neural toxicity associated with prolonged glutamate release [49]. Blockade of NMDA receptors by memantine could confer disease-modifying activity in AD by inhibiting the “weak” NMDA receptor–dependent excitotoxicity that contributes to the neuronal loss underlying the progression of dementia [49]. As such, memantine is not effective until weakened neurons become vulnerable to glutamate-induced excitotoxicity, and therefore it cannot substitute for ChEIs because of its inability to enhance cholinergic neurotransmission required for memory and learning [49].

Management of Moderate to Severe Disease

Memantine is approved for the treatment of moderate to severe AD on the basis of a study in which patients with moderate to severe AD who received 20 mg memantine monotherapy showed less decline in cognition and function while maintaining good tolerability after 6 months compared with those who received placebo [50]. The ChEI donepezil also recently has been approved for use in severe AD.

Recently, donepezil 23 mg/day has been approved for the treatment of moderate to severe AD. Results from a 24-week, randomized, double-blind study reported that donepezil 23 mg/day was associated with greater benefits in cognition (as assessed by the Severe Impairment Battery) compared with donepezil 10 mg/day, although the between-treatment difference in the Clinician’s Interview-Based Impression of Change plus Caregiver Input Scale was not significant. The most commonly reported side effects with donepezil 23 mg/day were nausea, vomiting, and diarrhea, which occurred at a higher incidence than with donepezil 10 mg/day [51]. Combination therapy of a ChEI and memantine is rational from a pharmacologic perspective because the agents have different mechanisms of action. In a randomized controlled trial, patients with moderate to severe AD who were already receiving donepezil derived significant benefit from the addition of memantine in terms of cognition, ADLs, global outcome, and behavior [27]. There are also economic benefits associated with the addition of memantine to donepezil treatment for patients with advanced AD. A
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Other Drugs and Interventions

Several other treatments have been suggested as potentially beneficial for AD, including non-steroidal antiinflammatory drugs, oestrogens and statins. A large, placebo-controlled RCT of vitamin E (1000 IU, twice a day over 2 years) in moderate AD, was found to significantly delay the time to a composite outcome of primary outcome measures, but a study in MCI has been negative and the conclusion of a Cochrane review is that there is insufficient evidence for the efficacy of vitamin E in the treatment of AD or MCI [52]. Studies of steroidal, non-steroidal and cyclo-oxygenase-2 inhibitors in AD and MCI have been negative yet have had potentially serious side effects.

Many other compounds, such as piracetam, nicergoline, selegiline, vinpocetine, pentoxyphylins and Cerebrolysin are prescribed in some countries as treatments for AD. For example, a recent Cochrane review of piracetam, one of the most widely studied drugs to date, found poor study design, possible publication bias and that overall the evidence from trials did not support the use of piracetam in people with dementia or cognitive impairment [53]. A review of 6 Cerebrolysin trials found an effect on global outcome but no consistent effect on other scales. Further evidence is therefore required before its use can be recommended [54]. Similarly, a Cochrane review of selegiline found no evidence for its efficacy in AD [55]. At present, therefore, there is no convincing evidence for efficacy of any of these drugs for AD.

Management of Behavioural and Psychological Symptoms

Management of BPSD begins with careful search for trigger and/or exacerbating factors that including environmental cues, physical problems [infections, constipation], medication and depression or psychosis. As studies of BPSD indicate a high placebo response, safe non-pharmacological management [education, exercise, aromatherapy, sensory stimulation, personalised music] should be tried wherever possible in the first instance as symptoms may naturally resolve within a short time. The beneficial effects of ChEIs and memantine for mild BPSD have been described above, but a recent RCT found donepezil did not help clinically significant agitation in those with moderate to severe AD [22]. Both conventional and atypical antipsychotics reduce BPSD, with particular effects demonstrated for risperidone for agitation/aggression and psychosis [56,57]. However, antipsychotics have important and potentially serious side effects, most especially increased stroke risk, increased mortality, parkinsonism and cognitive impairment [58]. They should be used with caution, at low dose, and for the shortest period needed only for those with moderate to severe symptoms causing distress and after careful assessment of risk and benefit and after discussion with care-giver and, where possible, patient. There is no evidence that conventional agents are any safer in regard to risk of stroke or mortality than atypical agents and they have a less established evidence base and greater side effects [59]. Low doses of antipsychotics should be used with careful monitoring, and drugs prescribed for the minimum period required. When BPSD have settled, antipsychotics can be withdrawn in most cases without re-emergence of BPSD, unless behavioural disturbance is still present [60]. Evidence for other drugs is limited, carbamazepine may help aggression, though most studies of valproate have been negative.
Antidepressants, especially Selective serotonin reuptake inhibitors [SSRIs], may be useful for depression in dementia and do not have the adverse anticholinergic effects of older tricyclics [63].

Duration of Management

Placebo-controlled clinical trials with marketed cholinesterase inhibitors generally have lasted 6 months, with a few exceptions lasting up to 12 months or longer. Inferences are made that if the drugs are effective over this period then they will continue to be beneficial far longer, perhaps indefinitely. Over the long term, however, as patients inevitably worsen, it becomes even more difficult to determine whether any given individual is benefiting from the drugs.

In some 3-month-long and 6-monthlong trials, after medication has been discontinued patients on average return to the cognitive level of the patients contemporaneously treated with placebo within 6 weeks. Such findings are taken to indicate that the drugs have overall symptomatic effects and that continuous use is required to maintain benefits.

Some observational studies using clinic databases or open-label extensions of clinical trials suggest that patients who continue cholinesterase inhibitors over at least 1 year have a delay in nursing-home placement compared to those who cannot tolerate or do not take them, and that the addition of memantine could further contribute to the delay [64-67]. These observations, however, are not controlled and are subject to the potential bias that patients who experience a less progressive course continue their medications, while patients who are destined to progress more quickly do not continue, resulting in apparent therapeutic effects that are illusory. Moreover, comparisons are made between cohorts from time periods both before and after the ready availability of the cholinesterase inhibitors [68]. These observational studies, however, contrast with the long-term controlled trials in MCI and with observations from the Australian Imaging Biomarkers and Lifestyle datasets, where the use of cholinesterase inhibitors over the long term is associated with faster decline [69,70]. Thus, duration of treatment remains an unresolved issue.

Withdrawal of Cholinesterase Inhibitors or Memantine

Discontinuation of cholinesterase inhibitors has been associated with worsening of cognition and confusion in some patients. This effect was evident in a clinical trial in which donepezil was stopped after a fixed period of 12 weeks and patients were then randomized to continuing drug or to placebo as well as when patients were discontinued from some 6-month trials [71]. Yet worsening of behavior and confusion do not appear common when the drugs are stopped in clinical practice, as is frequently done. In clinical practice only 19% to 23% of patients continued to take donepezil or rivastigmine for more than 1 year, and about one-third discontinued the drugs within 2 months [72].

Tapering and withdrawal of donepezil after maintenance treatment for an average of 2 to 3 years was formally tested in a randomized controlled trial of severely impaired patients with Alzheimer disease; continuing donepezil was compared with discontinuing it, and, simultaneously, starting memantine was compared with not starting it [73]. Over the 1-year follow-up period, continuing donepezil was associated with better cognitive scores and ADLs, and adding memantine when donepezil was discontinued was better than not adding it. Many patients, however, discontinued donepezil without difficulty; notably, only half of the patients who were assigned to continue donepezil actually continued treatment beyond the 1-year follow-up, suggesting that many patients perceived that continuing donepezil, at least under double blinded conditions, was not effective. Thus, the outcomes support decisions either to continue medication or to taper and discontinue it when physicians are uncertain of continuing benefit [74]. This trial also did not support the typical use for memantine as an add-on to donepezil, showing that the add-on was not better than
continuing donepezil alone, a finding that adds to the controversy of whether the drugs taken together are better than either alone. It is generally good practice to taper these medications before discontinuing, even though both donepezil and memantine have long terminal half-lives.

**Future Therapeutic Approaches and Management of AD**

There are three feet on AD course modifying research.

First is to select high-risk population with current evidence and to provide primary prevention. This step aims to manage modifiable risk factors [75]. Second is to diagnose patient at preclinical phase, which took 10-20 years before symptoms occur. Researchers focus on new neuroimaging techniques, new laboratory and CSF investigations and genetic studies [75]. Third is to discover disease-modifying molecules. Studies are mainly focused on: [1] to inhibit extracellular amyloid plaque accumulation and to inhibit intracellular tau based neurofibrillary tangles accumulation [75,76].

**Anti-amyloid agents**

The initial process of AD is not determined yet, but one of the main proposed pathophysiological processes is ‘Amyloid Cascade Hypothesis’. All autosomal dominant AD genetic forms are due to mutations of amyloid metabolism encoding genes. Although ‘Amyloid Cascade Hypothesis’ does not capture all aspects of disease process, there is clinical and experimental data showing toxic effects of accumulated amyloid plaques. Focused amyloid-directed therapies could be divided to three classes including secretase modulators, amyloid anti-aggregants and immunotherapies [77].

**Secretase modulators**

To decrease Aβ production, research aimed to modulate enzymes that breakdown amyloid precursor protein [by stimulating α secretase or inhibiting γ and β secretase activity]. Whereas effective α secretase was infrequently identified, numerous γ and β secretase inhibitors were developed. γ secretase have critical role in Aβ generation but this enzyme has multiple cleavage actions including notch receptor signaling and thought to have important side effects. Currently developed β secretase inhibitors also failed to show disease-modifying effects but there are still ongoing researches [78].

**Amyloid anti-aggregants**

Another point is to prevent aggregation of amyloid in non-soluble forms. It’s known that Aβ forms oligomers, fibrils and then deposition of amyloid plaques exists. New studies also report soluble form of Aβ have also toxic effects. Tramiprosate, colotrinin, clioquinol are some of the studied anti-Aβ aggregation agents. Phase II and III studies showed conflicting results, including no effects and minimal effects. There are ongoing studies to research current molecules and to develop new molecules [78,79].

**Amyloid removal [Immunotherapy]**

Although there is no proven exact mechanism how immunotherapy might attenuate Aβ plaques in the brain, some mechanisms have postulated. Therapeutic aim is to induce a humoral immune response to fibrillary-Aβ42 or passive administration of anti Aβ antibodies. First studies of active vaccination were halted due to induction of serious side effects-meningoencephalitis. There are alternative new molecules developed and ongoing Phase I-III trials with active and passive immunization (CAD106, Bapineuzumab, Solanezumab, Intravenous Immunoglobulin) [80, 81].

**Tau-based therapies**

Hyperphosporylated tau aggregates in neurons and forms neurofibrillary tangles [NFT], lastly causes neuronal death in AD. Tau is a microtubule- associated protein and encoded
by the MAPT gene and has functions like, to assemble microtubules and regulate axonal transport. Hyperphosphorylated tau has been shown to cause, disruption of mitochondrial respiration and axonal transport. It’s important to emphasize that tau hyperphosphorylation is also regarded as pathologic hallmark of other neurodegenerative diseases, including Pick disease, progressive supranuclear palsy, corticobasal degeneration, and frontotemporal dementia with parkinsonism (FTD-P). FTD-P is caused by mutations of tau encoded MAPT1 gene. Thus support tau dysfunction could drive neurodegeneration without amyloid deposition [82].Tau based therapies are still at conceptual stages and include passive immunization against tau, preventing tau hyperphosphorylation and anti-aggregants of tau. Methylthioninium chloride and lithium are some of the agents with ongoing studies. There are also some trials ongoing about anti-tau vaccines at AD [83,84].

<table>
<thead>
<tr>
<th>Name</th>
<th>Company</th>
<th>Phase</th>
<th>Target</th>
<th>Binding domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affitope AD02</td>
<td>Affiris/GlaxoSmithKline</td>
<td>II</td>
<td>Aβ1–6</td>
<td></td>
</tr>
<tr>
<td>CAD106</td>
<td>Novartis</td>
<td>II</td>
<td>Aβ1–6</td>
<td></td>
</tr>
<tr>
<td>Vanuitde cridifar</td>
<td>Elan/Johnson &amp; Johnson/Pfizer Inc.</td>
<td>II</td>
<td>Aβ1–6</td>
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<tr>
<td>ACI24</td>
<td>AC Immune/Bayer Healthcare Pharmaceuticals</td>
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<td>Merck &amp; Co.</td>
<td>I</td>
<td>Not published</td>
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<tr>
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<td>Pyroglutamate modified</td>
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<tr>
<td>Aβ UB311</td>
<td>United Biomedical</td>
<td>I</td>
<td>Aβ1–14</td>
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<tr>
<td>AN1792</td>
<td>Elan</td>
<td>Terminated</td>
<td>Aβ1–42</td>
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Table 1: Ongoing and terminated active amyloid-beta immunotherapy clinical programs in Alzheimer’s disease [85].

