Alzheimer’s Dementia: Current Data Review

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ABSTRACT

The review focuses on current data on Alzheimer’s dementia, a clinical syndrome characterised with acquired deterioration of cognitive functioning and emotional capacities, which impairs everyday activity and quality of life. Alzheimer’s dementia is the most common type of dementia in clinical surveys. The diagnosis of Alzheimer’s dementia is primarily based on symptoms and signs and memory impairment is clinically most significant. Cholinesterase inhibitors – donepezil, rivastigmine and galantamine are considered to be the first line pharmacotherapy for mild to moderate Alzheimer’s disease. Currently, no effective pharmacologic interventions have been researched enough to support their use in prevention of Alzheimer’s dementia. Studies suggest that healthy lifestyle, ongoing education, regular physical activity, and cholesterol control, play a role in prevention of Alzheimer’s dementia.

Key words: Alzheimer’s dementia, cognitive functioning, memory impairment, pharmacotherapy

Introduction

Dementia is a clinical syndrome characterised with acquired deterioration of cognitive functioning and emotional capacities, which impairs everyday activity and quality of life. The dementias can be categorized according to etiology, neuropathology or clinical presentation. Four major groups of dementias have been defined: Alzheimer’s dementia (AD); the Parkinson’s group (including Lewy Body disease, dementia of Parkinson’s and Alzheimer’s dementia with Parkinson’s); the frontotemporal group (including Pick’s disease and Semantic dementia); and the vascular group (including large and small vessel disease). This review focuses on the Alzheimer’s dementia, named after German doctor Alois Alzheimer who, in 1906, found changes in the brain (amyloid plaques and neurofibrillary tangles) of a woman who died, for that time, of an unknown mental disease.

Epidemiology

AD is the most common type of dementia in clinical and autopsy surveys. AD is a neurodegenerative disorder that is estimated to affect 15 million people around the world. It is estimated that by 2050 the number of patients with AD could be as high as 25 million. The current prevalence of AD in the U.S. is estimated at 4.5 million, a number expected to rise threefold over the next 50 years as the population ages.

Etiology/Risk Factors

Cerebral degeneration, with selective neuronal death induced by extracellular amyloid deposits in the form of senile plaques and intracellular neurofibrillary tangles composed of helical paired tau protein, is the best-studied pathological event related to AD. Neurofibrillary tangles are composed of an abnormally hyperphosphorylated intracellular protein called tau, tightly wound into paired helical filaments and thought to impact microtubule assembly and protein trafficking, resulting in the eventual demise of neuronal viability. The extracellular amyloid plaque deposits are composed of a proteinaceous core of insoluble aggregated amyloid-β (Aβ) peptide and have led to the foundation of the amyloid hypothesis. In AD, multiple regions of brain gray matter have a profound neuronal loss, including basal forebrain, hippocampus, entorhinal, and temporal cortices. Braak and Braak suggest that the neurodegenerative process begins with neuronal loss in the glutamatergic pathways of the brain.
The amyloid cascade hypothesis is one of the theories of pathogenesis for Alzheimer disease. The most important abnormality is an excess of Aβ peptides brought about through either overproduction or failure in degradation. It seems that late-life onset AD results from a failure of metabolism and degradation of Aβ, while mutations in the «Alzheimer genes» (Presenilin I, Presenilin II, and APP) leads to overproduction of Aβ. Previously, it was considered that the plaque was necessary to initiate this toxic cascade, but it is now considered more likely that the Aβ monomers and oligomers initiate the process, long before organizing into plaques.

Secondary protective responses such as microglial activation, an inflammatory response and free radical formation are part of the toxic cascade induced by amyloid accumulation, which ultimately contributes to neuronal death, leading to the clinical manifestations of dementia.

Beside mutations in APP, PS1 and PS2 genes molecular genetic studies have found that polymorphisms in APOE gene are implicated in AD pathogenesis. APOE has critical functions in redistributing lipids among CNS cells for normal lipid homeostasis, repairing injured neurons, maintaining synapto-dendritic connections, and scavenging toxins. In Alzheimer’s disease, apoe acts directly or in concert with age, head injury, oxidative stress, ischemia, inflammation, and excess amyloid beta peptide production to cause neurological disorders, accelerating progression, altering prognosis, or lowering age of onset.