<table>
<thead>
<tr>
<th>Name</th>
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<th>Trial population</th>
<th>Binding domain</th>
<th>Target</th>
</tr>
</thead>
<tbody>
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<td>Eli Lilly and Company</td>
<td>III</td>
<td>Prodromal and mild AD</td>
<td>Aβ16–23</td>
<td>Soluble Aβ</td>
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<tr>
<td>Gantenerumab</td>
<td>Roche</td>
<td>2/3</td>
<td>Prodromal and mild AD</td>
<td>conformational</td>
<td>Aggregated Aβ</td>
</tr>
<tr>
<td>BAN2401</td>
<td>Eisai/ BioArctic Neuroscience/Eisai</td>
<td>2b</td>
<td>MCI due to AD or mild AD</td>
<td>conformational</td>
<td>Soluble Aβ protofibrils</td>
</tr>
<tr>
<td>Crenezumab</td>
<td>Genentech/Roche</td>
<td>2</td>
<td>Prodromal and mild/ moderate AD</td>
<td>Aβ 12-23</td>
<td>Soluble oligomeric/ fibrillar Aβ and plaque</td>
</tr>
<tr>
<td>Bapineuzumab</td>
<td>Elan/ Pfizer Inc./ Johnson &amp; Johnson</td>
<td>Intravenous and subcutaneous programs terminated</td>
<td>Mild/moderate AD</td>
<td>Conformational Aβ</td>
<td>Fibrillar Aβ</td>
</tr>
<tr>
<td>BIIB037</td>
<td>Biogen Idec/ Neuroimmune Therapeutics</td>
<td>1</td>
<td>MCI due to AD or mild AD</td>
<td>Aggregated Aβ</td>
<td>Soluble and aggregated Aβ</td>
</tr>
<tr>
<td>AAB003</td>
<td>Elan/Pfizer Inc./ Janssen</td>
<td>1</td>
<td>Mild/moderate AD</td>
<td>Aβ1–6</td>
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</tr>
<tr>
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<td>1</td>
<td>Mild/moderate AD</td>
<td>Not published</td>
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<td>AD</td>
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<td>Pfizer Inc.</td>
<td>1</td>
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<td>Aβ33–40</td>
<td>Soluble and aggregated Aβ</td>
</tr>
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</table>

Aβ, amyloid-beta; AD, Alzheimer’s disease; MCI, mild cognitive impairment.

Table 2: Ongoing and terminated passive immunotherapy clinical programs in Alzheimer’s disease [85].

As for conclusion, Aβ immunotherapy has gained a lot of attention and emerges as one of the most attractive approaches for disease intervention in AD. Aβ neurotoxicity has been shown to be caused by soluble protofibrils rather than insoluble fibrils, and this highlights protofibrils as targets for immunotherapy. Other encouraging efforts in immunotherapy as well as in the small-molecule field offer hope for new innovative therapies for AD in the future.
References


Elderly persons are at increased risk for developing dementia, and this risk increases with age. Alzheimer’s disease is the most common disease of dementia and is characterized by a gradual progression of cognitive impairment that interferes with the patient's independent activities of daily living. Alzheimer’s disease has severe effects not only on patients but also on their caregivers. Alzheimer’s disease is a growing health issue characterized by declines in brain functions that are irreversible and is one of leading causes of death among elderly people. Alzheimer’s disease is a disease that both accelerates the physiological changes due to the old ages and masks those changes with the deterioration in cognitive function developing together with it. Fallings, urinary and fecal incontinence, pressure ulcer ulceration, infections, polypharmacy and thromboembolic events are the most common reasons of the mortality and morbidity in elderly patients with Alzheimer’s disease. For the early diagnose of these events and the optimum management of elderly patients with Alzheimer Disease, comprehensive geriatric assessment should be recommended.

Keywords: Aging; Alzheimer’s Disease; Geriatric Assessment

Introduction

Alzheimer Disease (AD) is prevalence of which is very high in geriatric population and is characterized by loss of cognitive and social functions so that can affect the daily life of the person. It is estimated that the disease affects 24 million of people worldwide and this number will be reached to 80 million by 2040 [1]. It is reported that prevalence of the disease is 13% and 43% among the people older than 65 and 85 respectively in USA. While in Europe the prevalence of AD is 0.3% among the people of ages between 60-65, this number reaches 10.8% among the people of ages between 80-89 [2,3]. Prevalence of AD among the people aged 70 years and over in Turkey has been determined as 11% by Turkish Alzheimer’s Prevalence Study. According to this value, it is predicted that there are 250.000-300.000 patients with AD in Turkey [4].

Along with deterioration of cognitive functions which is significant especially during stress period and senility, decrease in organ system reserves, homeostatic control and
ability to adapt to environmental factors may result in impaired stress capacity. This kind of processes makes the patients vulnerable to traumatization/physical injuries and many diseases. Particularly the cases like urinary and fecal incontinence, falls, decubitus ulcers/pressure sores, malnutrition, infections and polypharmacy raise morbidity and mortality.

**The Urinary and Fecal Incontinence**

In the general population prevalence of incontinence rises with age, with estimates of up to 15% of older women and 2-11% for older men experiencing daily urinary incontinence, with higher rates for those living in care homes [5]. Prevalence of fecal incontinence among people aged over 60 is 5.1% in man and 6.2% in women [6]. Urinary incontinence in patients with AD results from the coming together of impaired cognitive functions, neuro-urinary pathologies, age-related changes, comorbidities and multifactorial reasons due to medical therapies [7].

Disappearance of central cortical inhibitory effect on sacral micturition leads to incontinence in AD [8]. Along with this, age-related decreased post-menopausal estrogen levels, decreased urethral pressure, prostatic hyper trophy, changes in bladder functions and to be susceptible to infections due to impaired immune functions precipitate urinary incontinence in these patients. The reason why urinary incontinence is so important is that it may cause lots of complications; particularly psychosocial complications. It may lead to a range of complications like maceration and irritation signs on skin, decubitus ulcers especially in patients confined to bed or a wheelchair, infections and delayed healing of the pressure sore or surgical wounds [9]. Urinary continence, which is a very unpleasant and hard situation for patient, healthcare personnel and family members who are responsible for the patient’s care, is one of the most important indications in USA and Northern European countries to put an elderly person in a nursing home [10]. In a study, have emphasized in one of their studies performed on geriatric cases with overactive bladder that trospium can be a good option for the treatment because of its suitability for polypharmacy, less side effect profile and high effectiveness [11]. This study is important because it shows us trospium unlike other bladder antimuscarinics does not have any negative effects on cognitive process in patients with late-onset Alzheimer disease.

In addition to this, it can be said that it affects cognitive process positively by boosting the wellbeing in the patient with both urge incontinence and AD in order to make them regain their autonomy. Another thing we should consider is this wellbeing issue also contributes the caregivers doubtlessly. This favorable effect is possible results from low lipophilicity and poor penetration of trospium through blood brain barrier. Because of the same reason, fewer central system side effects are seen in the cases [12, 13]. In the case of recoverable reasons, the underlying pathologies should be treated, however in chronic urinary incontinence; medical, surgical or rehabilitative treatment should be applied accordingly to incontinence type of the patient [7].

**Falls**

Falls, one of the geriatric syndrome, is an important health problem that leads to limitation of mobility, dependency in activities of daily living, increased need for institutional care and threatens independency of elderly persons [14]. In USA, falls are responsible for 5.3% of all hospitalized elderly patients. Falls are one of the most serious and most frequently seen problems that elderly patients encounter. In a study, it is indicated that 35% of people over 65 and 50% of people over 85 falls every year [15]. Falls are more commonly seen in elderly people living in nursing homes. 50% of elderly people staying at institutes for healthcare falls at least once in a year, and 40% of them falls more than once in a year. Incidence of falls in institutes is 1.5 per bed annually [16]. Increase in falls incidence in patients with Alzheimer Disease results from multiple factors like impaired muscle power, decreased visual and auditory functions, decreased proprioception, shortened of reaction
Risk factors for falls that are commonly seen in patients with AD and other older populations are classified as individual and environmental risk factors [17]. Individual risk factors are side effects of medicines, balance problems, muscle weakness, sensational impairments, decreased cognitive functions and communication, senility and concomitant disorders. Inadequate lighting, objects that may cause stumbling, inappropriately high and large stairs, irregular or wet floors are named as the environmental factors [18].

In patients with Alzheimer Disease, balance and coordination are impaired by progression of the disease. Balance means an ability to provide body control on a supportive floor to prevent falls. In patients with AD, loss of balance and falls are commonly encountered due to affected afferent and efferent mechanisms that maintain the balance [19].

Some strategies have been planned to prevent falls, and generally most of them are about environmental risk factors. The measures aimed changes in physical environment are accepted one of the most successful strategies. Along with concomitant disorders, immobility after falls in patients with AD increases the mortality. Immobility is an important issue because it may cause impaired hygiene and infections like pulmonary pathologies and decubitus ulcers. To evaluate a patient with a history of falls or a patient with fall risks; reason of falls, pattern of falls, medical history, evaluation of vision, neurologic assessment, skeletal system assessment and cardiovascular evaluation are should be done carefully. Because falls can be early sign of a disease, a detailed geriatric assessment is extremely important.

Decubitus Ulcers

Decubitus ulcers are lesions that formed by long term pressure application on an underlying tissue. Generally it results from compression of soft tissues between bony processes and external surfaces. Pressure sore can be seen as a superficial erythematous lesions or a deep ulcer that can reach the bone. 95% of decubitus ulcers appear on protrusions at lower body. They are most commonly seen at ischium (28%), sacrum (17-27%), trochanter (12-19%), and heels (9-18%) [20,21]. One of the predisposing factors of pressure ulcers is Alzheimer disease and decubitus ulcer is a geriatric syndrome that especially seen in later stage of the disease. Along with cognitive impairment in patients, urinary and fecal incontinence, malnutrition, infections facilitated pressure ulcers to be formed. In addition, so do suboptimal care conditions [20-22].

Measures to prevent decubitus ulcer should be considered as soon as risk factors appear. An effective preventive program consists of a medical care, a good nursery care, an appropriate education, a reinforced patient and relative’s compliance, and application of appropriate decompressive devices. Decubitus ulcers are more commonly seen in patients hospitalized or in patients in nursing homes [22]. Concomitant comorbid diseases of patients are effective on both of progression and healing process of lesions. Regular skincare should be done in patients with AD. Skin should be kept clear, not dry and it should be moisturized by appropriate creams and oils. As they are dependent, the patients with AD have a tendency to malnutrition. Special attention should be paid to their nutritional state and positive nitrogen balance should be maintained. 1.5-2 g/day protein should be given [23]. Nutritional state of the patients, albumin and prealbumin levels should be followed up regularly. In some studies, it has been showed that vitamin C supplementation is effective in patients with decubitus ulcers. As zinc is required for protein synthesis, it should be replaced and pomades including zinc should be applied on macerated areas. Position changes in every 2 hours are key to preventing pressure sores. Also special beds and cushions can be helpful to decrease pressure [24].

Malnutrition

In patients with AD, malnutrition is seen more commonly. That is because of impaired cognitive functions, impaired deglutition and changes in sense of taste [25]. In addition to these factors, age-related physiologic and functional changes and other changes in daily
life may precipitate malnutrition. Energy requirements in senescent period are less than in adulthood. But it may increase in case of diseases, mutilation/injuries or fractures. In these kinds of cases, if the patient can not be nourished sufficiently, it may cause chronic nutritional deficiency. Malnutrition leads to increase in incidence of chronic diseases and mortality in these chronic diseases. Under normal circumstances, energy requirement in an elderly is 30 calorie/kg or at least 1200 calorie/day [26,27]. In general, health problems like infections, operations, injuries and fractures increase protein requirements. If we consider age related decreased immune system functions, 1 gr/kg protein may be sufficient for a day. In some cases like chronic kidney disease, protein intake must be limited, it is arranged accordingly [28]. 60% of daily energy intake should come from carbohydrates. It is important to take sufficient carbohydrate, as its deficiency leads to use of proteins as an energy source. But overconsumption of carbohydrates causes being overweight by transformation of carbohydrates to lipids. Carbohydrate requirements should be met from cereals, bran cereal flour, vegetables and fruits [27]. Vitamin and mineral requirements increase in senescent period due to decreased energy demand, impaired body resistance, movement restriction and increase in incidence of chronic diseases. Vitamin and mineral deficiencies affect progression of acute and chronic diseases and may lead to deaths. If there is no special health problem preventing usage of vitamin and minerals in body, or no limitation of nutritional intake, vitamin and mineral needs with exception of vitamin D can be met from a good arranged diet. As overconsumption of some vitamin and minerals may cause toxic effects, supplements should be taken by advisement of doctors and dieticians. If there is no any necessity, requirements should be met from foods. The body losses approximately 2.5 liters of water (15-20 glasses of water) by urine, stool and respiration everyday. This loss should be replaced. Because body fluid loss increases in the case of hot weather, heavy exercise, fever, diarrhea and consumption of foods rich in protein and salt, amount of fluid intake needs to be increased. During senescent period of life at least 8-10 glasses of water (1500 milliliter) should be consumed [26].

\section*{Infections}

Immune response shows decline with age. Along with this decline, malnutrition, poor personal hygiene, problems with swallowing make the patients with AD more susceptible to infections, and make the infections that already developed to be more serious. Basically Urinary Tract Infections (UTI) and respiratory system infections are common in patients with AD [30]. In elderly people, description, diagnosis and management of UTI are extremely complicated. In elderly, this kind of infections may cause some unspecific symptoms like anorexia, weakness, etc., may lead to chronic genitourinary symptoms such as incontinence, and also make Alzheimer worse. That’s why even asymptomatic bacteriuria is treated nowadays. However, it is a fact that urinary tract infections in patients with AD cause a prominent increase in morbidity and mortality. Dysuria, frequency and urgency are common symptoms but they should be assessed carefully, because they can be seen without an infection [17]. Alzheimer’s patients who have urinary tract infection need to be treated but diagnosis should be relying on a careful clinical assessment. A positive urine culture
may not be a sign of a true urinary tract infection. Because culture can not discriminate colonization and contamination. That’s why specialists should treat the patients, not the culture results to prevent irrational use of antibiotics. Interestingly, some specialists recommend urinary cultures in elderly people just to confirm antimicrobial susceptibility. Asymptomatic bacteriuria needs to be scanned and treated only in selected populations. If there is no benefit shown, it is recommended that antimicrobial therapy should be avoided [30].

Respiratory system infections especially pneumonia is an important cause of death in people over 65 in developed and developing countries. In elderly people, pneumonia is among the first 10 leading causes of death. Even the cases whoes are healthy otherwise or the cases with low risk factors can be susceptible to respiratory system infections due to the changes in immune system. Age related decline in immune system against infection agents such as influenza virus and Streptococcus pneumoniae that required antigen specific immune response (adaptive-innate immunity) is most important reason of this susceptibility. Vaccination of elderly adults, especially pneumococcal vaccination, is very important [31]. Along with these facts, it is reported that atypical antipsychotics which are used for the treatment of behavioral disturbances in Alzheimer’s patients, increase the risk for pneumonia and hip fracture [32].

**Polypharmacy**

A grade number of medicine use may lead to some problems such as serious side effects, drug-drug interactions and this may cause poor compliance to treatment. Alzheimer’s patients generally expose to polypharmacy, because they have comorbidities due to advanced age and need to be assessed by number of different specialists. Decrease in saliva and stomach motility is seen in Alzheimer’s patients with increasing age. Decline in splanchnic blood flow, changes in body composition, %30 declines in blood flow to kidneys and liver parenchyma, approximately 8-10 ml/min decrease in glomerular filtration rate after age of 30 take place. This situation changes drug pharmacodynamics and pharmacokinetics. Along with toxic effects of polypharmacy, drug-drug interactions may lead to decrease in the expected benefit and exacerbate toxicity. That’s why all the medicines patient is on should be assessed one by one at every visit, and ones that patient’s going to take should be marked. Appropriate storage conditions for medicines should be provided to prevent forgetting and taking more than need [7].

As a result, Alzheimer Disease is a disease that has an increasing incidence concordant with increasing number of elderly population, and can be diagnosed with 90% probability by using combination of detailed and careful history taking, physical examination and laboratory techniques. The internal problems that added to heterogeneous neurologic profile of the disease make the clinical presentation very complicated. This complicated presentation which may lead to delayed medical diagnosis and treatment, can cause death of Alzheimer’ patient. Overcoming of some problems with a good communication with patient, a qualified follow-up of patient’s medical records, knowing very well the patients and her/his relatives, detailed assessment at every visit and relatives’ efforts provide more comfortable and healthy life to the patients with Alzheimer disease.

**References**


Nutritional Considerations in Patients with Alzheimer’s Disease

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Abstract

Alzheimer’s Disease (AD) is the most common type of dementia that is more commonly seen in advanced age group. The most important risk factors for AD are known as aging and genetic predisposition. However there are many modifiable risk factors such as especially obesity, hypertension, hypercholesterolemia, diabetes mellitus, alcohol, smoking and low physical activity leading to AD. Recently, it has been reported by several studies that some dietary factors like antioxidants, vitamins, polyphenols and fish decrease the risk of AD, while fatty acids, high calorie intake and alcohol consumption increase the risk of AD. Although there is no special diet to prevent AD, positive effects of Mediterranean diet has been shown. It is also very important to follow up body weight, evaluate the nutritional state in elderly people and inform the relatives about AD, because decline at body weight in patients may occur before the diagnosis. Evaluation of nutritional status should be provided in every stage of the disease. In addition, loss of appetite, weight loss and disphagia should be determined on time, and nutrition support therapy should be started immediately. When approaching to the nutritional problems due to aging and AD, participation of caregivers and relatives should be provided during management. In this section, role of nutrition on development and prevention of AD which is a very important disease of geriatric population, and nutritional problems that AD patients and caregivers encounter will be tried to explain.

Keywords: Alzheimer’s Disease; Diet; Nutrition

Introduction

Alzheimer’s Disease (AD) is the most common type of dementia in the world that is a progressive neurodegenerative disease and more commonly seen in advanced age group. It constitutes 60-80% of all cases with dementia. It was determined that 4.7 million people in United State of America (USA) have Alzheimer’s Disease in 2010. It is reported that the prevalence of the disease is 13% and 43% among the people older than 65 and 85 respectively in USA [1]. In Europe, the prevalence of AD is 0.3% among the people of ages between 60-65, this number reaches 10.8% among the people of ages between 80-89 [2]. It is predicted that the number of cases with AD will reach 100 million worldwide by 2050 and lead to a serious socioeconomic burden [3,4].
The most important risk factors for onset and progression of AD are aging and genetic predisposition (presence of epsilon 4 allele of apoprotein E gene). However it is determined that there are many modifiable risk factors leading to AD. By epidemiologic researches it has been demonstrated that low level of education, depression and especially cardiovascular risk factors such as obesity, hypertension, hypercholesterolemia, diabetes mellitus, alcohol, smoking and low physical activity increase the risk of AD and dementia [5-7]. In recent years numerous proofs on association between nutrition and AD have been provided. For instance, it has been reported that some dietary factors like antioxidants, vitamins, polyphenols and fish decrease the risk of AD, while fatty acids, high calorie intake and alcohol consumption increase the risk of AD [8].

Since AD develops in advanced ages, the feeding problems from disease’s process and nutritional problems due to aging overlap. Therefore health status and life quality of both caregivers and patients are affected unfavorably.

In this section, role of nutrition on development and prevention of AD which is a very important disease of geriatric population and nutritional problems that AD patients and caregivers encounter will be tried to explain.

The Association between Alzheimer’s Disease and Nourishment

There are many studies exploring the relation between AD and obesity. In spite of discrepancy of some results, most of them indicate us obesity may be a risk factor for AD. Actually low Body Mass Index (BMI) was reported as a risk factor for dementia long years ago [9]. It has been discovered that both low and overweight increase risk of AD age relatedly by a comprehensive and prospective research made in recent times [10]. The presence of a relation between obesity-overweight and AD has been reported in many studies [11-13]. However, the evidence relating obesity measured with Body Mass Index (BMI) with AD is conflicting. Obesity (BMI> 30 kg/m²) in midlife has been found to increase the risk of AD, whereas late-life obesity has been found to reduce the risk of AD [11]. It’s reported that the people with BMI>30 kg/m² in their midlife have 35% higher risk of dementia than the people having normal BMI in another research made by Profenno et al.; this result makes us predict that increase in prevalence of obesity may increase incidence of AD in the future [14].

When relation between AD and weight loss-malnutrition is investigated, we realize that it is a complication developing through the disease process rather than a risk factor. This relation will be discussed under the subtitle named as Malnutrition in AD.

The Association between Nutrition and the Risk of Alzheimer’s Disease

The pathophysiology of AD that is extremely complicated, consists of oxidative and inflammatory pathways and hormonal effects. Especially the enhancement in oxidative stress damages brain functions by increasing reactive oxygen species. When the association between nutrition and onset and progression of AD is investigated, it is reported that some nutrients like antioxidants, vitamins, fatty acids and carbohydrates increase the risk of AD. Although it is estimated that nutrient’s effects on AD are based on decreasing oxidative stress and amyloid beta (Aβ) deposition pathways, the exact mechanisms are not clear yet [15,16].

Antioxidants

**Vitamin A and β-carotene:** They are considered as important factors for prevention and treatment of AD because of their effects on inhibition of both Aβ oligomer and fibril production [17]. Plasma and serum levels of these vitamins have been found low in patients with AD [18,19]. Furthermore, in another study performed on elderly people, it’s been reported that higher β-carotene plasma levels are related with better memory performance [20]. However, data on the supplementation of only vitamin A in patient with AD were not available.
Vitamin C: It has been proven in vitro and in vivo, it decreases Aβ oligomer formation and oxidative stress [21,22]. However the relation between AD and vitamin C is not clear yet. Although the relation between decreased incidence and prevalence of AD and combined use of vitamin C and vitamin E for at least 3 years has been determined, an association between use of only vitamin C and risk of AD couldn’t be found by other prospective studies performed on large number of people [23-25]. As a result of these studies, it is predicted that precautions against vitamin C deficiency is more protective than supplemental vitamin C intake in addition to on a normal health diet [26].

Vitamin E (Alpha-tocopherol): It has been shown that Vitamin E protects cognitive functions by decreasing oxidative stress and clearing Aβ related free radicals [27-29]. Vitamin E occurs naturally in the form of tocopherols and tocotrienols. It is found in many foods, including mangoes, papayas, apples, avocados, tomatoes, red bell peppers, and spinaches, and particularly in high quantities in nuts, seeds, and oils. A positive relation is determined between especially high intake of a-tocopherols and γ-tocopherols which are Vitamin E forms and decrease in incidence of AD [30]. Lower total vitamin E levels are found in patients with AD and moderate cognitive impairment when compared with normal individuals [31]. Because of Vitamin E from supplements has not been shown to reduce Alzheimer’s disease risk, Vitamin E should come from foods, rather than supplements. Recommended amount of Vitamin E is 15 milligram for an adult [32]. As exact benefit of Vitamin E on prevention and treatment of AD has not been proved, routine Vitamin E intake is not recommended.

Selenium: It has been reported to play an important role in the antioxidative defense [33]. In some studies it was shown that supplementations of selenium-containing mixtures improved cognition [34, 35]. AD patients showed a significant lower Selenium level in plasma, erythrocytes, and nails when compared to controls [36]. Current knowledge provides no proof of a role of selenium (Se) in the treatment of AD. It is not clear that the low level of selenium in patient with AD whether is a reason or a result of the disease like in many other nutrient levels. Therefore more research is needed to explain the association of selenium with the risk of AD [37].

Ferulic acid, polyphenols (Quersetin, resveratrol), alpha lipoic acid, N-acetyl-L-cystein, curcumin, epigallocatechin gallate, gingko biloba and gamma-glutamyl cystein ethyl ester: They are another antioxidants stated that may prevent, delay and treat AD [38]. It is predicted that polyphenols have beneficial effects on cognitive functions and it’s been demonstrated by inhibition of Aβ formation in animal studies and by decreasing homocysteine concentrations in clinical studies performed on patients with AD [39,42]. There are many foods that include these antioxidants naturally in our diet; for instance; querstein in green tea, onion and apple; resveratrol in grapes used in red wine production, curcumin in turmeric; epigallocatechin gallate in black and green tea; vegetables, fruits, cereals in especially wheat; ferulic acid in eucalyptus, etc.

B Vitamins

Folic acid, Vitamin B₆ (pyridoxine) and B₁₂: it is estimated that they have roles in pathophysiology of AD by decreasing homocystein level and inhibiting oxidative stress [43,44]. It is reported that every 5 mmol/L increase in homocystein level raises the risk of AD by 40% [45]. Because high level of homocystein and low folate and B₁₂ levels are determined in patient with AD, a number of researches on this association have been made [46,48]. In a recently performed randomized placebo-controlled trial, 0.8 mg folic acid, 0.5 mg vitamin B₁₂, and 20 mg vitamin B₆ or placebo have been given daily to the patients with Mild Cognitive Impairment (MCI) for 2 years. At the end of the study, the homocystein levels in the group taking B vitamins have been found 30% lower than the other group on placebo. Furthermore, a prominent benefit on global cognition, episodic and semantic
memories has been reported in people who were given B vitamins and had avarage basic homocystein levels over 11.3 mmol/L [49]. However, no positive effect had been reported in other large placebo-controlled trials that investigated long term use of B vitamins and their combinations with folic acid [50,51]. Also in a recent study, it’s been shown that folate and vitamin B12 replacements reduce levels of homocystein but they do not decrease risk of AD [45]. Therefore adequate evidence related to positive effects of B vitamins on impairment of cognitive functions are not present yet.

**Vitamin D**

There are many researches that investigate the association between Vitamin D and risk of AD on of which antioxidants, antiinflammatory or Aβ formation pathways [52]. Vitamin D levels in patients with AD has been found lower than in normal individuals [53]. Some trials showing positive effects of vitamin D replacement on cognitive functions are present [54]. However we need placebo controlled randomised clinical trials in order to learn actual role of Vitamin D on protection against Alzheimer's Disease.