Recent studies show that these proteins are also involved in several neuroplasticity-signaling pathways (NMDA-PKA-CREB-BDNF, reelin, wingless, notch, among others). DNA damage caused by oxidative stress is not completely repaired in neurons and is accumulated in the genes of synaptic proteins. Several functional single-nucleotide polymorphisms (SNPs) in synaptic genes may be interesting candidates to explore in AD. Thus, experimental evidence shows that proteins implicated in AD pathogenesis have differential roles in several signaling pathways related to neuromodulation and neurotransmission in adult and developing brain. It has been suggested that oxidative stress effects on DNA and inherited variations in synaptic genes may explain in part the synaptic dysfunction seen in AD.

Earlier investigations have shown that permanent activation of glial cells in the brains of AD patients promotes the production of excessive quantities of free radicals, nitric oxide, and cytokines, which could be detrimental to neuronal cells. Damage to the blood-brain barrier by inflammatory processes results in the influx of peripheral immune system cells and local immune reactions.

Glutamatergic dysfunction plays an important role in the pathogenesis of this illness, although this disturbance is probably a secondary phenomenon to other neurochemical, genetic or metabolic changes, essential to the development of AD.

Of approximately 200 peptides that are known to exist in the body, 80 carry out functions as neurotransmitters and about 20 have been linked to AD. The most notable points in AD could be the reduction in substance P in the cerebral cortex, hippocampus, basal ganglia and cerebellospinal fluid; the diminished levels of somatostatin in the same structures except for the basal ganglia; the reduction in the amount of vasopressin except in the temporal lobe; and the increased levels of dynorphin and leucine enkephalin.

Regarding risk factors, age is the strongest risk factor for AD. Gender, marital status and living in an urban area have been suggested as possible risk factors for AD. Lower education has repeatedly been identified as a risk factor for the development of AD, while higher education correlates with older age at onset and possibly with lower overall risk. This pattern has been attributed to brain and cognitive reserve. Hypertension may impair cognitive functions and is related to the occurrence of not only vascular dementia but also AD, while the relationship between cholesterol and dementia varies, depending on when the cholesterol is measured over the life course – midlife high cholesterol level appears to be a risk factor for dementia, especially AD. There is also evidence for an elevated risk of both vascular dementia and AD in patients with type 2 diabetes mellitus, albeit with strong interaction of other factors such as hypertension, dyslipidemia and ApoE genotype. Population-based studies have shown that those with type 2 diabetes mellitus have an increased risk of cognitive impairment, dementia, and neurodegeneration. There are many mechanisms through which diabetes could increase risk of dementia, including glycemia, insulin resistance, oxidative stress, advanced glycation endproducts, inflammatory cytokines, and microvascular and macrovascular disease.

Investigations have targeted three so-called «Alzheimer genes», Presenilin I, Presenilin II, and APP, which are thought to work through increased production of Aβ peptides and are held responsible for many familial cases of AD. These genes are accounting for around 5% of cases, usually the early-onset variant. Most AD cases, particularly with onset after the age of 65, occur in the absence of one of the causative genes and without an identified family history. The major susceptibility gene associated with late-onset AD cases is apolipoprotein e4 (APOe4). By age 85 those homozygous for the APOe4 allele (2% of the population) have a 50–90% chance of developing AD, and those heterozygous for the APOe4 allele (15% of the population) have a 45% chance, in contrast to the 20% chance in the general population.

Although the APOe4 allele is the only proven genetic risk factor for the late form of the disease, genetic epidemiological studies suggest that other loci are also involved.

It is important to stress the role of lifestyle in development of AD. Patients with varied activities, including in-
tellectual, physical, recreational and social activities, are less likely to develop AD. Also, social network size seems to play a role in preserving cognitive functioning.

**Diagnostic Criteria**

The diagnosis of AD is primarily based on symptoms and signs, according to DSM-IV-TR and ICD-10 diagnostic criteria. Memory impairment is clinically most significant. The presence of characteristic symptoms such as problems with retaining recent information or problems to come up with words are suggestive of AD. Language, praxis and recognition skills, are affected even early in the presentation, while motor and sensory symptoms are absent until late in the course of the disease. AD has a gradual and progressive course, typically 10 years from diagnosis to death. The cholinesterase inhibitors have had some effect on the course of disease for individual subjects, though population trends have been harder to demonstrate.

Assessment of cognitive functioning is necessary for making initial diagnosis of dementia. For this reason, measuring scales are used in patients with dementia for assessment of cognitive functioning, psychopathology and psychosocial functioning.