**Metal Ions**

It is thought that zinc, iron and copper have a role in pathogenesis of AD by forming reactive products in the form of metal amyloid complexes [55]. It is reported that there is an association between zinc deficiency and cognition loss in patients with AD [56]. It has been shown by in vivo trials that Aβ and tau proteins decline and related memory impairments are delayed by giving zinc to the rat models [57]. Higher amounts of copper detected in patients with AD than normal individuals in a meta-analysis corroborates the idea of the role of copper dysfunction on AD pathology [58,59]. However in a recent prospective, randomised, placebo controlled trial, it’s been reported that oral copper supplementation has no effect on cognitive functions in patients with AD [60]. It’s stated that iron is especially effective on oxidative stress pathways in patients with AD [61,62]. There are some studies that support iron supplementation to improve attention and concentration [63]. But in the elderly patients, it is recommended that excessive iron intake by diet should be avoided [64]. Overall, modulating metals has been proposed as a therapeutic strategy for AD [65]. Bivalent cation chelators (clioquinol) are being developed as a novel AD drug [66].

**Fatty Acids**

The association between each fatty acid and risk of AD has been investigated by many epidemiologic and animal studies. Saturated fat is found primarily in dairy products, meats, and certain oils (coconut and palm oils).Trans fats are found in many snackpastries and fried foods. Also polyunsaturated fat is found primarily in Mediterranean diet products such as fish. It is reported that Omega-3 which is a polyunsaturated fatty acid provides protection against the risk of AD, on the contrary increased saturated fatty acids and transfatty acids may increase the risk of AD [67-70]. It is predicted especially these positive effects of omega-3 are via Dacosa Hexaenoic Acid (DHA) and Eicosa Pentaenoic Acid (EPA) [71,72]. However, in randomised controlled clinical trials have not supported a therapeutic role for omega-3 fatty acid (with EPA and DHA) supplementation in the treatment of AD because of data show that they did not slow the rate of cognitive impairment and functional decline [73-75].

**Carbohydrates**

It is reported that obese and diabetic individuals have 4 times higher risk of developing AD, and raised prevalence of obesity and diabetes will increase incidence of AD [14]. The main problem in both obesity and diabetes is insuline resistance. Decrease in both insulin levels and insulin receptor expression, and insulin resistance have been reported in patients with AD [76,77]. It is predicted that many proteins in brain neurons become more sensitive to glycation after excessive glucose exposure, and this may lead to risk of AD [78]. Since
an important step in the pathophysiology of the AD is represented by advanced glycation end products in important plasma proteins concerned with fat, cholesterol, and oxygen transport, this leads to cholesterol deficiency in neurons, which significantly impairs their ability to function. Like in many other studies, a diet which is rich in carbohydrates can be harmful for the patients with AD [79,80]. However, in a large prospective study, it's been determined that glycemic load reflexing carbohydrate content in food was not associated with a higher risk of AD [81]. Although there is no reliable data of the detrimental role of a diet high in carbohydrate on AD from randomised controlled trials but high caloric diet is not recommended for AD patients.

The Association between Diet Pattern and Alzheimer’s Disease

There is no defined diet that prevents dementia. A number of diets have been examined and it is emphasized that Mediterranean diet has more positive effects among them. A Western diet is characterized by higher intake of red and processed meats, refined grains, sweets, and desserts [82]. A high-fat Western diet may play a role for development of AD. There were any available data from epidemiological studies exploring Western diet and the risk of AD. Traditional Japanese diet is characterized by increased intake of fish and plant foods such as soybean products, vegetables, and fruits with decreased intake of refined carbohydrates and meat [83]. This diet pattern was associated with a reduced risk of AD [84]. A healthy diet is characterized by increased intake of fruits, whole grains, fresh dairy products, vegetables, breakfast cereal, tea, vegetable fat, nuts, and fish and decreased intake of meat, poultry, refined grains, animal fat, and processed meat [83]. It was reported that a healthy diet was associated with better cognitive performance and had a positive effect on the risk of AD [85,86]. The Dietary Approaches to Stop Hypertension (DASH) diet is characterized by high consumption of plant foods, fruits, vegetables, fish, poultry, whole grains, low-fat dairy products, and nuts, while minimizing intake of red meat, sodium, sweets, and sugar-sweetened beverages [83]. In a research on hypertensive, sedentary, over weight and/or obese individuals on DASH diet, it has been determined that neurocognitive functions of ones that follow the diet had a significant improvement [87]. The Mediterranean diet is characterized by increased intake of cereals, poultry, beans, nuts, olive oil, fish, fruits, vegetables and bread; a moderate consumption of alcohol; a lower consumption of red meat and dairy products. A beneficial association between consumption of Mediterranean diet and AD was shown in many studies [88,89]. Adherence to the Mediterranean diet may not only affect the risk of AD but also mortality in AD [90].

There is no diet recommendation defined based on available evidence for AD. The nutrition recommendations to decrease especially the risk of cardiovascular and metabolic diseases should be considered for prevention and treatment of dementia and AD. In the light of recent evidence, foods that are rich in omega-3, antioxidants, poly-unsaturated fatty acids and contain limited simple carbohydrates, in other words a nutrition pattern that contains fish, vegetable oil, vegetables without starch, fruits with low glycemic index, low extra sugar and moderate wine consumption should be recommended [91].

Malnutrition in Alzheimer’s Disease

When age-related physiologic changes and risky situations from social aspects (such as insufficient energy supply, skipping meals, not being able to cook and go shopping, oral hygiene problems, polypharmacy, social status, comorbid disorders, and being dependent to another person) overlap with the problems due to AD progression, it may lead to serious unintentional weight loss and malnutrition [5,92]. When disease progressing, weight loss and malnutrition which start as impairment of daily living activities in early stages, become a prominent problem. In a research done by Wolf et al. malnutrition rate in patients with AD has been determined as 92% [93].

Unintentional weight loss is an important sign and complain that indicates Protein Energy Malnutrition (PEM). Approximately 40% of patients with AD has weight loss. In advanced
stages of the disease, severity of weight loss increases progressively [92,94,95]. Weight loss leads to complications (like infections) and more dependency to caregivers. It is reported that weight loss over 5% in patients with AD is an important risk indicator for mortality [94]. It is stated that malnutrition which occurs as PEM in elderly people affects development and progression of chronic diseases unfavorably, furthermore it has some causality on increase in mortality [5,96]. Malnutrition is especially frequent in patients living at home [97]. Malnutrition develops more commonly in AD patients than normal individuals [98]. It is reported malnutrition is an indicator of disease progression and unintentionally weight loss refers rapidly worsening of cognitive function [99,100].

Weight loss begins in the early stages of disease even before diagnosis and it worsens with disease’s progression. In advanced stage AD, feeding difficulties are present commonly. Patients forget to eat and go to shopping for cooking, they skip meals and show resistance to food consumption. And also they may become more sensitive to taste and smell and may have some chewing, swallowing, and utensils using problems or may aspirate what they eat. They may be disturbed by noise, lights or crowding during their meal [101]. A serious weight loss in a patient due to changes in dietary habits may cause feeding with a tube which is costly and not effective [95].

**Approach to Nutritional Problems in Alzheimer’s Disease**

Because of lack of appetite in patients with AD, feeding should be provided when the patient has desire to eat something instead of regular mealtimes. The appetite of the patients can be better in early times in a day. That’s why break-fast and lunch should be considered as more important mealtimes. Most of the patients can need some simple directions to complete their meals. Eating with hands instead of using utensils should be tolerated [102]. Providing foods patient prefers or likes may increase food consumption [103]. Making simpler the environment may prevent patient’s distraction during meal. A light music through out meal may prevent agitation [104]. It is reported that cooking bread or pop corn at mealtimes increases appetite and food consumption [105].

It is recommended that dietary limitation should be avoided, liquid nutrients should be given between meals to support energy intake and vitamin-mineral supplements should be provided. However semi-solid foods should be preferred to liquid ones to avoid aspiration risk [101].

In every stage AD, apetite of the patient and food consumption at every meal should be paid attention to prevent malnutrition. If required, consumed food at meals should be recorded and counting calories may be done. If malnutrition is determined by tests performed during clinical follow ups, supplementary nutritional products should be given in early periods. When choosing a supplementary product, chronic diseases of the patient should be considered.

When deciding how to feed (with a tube or gastrostomy) the patient in advanced stage of AD, patient’s values and scientific evidences should be considered altogether. Evidences that support positive effects of tube-feeding on preventing aspiration, decreasing risk of infection and extending survival are not sufficient. If long term feeding is considered or patient has disphagia, healthcare providers should proceed with Percutaneous Endoscopic Gastrostomy (PEG) as soon as possible. European Society for Parenteral and Enteral Nutrition (ESPEN) does not recommend tube feeding in patients with terminal AD [106].

A good relationship between patient and caregiver that is responsible for patient’s nourishment may improve patient’s nutritional status. A helpful, concerned, compassionate caregiver may succeed to increase food consumption of the patient. Changes in nutritional habits of patients with AD cause their caregivers to live a stressful, depressed and isolated
from social life. Insufficient knowledge of caregivers about nutrition and emotional and economical burdens affect the healthcare to the patients [95,101,107]. It is reported that stress in caregivers is related with weight loss defined in AD [95]. Assessment of stress in caregivers and providing sufficient physiological support may increase life quality of the patient with AD [35]. Nutrition education programs towards caregivers are considered as best method to prevent patient’s weight loss, improve nutritional status, and provide sufficient knowledge about nourishment and stress management [95,108-111]

As the result, incidence of dementia and AD which is most common type of dementia, has been increasing due to increase in population, prolongation of lifespan, increase in elderly population. Although there is no special diet to prevent AD, positive effects of Mediterranean diet that contains omega-3, antioxidants, and foods that are rich in polyunsaturated fatty acids and includes limited carbohydrates, has been shown. It is very important to follow up body weight, evaluate the nutritional state in elderly people and inform the relatives about AD, because decline at body weight in patients may occur before the diagnosis. Nutritional status evaluation should be provided in every stage of the disease. In addition, loss of appetite, weight loss and disphagia should be determined on time, and nutrition support therapy should be started immediately. When approaching to the nutritional problems due to aging and AD, participation of caregivers and relatives should be provided during management.

References


Alzheimer’s Disease (AD) is a degenerative brain disorder in which the societal burden of this disease is expected to increase over the next 40 years. As the disease progresses, patients become more irritable and lose their independence in performing activities of daily living, and need a close caregiving. Caregivers of dementia patients are usually known as informal caregivers. At this step it has to be accepting that caring for a patient with cognitive and neuropsychiatric impairments is a stressful life event and caregivers carry a heavy psychological burden. Numerous studies have noted that the problems that mainly affect the caregiver range from simple physical fatigue, problems with the family and at work, feelings of incapacity and inadequacy, sleeping difficulties, depression, anxiety, and lower levels of life satisfaction, especially when compared to non-caregivers. Last 30 years with the awareness about this issue, social support and caregiver education programs motivated lots of the area. Positive scientific clues also found that support projects/programs that are established to provide social support are useful in alleviating caregivers’ distress. The last 10 years have marked a clear shift to a more person-centered, relationship-based model for caregivers to support optimal wellness in persons with AD. In the next future behavioral approaches that framed care approaches around caregivers tailoring approaches to match the person with dementia. This issue will merits more attention not only scientist but also social workers.

Keywords: Alzheimer’s Disease; Caregiver; Caregivers’ Distress; Social Support; Burden; Social Cost

Alzheimer’s disease is a degenerative brain disorder characterized by progressive dementia that culminates in death. It affects 3% of those over the age of 65 and up to 50% over the age of 85, resulting in a cost of over $100 billion a year in the USA [1]. Due to the ageing population, the societal burden of this disease is expected to increase over the next 40 years [2]. The hallmark of Alzheimer’s disease is the insidious onset of memory
loss, although one or more additional areas of cognitive impairment are usually evident on examination. Slow but relentless progression leads to worsening cognitive and behavioral problems, as the result of widespread areas of cortical dysfunction.

As the disease progresses, the cognitive impairments are accompanied by neuropsychiatric symptoms. Patients become more irritable and lose their independence in performing activities of daily living. In the later stage, the patient’s loss of independence requires the presence of a caregiver who can assist with day-to-day tasks. Without caregivers, people with dementia would have a poorer quality of life and would need institutional care more quickly, and national economies would be swept away by the advancing demographic tidal wave. However, this support comes at a cost of caregiver distress and poorer quality of life [2].

Assisting a person affected by cognitive disorders can drain the emotional resources of any individual so much that the caregiver is often defined as “the hidden patient” due to the not unlikely possibility of developing mental and physical symptoms. In fact, caregivers end up dedicating less time to their own needs and to other family and professional roles, thus neglecting their own personal health and social life [3,4].

**Burden among Caregivers of Patients with Alzheimer’s Disease**

Caregivers of dementia patients are usually family members, the majority of whom are female and a child or spouse of the patient [5]. These family caregivers are also known as informal caregivers. Caring for a patient with cognitive and neuropsychiatric impairments is a stressful life event and caregivers carry a heavy psychological burden [6,7]. Burden refers the impact of the illness on the caregiver, and it is a term that expresses the comprehensive effect on the caregiver’s global needs in the course of looking after the patient (ie, physical, psychological, and social). Numerous studies have noted that the problems that mainly affect the caregiver range from simple physical fatigue, problems with the family and at work, feelings of incapacity and inadequacy, sleeping difficulties, depression, anxiety, and [8,9] lower levels of life satisfaction [10], especially when compared to non-caregivers [11]. Many of the demands of caregiving may contribute to increase in burden. For example, caring responsibilities consume large amounts of caregivers’ time and many caregivers are forced to restrict the time they would otherwise spend with friends and family, or building social networks, quite often leading to an overall loss of social contacts and jobs [5]. This deprivation of social interaction causes caregivers to experience feelings of social isolation [12]. Moreover, caregivers not only encounter the psychological burden associated with caregiving but also are at an increased risk of developing physical health problems, such as including cardiovascular problems, lower immunity, poorer immune response to vaccine, slower wound healing, higher levels of chronic conditions (such as diabetes, arthritis, ulcers, and anemia), and use of prescription medications, poorer self-rated health, decreased engagement in preventative health behaviors such as exercise, and greater likelihood of smoking, drinking alcohol, and poor sleep patterns.. Because of time constraints, caregivers may not attend to their personal health issues [13]. Consequently there are several factors that contribute to burden of caregivers of patients of AD. For a better discussion we can summarize them with a number of subtitles.

**Patient Related Factors**

First symptom of AD is (generally) related to memory dysfunction. However as the time progressed patients lose their independence and also exhibit neuropsychiatric symptoms. Neuropsychiatric symptoms and loss of cognitive functions cause behavioral problems and incontinence. These are the principal patient related factors that predict caregiver burden. Several studies indicated that there is a strong relationship between caregivers’ burden and patients’ behavioral problems [14,15]. For example, in their studies Shaji et al., [16] showed that most frequently identified neuropsychiatric symptoms among their study group
patients (mostly AD patients) were paranoid and delusional ideations. One another study found that aggression and wandering also frequently cause caregiver burden [17]. Allegri et al [18] indicated that there is a strong relationship between caregiver burden and behavioral disturbances. Specifically, hallucinations, unusual behavior, and abnormal behavior at nighttime are mostly related to caregiver burden. Some pharmacologic treatment studies support this situation. There is enough evidence that pharmacological interventions with cholinesterase inhibitors are efficient in reducing the severity of psychiatric disturbances in AD. Thus caregivers’ burden tends to decrease after the treatment with cholinesterase inhibitors [19]. Consequently behavioral problems of patients make caregivers to cope with caregiving demands harder, so they cause to increase the caregiver burden.

Findings about the relationship between patients’ cognitive status, disease stage and caregivers’ burden are inconsistent. Some findings indicate that there are no relationship between patient’s cognitive dysfunction and caregiver’s burden [18] whereas other, especially pharmacological studies, claim that an improvement in patient’s cognitive functions cause a decrease in caregiver’s burden level [20]. Patient’s diagnoses may affect the caregiver burden. Caregivers of patients with mild AD reported more severe burden than caregivers of amnestic Mild Cognitive Impairment (aMCI). Wontedly, the factors that cause the difference in severity of caregiver burden were neurobehavioral symptoms and daily living activities [14]. Daily living activities represent patient’s ability in daily functioning and independence. Thus it is also an important factor that predicts caregivers burden [21,22]. Loss of daily functioning of a patient create a high level of caregiver-burden because careers have to waste much of their time to assist patients’ daily function. Caregivers may quit their jobs to stay at home and take the responsibility of caring for a patient who cannot overcome daily routines.

Caregiver Related Factors

Caregivers of patients with AD exhibit high levels of burden and depression especially when compared with caregivers of non-demented patients such as physical disability [23]. Papastavrou et al., [24] found that 68% of AD caregivers reported highly burden and 65% exhibited depressions. These rates are very high and some factors such as caregivers’ socio-demographic status and ability to cope with caregiving demand, are also related to caregiver burden [20,24,26]. To identify this factor may be helpful to alleviate caregiver burden therefore increase the quality of patient’s life. Because the link between caregiver well-being and patient’s quality of life is clear [5].

Although there are some inconsistent findings in literature, caregivers’ demographic is a predictor for burden. There is a relationship between age and burden [27] but how age influence caregiver burden is not clear. Some findings show that younger age is related to caregiver burden [28,29] other show advanced age is a stronger risk for caregiver burden [30]. Previous studies also showed that family caregivers may be motivated to provide care for several reasons: a sense of love or reciprocity, spiritual fulfillment, a sense of duty, guilt, social pressures, or in rare instances, greed [31,32]. Daughters-in-law reported more burden when caring for patients with dementia compared to other caregivers [33,34]. This can be explained by daughters-in-law tending to perceive looking after their parents-in-law as a filial obligation [35]. Because daughters-in-law have a consanguinity relationship with patient and tend to as a role that stems from others’ expectations contributes to caregiver burden [36]. Ongoing life with AD commonly influence caregiver burden [28]. The relationship between length of providing care and depression were reported as significant [36]. Role adaptation which is assumed as an outcome of providing care for a longer period of time may alleviate caregiver burden. Baseline relationship closeness between patient and caregiver may predict caregiver burden. There is some evidence that higher baseline relationship closeness is related to lower caregiver depression [37]. Gender may influence caregiver burden. Females report higher levels of burden [38,40]. However it is important
to note that male caregivers receive support or assistance from their wives. Moreover, they may regard caregiving as a duty by providing instrumental support [35].

Disagreements about the division of responsibility for care are also a problem and may cause conflicts between the primary caregiver and other family members, which we assume to be a secondary source of caregiver burden [40]. Thus, dementia is not only a neurological syndrome but also a community health problem, especially for developing countries where more than 60% of patients live and usually receive care in the home [41].

Coping strategies used by caregivers to deal with caregiving stressors may contribute caregiver burden. A growing body of research suggests that using adaptive coping strategies provide resilience to caregivers against stress caused by caregiving demand [29,34].

In developing countries, caregivers also face more severe problems. First, family members do not generally have adequate knowledge of dementia, meaning that an early and timely diagnosis of the disease is often missed [43]. Caregivers often lack opportunities to receive social or health services and access to institutions that provide long-term care. Public health policies that are inadequate require the family caregiver to care for the dementia patient in the home [16]. However, due to their low or middle-level income, caregivers also have difficulties in affording care for their patients. Consequently, the psychological morbidity rates of caregivers are greater in developing countries than in other countries. The 10/66 Dementia Research Group [44] reported that the psychological morbidity rates of dementia caregivers ranged from 40% to 75% in low or middle-income countries. Consequently either patient related factors or caregiver related factor influence the burden of caregivers of patients with AD. These people exhibit higher levels of depression and greater burden. They lack of awareness and enough information about AD. To alleviate their burden, they also express need for social support [45]. Thus this will be helpful for caregivers if new community health policies including providing social support and information to increase the awareness about AD are developed.

Social Support Requirements

There are a number of ways that social support can be conceptualized. However basically social support can be defined as a process of providing or exchanging resources to another person when it is needed [46]. It is very clear that social support contributes to a person’s ability to cope with stress [26]. On the other hand, a lack of social support leads to feelings of loneliness, helplessness, and social isolation. A positive relationship between social support and psychological well-being has generally been found [12]. Support provides a buffer against burden and stress for caregivers by increasing the perception that resources are available to handle stress. Previous studies found similar findings for AD caregivers. Participants reported higher need of social support when they have higher level of caregiver burden [47] Studies have indicated that social support is useful in reducing caregivers’ burden. For example, support services are perceived as very important by caregivers [48, 49]. Providing respite care is also important because it is helpful for caregivers in coping with stress [50]. Studies also found that support projects/programs that are established to provide social support are useful in alleviating caregivers’ distress [51]. There is also a strong negative relationship between social support and anxiety [8], and caregivers tend to report increased levels of life satisfaction when they receive the necessary social support [10]. The main reason why social support is closely related to caregiver burden may be explained by high demands of caregiving. Caring for a patient with AD is a time consuming process and may results in changes in the social network of caregivers. However these changes often result in greater social isolation, less opportunity to engage with others, feelings of helplessness, and even cognitive decline [13,52]. According to the buffering hypothesis of social support under some conditions social support protect individuals from negative outcomes of distress [53]. Thus having higher levels of social support prevents individuals from feeling helplessness and provides a sense of stability in life situations. When putting
these suggestions together, it is not surprising that caregiver tend to seek social support when they encounter caregiver burden.

The results indicated that social support is an effective variable for reducing feelings of anxiety and burden. However, it is not always possible for caregivers to find social support. In high-income countries, public health services may meet the caregivers’ needs of support, but in middle and low-income countries, the public health system is often inadequate to meet these needs [11]. However social support is not a unitary concept so it is important to know the source of support to make more detailed interpretation. Support can be in several types such as instrumental support (helping with daily living needs and housework), emotional support, and informational support (information and knowledge from both health professionals and from those who have experienced similar situations). According to their needs caregivers may seek these types of support. For example instrumental support indicates receiving assistance for the basic daily living activities of patients such as eating, dressing, and bathing. Because caregivers waste a lot of time in providing daily needs of patients, having instrumental support may allow caregivers more time. Having or lacking instrumental support also causes some physiological outcomes. In a previous study lower quality of instrumental support linked to physiological stress [54]. According to the result of the study caregivers who had lower level of instrumental support showed higher levels of plasma cortisol. Researchers interpreted this finding as a result of imbalance between the supply of instrumental support (by other family members) and the perceived need for it (by caregivers). Actually this is consistent with other expectations which discussed before and suggested that disagreements about the division of responsibility for care could cause family members conflict. Type of the assistance is also important to increase the effectiveness of social support. Formal assistance for instrumental daily activities was found more associated with decrease in caregiver distress when compared to informal assistance [55]. On the other hand, when it comes to emotional support caregivers tend to prefer social workers who have shared experiences with themselves. This means that when emotional support is offered by social workers who have experience of being family carer, caregivers most likely accept this offer when compared to other professionals [56]. They want those who give them emotional support to fully understand the issues about what they experience. Thus caregivers may benefit from other caregivers' experience or existence. This can be seen in a previous study which was carried out by O'Connor et al.,[57]. This study showed that even caregivers meet with other caregivers in a 3D virtually environment, this online support groups decreased their distress. Besides instrumental and emotional social support, caregivers are also concerned about their inadequate income [58] and tend to seek financial social support [45]. This is consistent with previous studies which indicated that financial costs associated with informal caregiving were a significant factor in caregiving burden [59]. Estimated cost of providing care for patients with AD includes not only cost of providing care but also lost earnings of caregivers. The annual cost of caregiving for per AD patients was estimated in a ranged from $12,730 to $57,937 [60]. This highly cost reveals the need for financial social support to caregivers able to maintain appropriate care. Most of caregivers have inadequate knowledge about the disease. Providing information about causes and progress of AD, behavioral problems that may encounter or opportunity for them to use available services can be helpful for caregivers. In their study Rosa et al., [61] found educational needs of caregivers as “Effective caregiver-to-patient communication”, “Correct cognitive disorder management” and “Correct behavioral disorder management”. Besides focusing on caregiving burden, some studies also focus on improving caregivers’ well-being and satisfaction of relationship between caregiver and patient. Carbonneau et al.,[62] showed that their education program for caregivers has a positive impact on relationships between patient, caregivers and other family members.

Consequently caring for a patient with AD is highly stressful and exhausted progress, and caregivers often seek support to decrease their burden and increase well-being. Any
kind of support can be helpful to alleviate caregiving distress even support is provided by phone call, e-mail or a software that creates virtual platform [57,63,64]. A crucial part of helping family caregivers is linking them with local support, best done through local Alzheimer’s Associations. Alzheimer’s Associations provide information, emotional support, practical advice, support groups, training programs, help sheets, toll-free helplines, and useful Web sites. They are powerful advocates for people with dementia and for their families with governments and service providers, as well as funding research. As these results show educational and social support programs are needed by caregivers and new policies and services that provide these programs should be established.

**Caregiver Education**

Dementia care education has come a long way in the last 30 years. It has paralleled the increase in knowledge about AD itself. In the 1970s, persons experiencing AD were seen as experiencing a degenerative brain disease that little could be done about. In fact, the old mantra of clean, dry, and fed was pretty much the Standard of the day. As the “old culture” of AD care was increasingly challenged, it also became clear that caregivers needed specialized knowledge and skills to work with persons with dementia.

AD care education initially was an extension of the medical model. Persons who were “experts” in dementia care were up to date on the most current break through on neurofibrillary tangles and beta amyloid plaques. Learning that AD was not normal aging or “senility” was actually a big first step in the history of dementia care.

In the next future behavioral approaches that framed care approaches around caregivers tailoring approaches to match the person with dementia. During this time we often said that by using such strategies, we set the stage for good AD care. A variety of simple strategies (eg, approach gently, make eye contact with the person, smile, go slowly, break down tasks into component parts) were all care techniques that increased the caregivers’ success in providing physical care to persons with AD.