The most commonly used instrument for assessment of cognitive deterioration is Mini Mental state Examination (MMSE). It takes 5–10 minutes to complete the MMSE, and maximum result is 30 points. In many countries MMSE has become a part of routine practice. Alzheimer disease assessment scale (ADAS) also measures cognitive functioning, memory, concentration, mood, behavioral disturbances. It is consisted of 21 items. The time to complete ADAS is around 45 minutes. Severe impairment battery (SIB) is used to assess cognitive functioning in patients with severe AD, while Multidimensional observation scale for elderly subjects (MOSES) is used to assess cognitive and psychosocial functioning. Cohen-Mansfield Agitation Inventory (CMAI) is used for assessment of manifestation and frequency of agitation in patients with dementia. Neuropsychiatric inventory (NPI) is a scale used for assessment of psychopathology in patients with dementia.

**Treatment**

Tacrine was the first cholinesterase inhibitor approved by the Food and Drug Administration (FDA) for the symptomatic treatment of AD but was subsequently withdrawn from the market place due to hepatotoxicity, resulting in an unacceptable risk benefit profile for the drug. Other cholinesterase inhibitors – donepezil, rivastigmine and galantamine have better safety and tolerability profiles, and are considered to be the first line pharmacotherapy for mild to moderate Alzheimer’s disease. These drugs have slightly different pharmacological properties, but they all work by inhibiting the breakdown of acetylcholine by blocking the enzyme acetylcholinesterase. Donepezil and galantamine are both selective acetylcholinesterase inhibitors, whereas rivastigmine is an inhibitor of both acetylcholinesterase and butyrylcholinesterase. The most that these drugs could achieve is to modify the manifestations of Alzheimer’s disease.

In 2003, memantine, an N-methyl-D-aspartate (NMDA) antagonist, was approved for the treatment of moderate severity AD. Memantine, a moderate-affinity, voltage-dependent, uncompetitive antagonist of NMDA receptor, shows neuroprotective effects in patients with moderate-to-severe AD. Memantine is a drug with neuron-permeable and cognition-enhanced properties, which can be combined with other treatments for AD. Thus, memantine does not stop or reverse AD, but its moderating effect in protecting the brain from the toxic levels of calcium, allows normal signaling among brain neurons. Oxidative stress and glutamate induced excitotoxicity are thought to play a critical role in the neurodegenerative process of AD. With advancing age, neurons encounter increased oxidative stress and impaired energy metabolism, which compromise the function of proteins that control membrane excitability and subcellular Ca(2+) dynamics. Toxic forms of amyloid beta-peptide can induce Ca(2+) influx into neurons by inducing membrane-associated oxidative stress or by forming an oligomeric pore in the membrane, thereby rendering neurons vulnerable to excitotoxicity and apoptosis. Although the precise molecular mechanism of beta-amyloid protein neurotoxicity remains elusive, our and other numerous findings have demonstrated that beta-amyloid protein directly incorporated into neuronal membranes forms calcium-permeable ion channels (amyloid channels) and resulted in an abnormal elevation of the intracellular calcium levels.

Blockade of the NMDA receptor, one of the principal excitatory glutamate receptors in the brain, has been shown to have neuroprotective effects in a number of acute preclinical in vitro and in vivo models.

The mechanism of action of some new investigated compounds include interfering with Aβ aggregation, enhancing its metabolism, diminishing the production of toxic Aβ peptides and enhancing the enzymatic formation of non-soluble Aβ peptides. One of the therapeutic targets is the Aβ itself. A number of strategies to reduce soluble Aβ are currently being employed both preclinically as well as clinically, and include antibody based approaches, and reagents that disrupt the structure of Aβ, such as metal chelators.

Two β-secretase genes have been identified in humans, referred to as BACE-1 and BACE-2, colocalized with APP in the endosomal compartment. Only BACE-1 is significantly expressed in brain, particularly in neurons. Inhibition of β-secretase is one of a promising strategy for treatment of AD, and specific BACE-1 inhibitors should have therapeutic potential to slow or halt the progression of this disease.

Depressive symptoms are present in two thirds of patients with dementia. It is necessary to apply antidepressants in those cases. Selective serotonin reuptake inhib-
The antidepressant drug therapy\(^44\). In the study that compared the N-acetyl-aspartate (NAA) to creatine ratio, suggested increased turnover of N-acetyl-aspartate compared to almost identical values of N-acetyl-aspartate. Authors concluded that significant increase in cholinergic side effects. Atypical antipsychotics are the preferred treatment for symptoms such as delusions, hallucinations, agitation and aggressive behaviour. The most widely used are olanzapine and risperidone\(^45\).