The last 10 years have marked a clear shift to a more person-centered, relationship-based model for caregivers to support optimal wellness in persons with AD. Once the notion that persons with AD are whole persons and have the right to still be actively engaged in their own lives became commonly accepted, a great shift began. Now caregivers were seen as crucial players in the delicate balance of supporting the personhood of those with AD. A number of principles are central to this model: (1) the person with AD is an individual with value in his/her own right, (2) to provide excellent care we need to enter into human relationships with the individual, and (3) that a critical challenge is for caregivers to be willing to see the world through the eyes of the person with AD. All these principles drive the fabric of the care relationship. Another important principle that is inherent in person centered dementia care is the value and well-being of the caregiver. It is becoming an accepted notion that if the caregiver is not valued, respected, and seen as an essential partner in the relationship of care, the person with AD is much more at risk for not being seen as a person. Truly person-centered care is about committing to the dignity and personhood of both the caregiver and the patient with AD.

Caregivers are integral to quality of life of patients with AD. The high levels of burden and psychological morbidity are well documented, as factors that predict which caregivers are vulnerable to these. Interventions can ameliorate these effects and thereby improve the quality of the life of patients with AD. The management of the patient with AD requires a comprehensive plan that includes a partnership between doctors, health care workers, and families. Caregivers susceptible to negative effects can be identified and could be targeted for interventions.
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Abstract

Alzheimer’s disease (AD) is a neurodegenerative disease characterized by progressive loss of neurons manifested by loss of cognitive function, daily activity and mood changes. Pathophysiology of AD is quite complex and currently not fully understood. Even though widespread synaptic and neuronal loss, Amyloid Beta (Aβ) peptide accumulation at extracellular senile plaques, intracellular hyperphosphorylated tau proteins are known many years as histological findings, relationship between AD’s pathophysiology and these findings are not yet fully understood. In addition during AD, synaptic changes and loss, neuronal loss, mitochondrial and oxidative lesions, granulovacuolar degeneration and apoptotic changes associated with inflammation are observed. As a consequence of all these, changes in neurochemicals are also formed. Nowadays drugs used in the treatment of AD can not prevent the occurrence and progression of the disease. By treatment the symptoms of disease disappear and/or severity of the disease decreases. In recent years, many experimental studies built on Aβ, taupathy and the neurotransmitter system are able to come to the stage of clinical trials. Beside these, researches continue on new mechanisms such as oxidative stress, inflammation, mitochondrial dysfunction, lack of neurotrophin, caspase inhibitors and sirtuins which are thought to be involved in the pathophysiology of AD. It is hoped that results of intensive researches on new therapeutic approaches will provide significant improvements for the treatment of disease in near future.

Keywords: Alzheimer’s Disease; Therapeutic Approaches

Introduction

Alzheimer’s disease (AD) is a neurodegenerative disease characterized by progressive loss of neurons manifested by loss of cognitive function, daily activity and mood changes. Pathophysiology of AD is quite complex and currently not fully understood. Even though widespread synaptic and neuronal loss, Amyloid Beta (Aβ) peptide accumulation at extracellular senile plaques, intracellular hyperphosphorylated tau proteins are known many years as histological findings, relationship between AD’s pathophysiology and these findings are not yet fully established. In addition during AD synaptic changes and loss, neuronal loss, mitochondrial and oxidative lesions, granulovacuolar degeneration and
apototic changes associated with inflammation are observed. As a consequence of all these
events, changes in neurochemicals (cholinergic, serotonergic, noradrenergic, dopaminergic
decline and glutamate toxicity) also occur. Acetylcholine (Ach) is a neurotransmitter which
binds hippocampus to cerebral cortex. In AD, earliest and main pathology is impairment of
cholinergic system in the brain, particularly in areas associated with learning and memory
[1]. The loss in cholinergic neurons are associated with Aβ and tau pathologies.

In recent years glutamate toxicity is also considered in AD’s pathogenesis. Glutamate
is the main excitatory neurotransmitter in the brain. Glutamate rising by post-synaptic
N-Methyl D-Aspartate (NMDA) receptor activation, activates the voltage-gated calcium
channels and it leads to the influx of calcium into the cell and it facilitates apoptosis.
Furthermore glutamate induces formation of senile plaques an neurofibrillar tangles [2].

Nowadays drugs used in the treatment of AD can not prevent the occurrence and
progression of the disease. By treatment the symptoms of disease disappear and/or severity
of the disease decreases. Treatment must not only treat the symptoms of the disease, but
also prevent the formation of neurofibrillary tangles, amiloid plaques and inhibit neuronal
degeneration. Today, in order to stop amyloid peptid secretion, aggregation and tau
hyperphosphorylation many of the drug or agent are under clinical trial stage. Promising
drugs which is being used today and has reached the clinical trial stage will be reviwed here.

Therapeutic Targets Focusing On Amyloid Beta Cascade Hypothesis

Inhibition of Amyloid Beta Production

Neuronal plaques spesific for AD are composed of Aβ proteins. Aβ is a fragment of the
larger transmembrane protein that its function is not completely understood (Amiloid
Precursor Protein [APP]) by proteolytic pathways. APP metabolised by cutting a series of
proteolytic enzymes (α, β and γ secretase). α-secretase cuts the APP aproximately midline of
Aβ, it constitutes a soluble protein which is participating in the structure of neuronal cell
wall. However if APP is cleaved by other two enzymes from the amino terminus by β-secretase
or from the carboxy terminus by γ-secretase, the product is Aβ. The Aβs are composed of
40 or 42 amino acids in length. 42 amino acid form which is more amyloidogenic collapses
forming first aggregation [3]. After aggregation of Aβ into diffuse plaques, it turns, into
dense neuritic plaques. After the formation of neuritic plaques, inflammation, apoptosis
and excitotoxicity occur; this is a secondary cascade possibly associated with apoptosis-
mediated additional damage. Drug treatment strategies which are being developed in this
field, are focused on increasing the α - secretase activity, β-secretase inhibitors and gamma
secretase inhibitors and modulators.

Alpha Secretase Activators

A metalloprotease type enzyme, α-secretase, which is a member of the ADAM (A
Desintegrin And Metalloproteases) family is a nootropic and neuroprotective enzyme that is
important for neuronal development. Aβ formation is inhibited when the enzymatic cleavage
of APP occurs by the α-Secretase. Therefore, α-Secretase activators are thought to be useful
for treatment of AD.

Due to the similarities with Tumor Necrosis Factors (TNF) it is also called TNF Converting
Enzyme (TACE). α-secretase can be induced by Protein Kinase C (PKC) activators such
as phorbol ester. The drugs stimulating the receptors that act through PKC, muscarinic
agonists, statins, steroid hormones (oestrogens, testosterone), and nonsteroidal anti-
inflammatory drugs may increase the activity of α-secretase.

At mild to moderate AD, Etazolat (EHT-0202) that is a selective receptor modulator has
completed phase 2 studies [4,5]. Bryostatin-1 which is a macro cyclic lactone provides
α-secretase activation via PKC activation. Phase 2 studies of Bryostatin-1 are ongoing [6].
Exebryl-1 leads to a significant reduction of Aβ peptid production and accumulation in mouse brain. It is able to improve memory by regulation of α and β secretase activities [7].

**Beta Secretase (BACE1) Inhibitors**

β-secretase is a pepsin structured aspartilprotease which is found at golgi apparatus, endosome and in the cell membrane part. β-secretase is also called β-APP-Converting Enzyme (BACE). Beta-site APP-Cleaving Enzyme 1 (BACE-1) which is encoded on chromosome 11 is effective in Aβ production. Inhibition of BACE-1 reduces Aβ production.

In initial studies, quite potent β-secretase inhibition by two substances called OM99-1 and OM99-2 were shown. β-secretase enzyme inhibitors have also been found to increase the Aβ clarence in transgenic mouse models. Membrane transition state of these molecules is weak, in order to cross the blood brain barrier and achieve an effective level on the central nervous system, studies are ongoing [8].

After these molecules, CTS-21166 exceeded to phase I clinical trials by reduction brain levels of Aβ over 35%, and 40% reduction of plaque burden. It has been shown that the drug can be well tolerated in healthy volunteers and effectively reduce the plasma Aβ levels [9]. However, studies on MK-8931 which has very good oral bioavailability are progressing with the phase 3 studies [10]. In mouse models promising β-secretase inhibitors which has completed by other researches are KMU-429, 188 909 and GRL-8234 GSK.

**Gamma Secretase Inhibitors and Modulators**

The enzyme γ-Secretase which contains presenilin is a complex transmembrane protein. This enzyme consists of 4 parts which are presenilin-1 and 2, the nicastrin, presenilin enhancer 2 (PEN-2) and anterior pharynx-defective phenotype-1 (APH-1) [11]. The enzyme γ-Secretase is necessary for many physiological secondary signaling pathways and also synthesizes Aβ42 protein. Therefore, γ-secretase inhibitors, has been the subject of study for the treatment of Alzheimer’s disease.

DAPT is the first dipeptide compound having the γ-secretase inhibitor activity in vivo tests. It inhibits Aβ production in cells. However, it has been shown that high doses are needed to reduce Aβ levels in young APP transgenic mice brain [12].

Despite being bioavailable and brain-penetrant, toxicities associated with γ-secretase inhibitors hinder the development of therapeutic approaches targeting γ-secretase. The most commonly reported side effects of γ-secretase inhibitors are hematological and gastrointestinal toxicity, skin reactions and hair color changes [13-17]. Although LY-450139 and Semagacestat significantly decreased Aβ plasma levels in clinical studies, they were shown to impair cognitive function, increase skin cancer and infection risk and so they have been cut [18,19].

To overcome the above-mentioned toxicity problems, the notch sparing second generation of γ-secretase inhibitors has been developed. Avagacestat (BMS-708163), Begacestat (GSI-953) and NIC5-15 clinical studies has been initiated. Avagacestat phase 2 trials have been ended due to the absence of a positive effect on cognitive function compared to placebo, and gastrointestinal and dermatological system adverse effects [20]. A natural monosaccharide, NIC5-15, that is in the phase 2 study, has shown good tolerance and safety [21,22]. Promising results of Begacestat 1 studies are under clinical evaluation for the treatment of AD.

**Anti Beta Amyloid Aggregation**

Arresting of the accumulation or aggregation of abnormal Aβ’s at the fibrils and oligomers prevents the formation of neuritic plaques. While Aβ fibrils and Aβ oligomers showed toxic effects in cell cultures Aβ monomers does not show toxic effects. Aβ fibril formation resembles crystallization formation [23,24]. Aβ’s can not stay stable on some critical concentration and
precipitate [25]. This level of critical concentration may vary depending on Aβ’s type and on environmental conditions. For example, Aβ42 tends to create more fibrils compared to Aβ40. The level of concentration required for the generation of fibrils is lower for Aβ42 compared to Aβ40 [26]. Aβ fragments which are synthesized and released from cultured cells show negative effects on learning and memory by disrupting synaptic plasticity in the the synaptic links [27]. Certain compounds which prevents blocking of the fibril formation and Aβ collapse such as choly amide PPI 368, D-peptid PPI 1019 and L-peptid iAβ5p may contribute to treatment of Alzheimer’s disease. However, the effects of these compounds have been demonstrated only in vitro. There is no in vivo effects because they degrade in the plasma. This is the most important reason that prevents the clinical practices [28].

Studies in recent years have focused on three strategies to prevent the Aβ aggregation: anti aggregate compounds, metal complexing agents and immunization.

**Nonpeptidic Antiaggregates**

The first representative of this group is derived from propionic acid, tramiprosate. Phase 3 studies conducted with this drug was stopped due to low penetration to Central Nervous System (CNS) and poor potential [29,30].

Scyllo-inositol, one of the second generation drugs, is considered to have an effect to prevent Aβ aggregation and accelerate dissociation of aggregates. Inositol content of drug can help overcome the blood-brain barrier after peripheral administration and it can access the CNS in high concentrations. Phase 2 studies continues in mild-to-moderate Alzheimer’s patients [31]. Epigallocatechin-3-Gallate (EGCg), a polyphenol from green tea, has been shown to stimulate the alpha secretase activity in animal models and to inhibit Aβ aggregation. It has also multiple functions such as modulation of cell transmission, regulation of cell survival/death, and protection of mitochondrial function. Therefore, phase 3 trials for AD therapy is ongoing [32].

**Metal Complexing Agents**

In older ages metal ions such as copper, aluminum, iron and zinc concentrates more on the brain [33]. In AD, abnormal increase of metal ions in the neocortex may have an initiator role in increased formation of neurotic plaque due to Aβ42 [34,35]. In addition, detection of metal ions such as copper, zinc, and iron on Aβ plaque structure has led to the view that metal chelation treatment may be effective for AD [36]. Clioquinol (PBT2), an antibiotic, targets Aβ reactions with synaptic Zn and Cu. It has a powerful central nervous system permeability. It is proven to decrease Aβ42 concentration in the cerebrospinal fluid (CSF) and improve cognitive and behavioral performance; the phase 2 studies have been completed [37].

**Immunization**

Utilization of the immune system has been thought to find a solution for the main Aβ problem in the AD pathophysiology. Therefore, immunization has been tried as a therapeutic strategy of the disease. Abnormal immune response that damages tissue can be changed by forming various immune responses to stop pathological events in the tissue [38]. As the most striking example, it has been markedly demonstrated that after immunization with Aβ therapeutic effects were observed in transgenic mice model of Alzheimer’s disease [39,40]. Immunization created a secondary immune response against previously formed Aβ accumulation in the brain by stimulating inflammatory responses such as microgliyosis, astrosis, complement activation, formation and releasing of cytokines and acute phase proteins. In the first animal study, inhibited amyloid formation, reduced plaque formation and imoroved cognitive function were observed in genetically amyloid producing transgenic mice by vaccination with peptide [40,41]. This process is made by (i) administration of
peptides of Aβ itself or different parts of Aβ, as active immunization (ii) administration of antibodies generated against to the Aβ, as passive immunization [39,40].

**Active Immunization**

AN-1792 was the first human antigen Aβ1-42 tested in mice and leading to produce quick and large amounts of antibody that attaches to Aβ in the CNS. Phagocytosis took place with the activation of microglias. But because of aseptic meningoencephalitis and cerebral microhemorrhages occurred during studies, phase 2 studies were stopped. The formation of these complications has been linked to autoimmune responses and cytotoxic T cells [42,43].

After that, the vaccines without T cell epitopes were produced. Lately, phase 2 trials of CAD 106 which contains peptides of Aβ1-6 in mild AD have been completed. Molecule has been shown to not lead to meningoencephalitis [44]. UB 311 contains B cell epitopes (Aβ 1-14) and V950 (Aβ N-terminal conjugated to ISCO-MATRIX) are two promising vaccines their phase 1 trials are done. Recently, related studies with AD-01 and AD-02 which are the targeting the Aβ N-terminal fragment are underway [45].

**Passive Immunization**

Another way to inhibit the immune response is the to apply antibody directly. Although no change was determined in Aβ plaques, a rapid improvement in cognitive functions was observed in mice after the administration of monoclonal Aβ antibodies. Two basic action mechanisms take play in this improvement. The first is cleaning of antigen-antibody complex from locally activated microglial cells and increase in complex clearance. The second result of binding of Aβ with Aβ antibodies is to increase the solubility of Aβ and removal from plaque in the brain [47]. In summary, it is possible to remove amyloid plaques, save neuritic and glial function, reduce early tau hyperphosphorylation and cytopathology and to reverse the abnormal hippocampal synaptic plasticity by passive immunization [48-50].

Since therapeutic effect of Bapineuzumab (AAB-001) on cognitive or functional outcomes was not detected in patients with mild AD, the phase 3 studies were terminated [51]. Phase 3 studies of Solanezumab (LY2062430) and Gantenerumab in patients with mild AD are ongoing. Phase 2 studies of a new humanized antibody Crenezumab, which has a IgG4 backbone are continuing.

**Tau**

Backbone of Neurofibrillary Tangles (NFT) are the hyperphosphorylated tau proteins. Tau is bound to microtubules and plays important role in microtubule stabilization, cytoskeleton integrity and axonal transport. In the pathogenesis of AD, hyperactive kinases and/or hypoactive phosphatases lead to hyperphosphorylation of tau protein, which in turn disrupts the ability of binding to microtubules. The unbound hyperphosphorylated tau forms insoluble double stranded polymerizable filaments. In time it becomes intraneuronal NFT. NFT eventually cause cell death by disrupting the integrity of the cytoskeleton and axonal transport [52]. Studies have been conducted on kinase inhibitors and inhibition of tau aggregation for treatment of AD.

**Kinase Inhibitors**

Protein kinases play a central role in regulation of many mutually cell functions and guarantee the normal physiological state. However, Glycogen Synthase Kinase 3 Beta (GSK3β) and Cyclin dependent kinase 5 (CDK5) are the responsible enzymes in tau hyperphosphorylation. If these kinases are inhibited, Aβ accumulation can be prevented.

First class tau inhibitors are intended to regulate the tau’s phosphorylation by reducing associated kinase activity. Because deteriorated relationship between glycogen syntase kinase
3 beta (GSK3β) and protein phosphatase 2A (PP2A) increases the tau hyperphosphorylation and intracellular NFT formation [53].

Lithium and valproate have been shown to prevent tauopathy by inhibiting GSK3β in animal studies. However, in clinical studies in AD patients it has not been proven that they provide enough improvement on cognitive function [54,55]. Preclinical studies conducted with GSK3β inhibitor derivative molecules such as paullone, indirubin, and maleimide families came to dead end because of severe cytotoxic effects.

Another important kinase is CDK5 that causes tau pathology by taking part in tau phosphorylation. It has been shown that CDK5-selective inhibitors reduce levels of Aβ in preclinical studies [56].

**Inhibition of Tau Aggregation**

Another therapeutic approach is to prevent fibrillation of tau and provide the dissolution of fibrillated tau proteins. In the studies, methylene blue (Metiltioninium) was successful in completing the phase 2 trial [57,58]. TRx0237 is another methylene blue which has a better bioavailability. It has been shown to provide a better spatial learning in animal studies [59].

Nicotinamide, the precursor of coenzyme nicotinamide adenine dinucleotide (NAD⁺), was shown to prevent phosphorylation of tau in mice. In mild-to-moderate Alzheimer’s disease phase 2 studies are ongoing.

Epothilone D (BMS-241027) is an agent that inhibits tau aggregation by microtubule stabilization. It has improved behavioral and cognitive loss, inhibited the loss of neurons and limited the tauopathy in animal models. Currently phase 1 clinical trials are ongoing [60].

**Therapeutic Targets Focusing On Neurotransmitter System**

In AD, earliest and main pathology is impairment of cholinergic system in brain, particularly in areas associated with learning and memory. The loss in cholinergic neurons is associated with Aβ and tau pathologies. In recent years glutamate toxicity is also considered on pathogenesis of AD. Glutamate is the main excitatory neurotransmitter in the brain. Glutamate rising by post-synaptic NMDA receptor activation, activates the voltage-gated calcium channels and leads to the influx of calcium into the cell and thus facilitates apoptosis. Furthermore glutamate induces formation of senile plaques an neurofibrillary tangles.

Today, the most basic approach for AD therapy is to improve cholinergic neurotransmission in the brain. For this purpose, addition of acetylcholine precursors, acetylcholinesterase inhibitors (to reduce the degradation of acetylcholine), nicotinic and muscarinic receptor agonist and other drugs with cholinomimetic activity are used. Cholinesterase inhibitor drugs donepezil, galantamine and rivastigmin are the currently available treatments for the symptomatic treatment of AD. However, these drugs have a short half-life, their effect is temporary and poor, the therapeutic window is narrow, and also in clinical use, they have frequent and sometimes severe side effects. All these factors limit their usage in therapy. In order to develop drug with higher safety and effectivity intensive researches are ongoing. Recent investigations have focused on the development of novel acetylcholinesterase inhibitors.

Natural based acetylcholinesterase inhibitors consisting of alkaloids are some alternative medicines and herbs. These compounds, huperzine A and huperzine B, are composed of berberine and their semisynthetic derivatives [61].

In addition, some drugs as synthetic acetylcholinesterase inhibitors group are tacrine based dimers and hybrids. In this field studies on agents such as tacrine-donepezil hybrids, tacrine-indole hybrids, tacrine-huprine Y hybrids, tacripyrines, tacrine-ferulicacid
and tacrine-caffeic acid are continuing [61]. These agents take play role in both the acetylcholinesterase inhibition and in other activities associated with AD. Thus, while increasing cognitive function, they may be effective treatment options in preventing and slowing neurodegeneration.

Another neurotransmitter that is indirectly involved in neuronal degeneration and memory loss is serotonin. It has been shown that increasing the release of Ach and cholinergic transmission by inhibition of 5-HT6 (5-hydroxytryptamine 6) has positive effects on memory and learning disorders. In studies, the effect of 5-HT6 antagonists on protection from anticholinergic drug induced amnesia has been reported [62]. Recently serotonin antagonists, PRX-03140 (5-HT4 antagonist) and SB-742 457 (5-HT6 antagonist), have completed phase 2 studies. Lu AE58054 (5-HT6 antagonist) is ongoing phase 3 studies.

**Possibly AD Associated Other Treatment Approaches**

As mentioned above, therapeutic approaches targeting Aβ cascade and neurotransmitter system are not providing distinct solutions and led investigations on other mechanisms. The most well knowns are oxidative stress, inflammation, mitochondrial dysfunction, lack of neurotrophin, caspase inhibitors and sirtuins. This new many therapeutic potential associated drugs are under clinical investigation.

**Neurotrophin**

A protein which is secreted from neurons, Nerve Growth Factor (NGF), is necessary for the neuron development and maintenance of neuron life. It has been shown to prevent neuronal death in neurodegenerative diseases like AD [63]. Due to problems in crossing the blood brain barrier, NGF has searched for new molecules and began work on CERE-110 (Adeno-associated virus-based gene delivery vector expressing human nerve growth factor). Injection of CERE-110 to direct brain associated Phase 2 studies are ongoing [64]. Cerebrolysin has been shown to improve cognition and daily living activities in mild to moderate AD [65].

**Caspases Inhibitors**

Cysteine aspartyl proteases (caspases) that accelerate the apoptotic cascade have a role in the pathophysiology of AD. Increasing evidence has shown that, as an early event in AD, Aβ accumulation induces caspase activation so that causes caspase-induced fragmentation of tau. Tau cleavage seems like a critical event in the formation of NFT, thus caspase inhibitors, Z-VAD-FMK, Q-VD-OPh and Minocycline, were developed. Of these, minocycline, acts by inhibiting caspase 3 activation. Minocycline which has oral use with dual function as both anti-apoptotic and anti-inflammatory may be helpful in treatment of AD [66].

**Sirtuins**

Sirtuins (SIRT) are NAD⁺-dependent protein deacetylases. Seven sirtuin isoforms (SIRT1-7), which are differ in their highly conserved central NAD⁺ binding and catalytic domain, have been described in humans. Each enzyme presents a distinct biological activity role, due to their substrate specificities, subcellular localization and expression patterns [67]. There is an increasing data on the physiological functions of sirtuins and their involvement in disease-related mechanisms. Some of these mechanisms are oxidative stress, inflammation, cell-cycle regulation, and insulin secretion. Sirtuins have been associated with age-related disorders such as cardiovascular disease, cancer, metabolic disease and neurodegenerative disorders and also aging process [68].

The biological function of sirtuins are mainly related to the type of substrates they act upon, which can be categorized in three main groups: transcriptional regulating, metabolic regulating and apoptosis regulating.
In many studies, it was shown that sirtuins play important role in neurodegenerative diseases. SIRT1 has a positive effect in axonal protection from damage in an animal model of Parkinson disease. Additionally, SIRT1 overexpression protects from Alzheimer’s disease. Some studies have demonstrated that SIRT1 overexpression reduces Aβ production and the formation of plaques in mice brain. SIRT1 may be a new theupeutic molecule in learning and memory skills by activating the gene for brain derived neurotrophic factor [69].

It is known that the overexpression of SIRT2 can extend organism lifespan and is often correlated to caloric restriction since many years ago. But this association is still unclear. Studies in mice showed that SIRT2 inhibition increased acetylated tubulin, reduced hyperphosphorylated tau protein and restored cognition in AD transgenic mice. Additionally, SIRT2 inhibition displayed in vitro and in vivo neuroprotective effects in models of Parkinson’s and Huntington’s disease [70]. Furthermore, SIRT2 has been shown to accumulate in the aging brain [71].

Among human sirtuins, SIRT1 and SIRT2 remain the most studied and also best known to date. Many sirtuin inhibitors have been proposed for therapy against neurodegenerative diseases. In recent studies a number of sirtuin inhibitors have been discovered and reported. Some of their specific inhibitors have been proposed such as AGK2, salermide, splitomicin, sirtinol, EX-527, AK-7, cambinol and suramin.

There is solid evidence showing the association of SIRT2 to neurodegeneration and neurodegenerative diseases. AGK2 is the most known potent inhibitor of SIRT2 with an estimated IC50 (half maximal inhibitory concentration) of 3.5 µM, representing a significant increase over the low selective SIRT2 inhibitors like EX-527 and salermide [72,73]. It also inhibits SIRT1 and SIRT3 when its concentration is over 40 µM. The protective role against dopaminergic cell death of AGK2 was demonstrated in Parkinson’s disease [72]. AK-7 exhibits in vitro SIRT2 selective inhibitory activity [74]. In cultured neuronal cells and brain of mice, AK-7 was shown to reduce cholesterol biosynthesis and total cholesterol level in primary striatal neurons by inhibiting SIRT2. The effects on cholesterol homeostasis suggest that it can be used for AD treatment in the future [75]. In recent years, extensive research with SIRT inhibitors gives hope for the future treatment of neurodegenerative diseases such as AD.

With better understanding of reasons of Alzheimer’s diseases pathology, new treatment strategies will be developed, and new drugs which has less and more tolerable side effects will be used in the treatment. Especially in recent years, many experimental studies are built on Aβ, taupathy and the neurotransmitter system that were able to come to the stage of clinical trials. Beside these, researches continue on new mechanisms which are thought to be involved in pathophysiology of AD such as oxidative stress, inflammation, mitochondrial dysfunction, lack of neurotrophin, caspase inhibitors and sirtuins. It is hoped that results of intensive researches on new therapeutic approaches will provide significant improvements for the treatment of disease in the near future.