Antipsychotics are indicated in cases of psychotic symptoms in demented patients. Antipsychotics with high potency more often induce akathisia and parkinsonism in elderly population, while antipsychotics with low potency more often cause sedation, confusion, delirium and orstatic hypotension, along with periferal anticholinergic side effects. Typical antipsychotics are the preferred treatment for symptoms such as delusions, hallucinations, agitation and aggressive behaviour. The most widely used are olanzapine and risperidone\(^45\).

Benzodiazepines are used in the treatment of anxiety and agitation, primarily lorazepam and oxazepam because of lack of active metabolites and because these medications do not metabolize in liver. Side effects of such treatment include sedation, worsening in cognitive functioning, delirium and higher risk of falling. Anticonvulsives medications are used as mood stabilizers in non-psychotic patients with behavioral disorders\(^41\),\(^42\).

In a recent investigation that studied proton magnetic resonance spectroscopy (1H-MRS) changes in early to intermediate (3–6 weeks) responders to antidepressant treatment with selective serotonin reuptake inhibitors, authors concluded that significant increase in choline to creatine ratio from the first to the second spectroscopic scan during the antidepressant treatment, compared to almost identical values of N-acetyl-aspartate (NAA) to creatine ratio, suggested increased turnover of cell membranes as a mechanism of the early response to the antidepressant drug therapy\(^44\). In the study that assess whether changes in 1H-MRS measurable metabolites correlate with clinical outcome after donepezil treatment, the results indicated possible modest donepezil effect on prevention of neuronal functional deterioration in dorsolateral prefrontal cortex (DLPFC) which correlates with clinical outcome and point the use of 1H-MRS as technique of help in assessment of drug effect\(^46\).

Elderly population is more sensitive to pharmacotherapy, as a result of changes in pharmacodynamics (changes in number of neurons, changes of receptors) and pharmacokinetics (changes in absorption, distribution, metabolism, excretion and protein binding). Bearing this in mind, the lowest effective doses of psycho-pharmacs are to be used, following the general rule «start low, go slow», avoiding side effects as much as possible. It is necessary to recognize potential reasons for not taking therapy, such as living alone, impaired sight and/or hearing, and cognitive deterioration. Also, it is necessary to consider possibility of interactions between psychopharmacs and other medications, especially considering changes in pharmacodynamics and pharmacokinetics. It is assumed that in the future treatment efficacy will be monitored in vivo through amyloid imaging and serum/CSF biomarkers.

Many preventive approaches to AD have been identified, but no randomized controlled trials (RCTs) support their efficacy. Evidence from RCTs supports the effectiveness of blood pressure control in reducing incidence of AD, but demonstrates that postmenopausal women’s use of estrogen is ineffective in reducing it. Observational studies suggest that some preventive approaches, such as healthy lifestyle, ongoing education, regular physical activity, and cholesterol control, play a role in prevention of AD. These approaches can and should be used for every patient because they carry no significant risk. Currently, no effective pharmacologic interventions have been researched enough to support their use in prevention of AD\(^46\).

An interaction between the negative effects of aging and the positive plasticity processes associated with environmental enrichment can provide a counterbalance through which neuronal circuitry activity coding for specific cognitive or motor behavior could be restored\(^47\). Health professionals should educate patients, especially patients at higher risk of AD, about preventive strategies and potentially modifiable risk factors.

**References**

ALZHEIMEROVA DEMENCIJA: PREGLED NOVIH SAZNANJA

SAŽETAK

Ovaj pregled se usredotočuje na nove spoznaje o Alzheimerovoj demenciji, klinički sindrom karakteriziran stečenim oštećenjem kognitivnih funkcija i emocionalnih kapaciteta, koji dovodi do oštećenja svakodnevnog funkcioniranja i kvalitete života. Alzheimerova demencija najčešći je tip demencije u kliničkim istraživanjima. Dijagnoza Alzheimerove demencije primarno je bazirana na simptomima i znakovima, pri čemu je oštećenje pamćenja klinički najznačajnije. Inhibitori kolinesteraze – donepezil, rivastigmin i galantamin smatraju se prvom linijom farmakoterapije za blage do umjerene oblike Alzheimerove demencije. Do sada istraživanja nije potvrđeno farmakološko liječenje koje bi bilo učinkovito u prevenciji Alzheimerove demencije. Istraživanja ukazuju da zdravi stil života, kontinuirana edukacija, redovita tjelesna aktivnost i kontrola razine kolesterola imaju značajnu ulogu u prevenciji Alzheimerove demencije.