References


Abstract

Increasing prevalence and incidence of Alzheimer’s disease pointed the growing importance of protection studies. An early detection of the onset of neurodegeneration in AD is vital. It can provide a chance for an early treatment that may be helpful to prevent progression of the disease. Diagnosis of AD is based on neuropsychological tests and clinical consideration. However chemical, genetic, and neuroimaging biomarkers are also growing as main components of the exact diagnosis. Current managements of AD compromise the cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the N-Methy-D-Aspartate (NMDA) antagonist memantine for AD. However, in the next future disease-modifying drugs can be available for AD sufferers. Also additional social support and protection studies will provide additional information to routine clinical practice. At this section we will discuss ongoing clinical and experimental research and discuss near future expectations with the ligh of current evidence.

Keywords: Alzheimer's Disease; Biomarker, Cholinesterase Inhibitors; Disease-Modifying Drugs; Memantine; Sysmptomatic Management;

Clinical Aspects

About 5 million new cases are occuring every year with dementia, most suffering from Alzheimer's disease. In AD the years lived with disability is more than other disorders. The rapid increase in the number of patients will result with great economical and social burden.

Except well-known etiological factors including older age and limited genetic factors, exact etiological factors are undetermined. In addition to these factors, it is shown that disorders which causes vascular risk factors as smoking, high blood pressure, obesity, diabetes, and cerebrovascular lesions have prominent impact on dementia. And also psychosocial and educational factors including high education years, active social life, physical exercise and mentally stimulating activity have possible benefits in the pathogenetic process of the dementing disorders. According to US Disease Control and Prevention Centers the number of people over 65 years in the world is expected to be increased from 7% to 12% [1,2], and
AD prevalence will increase exponentially, especially in developing countries. There are still unknown parameters related with AD epidemiology and we need to broad-population based research especially for middle and low-income countries.

There are three mutations established resulting to autosomal dominantly herited AD including, presenilin-1, presenilin-2 and amyloid precursor protein, these familial AD patients constitute only 2-5 per cent of AD population [3] The remaining patients establish sporadic AD and have a complicated, heterogeneous pathophysiological process. Vascular pathway related gene mutations should be investigated at the future because of established effects of vascular risk factors at AD development. Vascular hypothesis is an established important risk factor at dementia. Smoking, alcohol abuse, obesity, hypertension, hyperlipidemia, nutritional factors, diabetes mellitus, ischemic heart and cerebral diseases are investigated areas of research.

**Nutritional Considerations**

The role of nutritional and dietary factors is controversial. Studies about dietary factors are insufficient and limited. Many follow-up studies have shown the benefits of antioxidants like vitamins E, C and mediterranean diet but also there are negative reports. B_{12} and folate supplementations have no benefits on cognition but by reducing serum homocysteine level may have benefits. It has been reported that a saturated fats and cholesterol rich diet increases the risk of AD, whereas polyunsaturated fatty acids may be protective. Fatty acids take a part in the synthesis of nerve cell membranes and necessary for synaptic plasticity and neuronal degeneration. Supplementation of antioxidants or diet which includes antioxidants such as vitamins E and C may prevent AD [4]. A long-term direct effect of uncontrolled hyperglycemia, hyperinsulinemia or impaired insulin response on neurodegenerative changes in the brain has been shown. We believe in that, there is no rational to assume whole metabolic syndrome components as risk factors for AD. To recognize diabetes mellitus and hyperinsulinemia as risk factors of disease seperately seems more rational.

**Psychosocial Factors**

A systematic review found that psychosocial factors and actively social lifestyle may reduce the risk of AD and dementia. An association of low education with an increased risk of dementia and AD has been reported in numerous studies. Education provides neural and cognitive reserve to cope with degenerative pathological changes in the brain and delay onset of the dementia. The risk for dementia and AD was also increased in older people with increasing social isolation and less frequent contacts with relatives. Poor social network is associated with cognitive decline. Rich and large social networks also influence cognitive function and different health outcomes through behavioral, psychological, and physiological pathways [5]. Mental activities including social activities, watching specific tv shows, dancing, playing musical instruments has protective effect in AD and dementia. Many studies showed that high complexity of work with people might reduce the risk of AD due to reducing rate of hippocampal atrophy [4].

We do not have enough information about toxic or inflammatory factors due to insufficient and limited studies. Heavy metals such as aluminum and mercury have been investigated as a risk factor for AD, and even taken of aluminum from drinking water may be a risk factor for AD. However, this is not confirmed yet. A higher level of C-Reactive Protein (CRP), interleukin-6 showed an association of increased incidence of dementia and AD. Also Non-steroidal Anti-Inflammatory Drugs (NSAIDs) may have beneficial effect against AD and dementia. Neuritic plaques in the brain are associated with inflammatory proteins. Therefore inflammatory mechanisms that cause neurodegeneration should be more searched. Neuropathological studies did not find association between use of NSAIDs and AD’s pathological changes. But we need more studies for getting more information to prevent dementia and AD [6].
Diagnosis and Definitions

The most commonly used diagnostic criterias of AD and recently developed new diagnostic criterias (IWG and NIA-AA) and DSM-V published at 2013 were discussed on previous chapters. At this chapter we will discuss promising evident and will discuss how these studies could change disease course at the near future. Neuropsychological tests need a comprehensive interview with the patient, including assessment of attention, behaviour, memory, language and personality. But it has shown that these behavioral tests may give false negative results for patients with mild symptoms.

Biomarkers are substances that are used as an indicator of a biological state, most commonly of a disease. Biomarkers are considered promising in early diagnosis. A good biomarker should differentiate different diseases and diseased tissues from healthy ones. There are two kinds of biomarkers including genetic biomarkers and biochemical markers.

Biochemical markers base on pathology of AD. Contemporarily the well known biochemical markers of AD are tau protein and Aβ level in CSF.

PET molecular imaging leads for diagnosing AD. As a result of 18F-FDG-PET, binding to Aβ fibrils were discovered. 18F-FDG-PET has approximately the sensitivity of 91%. 18F-FDG-PET crosses the blood-brain barrier and can determine the localization of NFT and senil amyloid plaques. Combining PET with other biomarkers and SPECT, provides a new pathway to early diagnosis.

MicroRNAs (miRNAs) comprise 1% of all human genes and play role in the pathogenesis of neurodegeneration and can be used as a signature for neurodegenerative conditions. miRNAs are especially found in high amounts in nervous system. Exosomes which are secreted by many cell types including vascular endothelium involved in neurological disorders, ease the transportation of miRNAs. Exosomes have significant potential as biomarkers because of their acquirement easily from blood and urine due to their constitution. The advantage of using miRNAs as biomarkers is easily detection with specificity and well preservation in formalin and also in fresh snap-frozen specimens. There are subgroups of miRNAs family and all these groups have sensitivity and specificity at 79-100% and 79-95%. Elevated hyperphosphorylated tau in exosomes obtained from CSF of AD with mild symptoms were detected which are normally present in accumulated exosomal amyloid peptides in the brain plaques. There are recent studies about plasma phospholipids levels which we hope to use as prediction if the normal individual will develop MCI or AD.

Genetic, Where To Go?

In addition to identification of three casual genes and APOE in AD, identification of CLU, CR1 and PICALM as novel risk genes in late-onset AD is promising. We need more detailed GWA meta-analyses to detect new risk genes with smaller effect sizes. But we need large population based studies to find undetected genes. On the other hand, including only isolated populations may reduce the genetic heterogeneity and possibility to find undetected genes.

GWA studies are insufficient to detect rare variants for now. New detection methods allow screening the complete allelic spectrum of AD in large AD populations. With the reducing costs of novel technologies, future GWA studies may include rare variants to provide associations of genetic variants in AD, which play an unknown role. Also genome studies might provide extensive re-sequencing methods to search different locuses in different chromosomes. No single method will explain the genetic spectrum of AD, more extensive approaches are recommended. The main issue over the next years will be about methods in the integration of analyses.

Complex diseases as AD are caused by a limited number of common variants with small predisposing effects. Contemporarily role of environmental and genetic factors are not well-
defined up to now. Although genetic searches are complicated, promising strategies are being developed to optimize comprehensive approaches, thus will provide us genetic risk profiles to improve medical healthcare [10].

**Therapeutic Approaches**

Potentially neuroprotective and restorative treatments such as neurotrophins, neurotrophic factor enhancers, and stem cell-related approaches are also under investigation [11,12].

**Antiamyloid approaches**

Aβ peptide cleavage from APP is catalyzed by first β- and then γ-secretase. This is called amyloidogenic pathway, which results with production of less toxic Aβ<sub>38-40</sub> about 95% or more toxic Aβ<sub>42</sub> less than 5%. In the nonamyloidogenic pathway, APP is first cleaved by α-secretase, then by γ-secretase to originate a smaller C-terminal fragment. Nonamyloidogenic pathway precludes Aβ<sub>42</sub> formation and in fact it is the predominant pathway for amyloid metabolism. Genetic and environmental factors may change this balance and increase production of toxic Aβ<sub>42</sub> peptide [13].

Both use of β- and γ-secretase inhibitors showed reductions in Aβ levels in the brain. In β-secretase inhibitors study, reduced Aβ production is showed in vivo. In γ-secretase inhibitors study, reduction of Aβ production has been shown with acute treatment in rodents with cognitive impairment and without effect on performance in controls. Plasma Aβ<sub>1-40</sub> level decreased but CSF Aβ<sub>40</sub> levels showed no significant difference. This study suggested AD associated with Aβ might be reversible with acute pharmological treatment. Gama-secretase is an essential protease for many substrates in addition to APP. Nonselective inhibition of γ-secretase caused anormal differentiation of lymphocytes and inhibited Notch signaling. Because of the side effects clinical trials were limited. Current studies based on γ-secretase selective inhibitors and modulators are ongoing [14,15].

Similar to γ-secretase, there are other substrates for β-secretase as peripheral nerve myelination. Beta-secretase inhibitors caused hypomyelination of peripheral nerves at mice [16]. Several small molecule agents of β-secretase inhibitors are under investigation.

Passive immunization, solanezumab, bapineuzumab, gantenerumab, crenezumab and ponezumab are currently being tested. In patients treated with antibodies against Aβ, slower rates of cognitive function decline have been showed. As an exception, neuropsychological tests showed differences, other outcomes showed no benefit and, on the contrary, in the vaccinated patient’s brain volume were smaller than control group. The study stopped when meningoencephalitis developed in 6% of patients. Further studies are needed [17].

As a NSAID, tarenflurbil is a γ-secretase modulator and still under investigation. Tarenflurbil modulates γ-secretase to produce less toxic form of Aβ<sub>42</sub> and reduces amyloid plaques. In a phase II trial highest dose receiving patients showed significant benefits on daily activities and adverse events delayed almost one year. Further testing of this agent is ongoing.

Peroxisome proliferator-activated receptor agonists decrease Aβ<sub>42</sub> levels through Insulin-Degrading Enzyme (IDE). In MCI and mild AD patient’s cognitive improvement were seen especially in patients without APOE ε4 allele. Insulin itself might improve memory in AD. Clinic trials are still going on about peroxisome proliferator-activated receptor agonists and intranasal insulin [18].

Receptor for Advanced Glycation End Products (RAGE) resides in blood vessel cells and transports Aβ across the blood-brain barrier. Inhibition of RAGE mechanism reduces Aβ accumulation. RAGE is one of the target points of drug development in AD [19].
Neuroprotective Approaches

Some of them supported slight delays in the progression to severe dementia. These agents are being reconsidered [20]. Astrocyte-modulating agents are being studied. Around Aβ plaques activated astrocytes reside and produce oxidative species. Astrocyte-modulating agents might intervent the role of activated astrosytes in AD pathogenesis [21].

Tau-related immunotherapy aims to reduce production of intracellular neurofibrillary tangles. Lithium reduces hyperphosphorylation of tau proteins and reduces APP but its toxicity limits its use in older patients. Recent clinical trials reduce amyloid process did not have convincing results on cognitive functions. Other approaches targeting NFT, synapses loss and neuronal death came into prominence. So, active and passive tau-related immunotherapies are in progress with promising results [22].

Studies with other compounds like nicotinic acetylcholine receptor agonists, monoamine modulators, AMPA-receptor modulators with potential benefits are in progress, but results are not yet conclusive. Nerve Growth Factor (NGF) treatment can be applied by surgical implantation of NGF-expressing cells or using agents that mimic endogeneous production of NGF. Xaliproden acts by activating endogenous production of NGF and reverses hippocampal choline acetyltansferase reduction. There are ongoing randomized, controlled, phase III trials assessing effects of this agent [23,24] Cerebrolysin is another peptide with neurotrophic activity and reduces Aβ accumulation. Studies demonstrated that cerebrolysin improves daily activities and cognitive function. Clinical investigation of this agent is ongoing [25]. NGF and NGF-related agents might have neurorestorative properties and studies of these agents are expected to continue.

Finally there are lots of the reports about disase modifying behavioral strategies and the importance of social support in the management strategies. Also there is a growing issue about the importance of primary prevention studies.

References


