Alzheimer's disease — a brief overview of patogenesis

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SUMMARY: Alzheimer's disease (AD) is a degenerative incurable disease of the brain characterized primarily by dementia, i.e. symptoms include impairments of memory, judgment, attention span and problem solving skills. AD brains on autopsy resemble other brains affected by dementia, e.g. reduced thickness of cortical grey matter, increased ventricle volume etc. Neuropathologically AD is characterized by accumulated deposits of misfolded and aberrated proteins. It has been discovered that ceramides in membrane are involved in pathogenesis of AD by facilitating β-secretase (production enzyme of Aβ). A specific distribution of neuronal nitric oxide synthetase has been noted in hippocampal formation and entorhinal cortex of AD patients compared with age-matched controls. Treatment-wise it would be better to start earlier because advanced neuronal degeneration is irreversible. In regards to treatment research, it should be directed towards developing reliable biomarkers and techniques for earlier and faster AD diagnostics.

KEYWORDS: Alzheimer's disease; TAU; Nitric oxide;

Alzheimer's disease (AD) is a degenerative disease of the brain characterized by the insidious onset of dementia. Impairment of memory, judgment, attention span, and problem solving skills are followed by severe apraxias and a global loss of cognitive abilities[1]. The clinical course of advanced dementia was described in CASCADE study (323 nursing home residents). The median survival was 16 months and the most common clinical complications were eating problems (86%), febrile episodes (53%) and pneumonia (41%)[2]. The number of people affected with AD was 26.6 million worldwide in the year 2006. This condition primarily occurs after the age of 60. By year 2050, it is believed that the number of people affected with AD will grow four times.[3]

In regards to neuropathology, AD is marked by severe cortical atrophy and the triad of senile plaques, neurofibrillary tangles and neuropil threads. On autopsy, a brain of a deceased individual who suffered from dementia shows decreased cortex volume, reduced thickness of cortical grey matter, increased ventricular volume etc. Some studies[4,5] in brains affected with dementia, based on stereological counting methods, showed no global cortical neuron loss, while brain of AD patients showed profound neuronal loss in entorhinal cortex and significant loss in the superior temporal sulcus region. Additionally, a difference was marked in the cortical cell volume when comparing brains affected with AD and non-AD affected brains. The mean cell nuclear volume of neurons in brains affected with AD was significantly larger than one of the controls, while the mean volume of cortical cell perikaryon in AD patients was not significantly different compared to the controls. The neocortical thickness was significantly larger in controls than in the AD cases. Volumes of the lateral and third ventricles in brains affected with AD were significantly larger than that of the controls.[4]

In addition to the difference in the neocortex of patients suffering from dementia, there are other disturbances in their archicortical structure (hippocampus). The hippocampal disorder is the characteristic feature of AD and leads to memory impairment, the biggest clinical symptom of AD. A study[5] that observed the differences regarding local hippocampal changes in AD and normal ageing came up with certain conclusions. Firstly, the mean hippocampal volume in controls decreased by 14% per decade between the ages of 65 to 85 years. Secondly, hippocampal volume in patients affected with AD tended to be lower than in controls at any age. Hippocampus of patients suffering from AD shows a topographic pattern with shape changes that are distinct only in the same part that changes over time in the 'healthy ageing'. Dorsolateral (CA 1; view figure 1.) and presubicular part of hippocampal head were affected only in AD, while the lateral part of subiculum in hippocampal head was affected only in ageing. The medial and lateral part of hippocampal tail (CA 1) were affected in both.

Brain atrophy is a result of augmented apoptosis of neuronal cells and the question of etiopathogenesis for this enhanced apoptosis remains unanswered. In terms of neuropathology, AD is characterized by the aberrative accumulation and deposition of misfolded proteins. The extracellular deposit is made of accumulative neurotoxic amyloid (Aβ) and the intracellular deposit is made of misfolded protein TAU that is abnormally phosphorylated. Accumulation of Aβ starts with amyloid precursor protein (APP) that contributes to Aβ throughout enzymatic reactions. This process includes β-secretase in the first step, and afterwards another enzyme named gama-secretase, in the second. APP and both secretases are integral membrane proteins of neuronal cells, as it follows, they are in interactions with their membrane lipids. Dysregulated metabolism of lipids has been recognized as an important factor in the pathogenesis of AD. On the other hand when considering genetics, the presence of ε4 allele of the apolipoprotein E is one of the recognized genetic risk factor for sporadic AD.

Ceramide represents one of the lipids that gets huge attention[6]. A disorder in sphingolipid metabolism results in accumulation

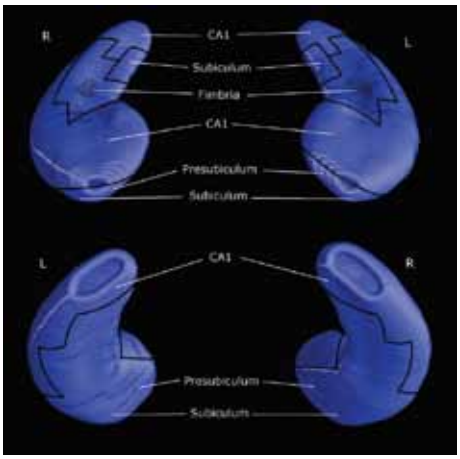

Fig 1. Cytoarchitectonic subregions mapped on blank MR-based models at 3T of the hippocampal formation of a healthy subject (Frisoni B G, Ganzola R, Canu E, Rüb U, Pizzini B F, Alessandrini F, Zoccatelli G, Beltramello A, Caltagirone C, Thompson M P (2008) Mapping local hippocampal changes in Alzheimer's disease and normal ageing with MRI at 3 Tesla. Brain 131: 3266-327)

of long-chain ceramides that are noticed in 'normal ageing' brain as well as in brains of AD-affected patients. Elevated basal serum level of ceramide is associated with higher risk for AD and consequently AD-affected patients show the same clinical finding in comparison to the 'normal ageing' brain. At higher concentrations ceramides promote the proapoptopic signal pathway. Aβ is neurotoxic in itself as well as ceramide, because they both promote apoptosis with their own signal pathways. Additionally, there is evidence that show an existing connection between ceramide and Aβ (figure 3.). Membrane ceramides embedded in lipid rafts promote the production of Aβ by increasing the half-life of the enzyme β-secretase through its posttranslational stabilization. The connection between Aβ and ceramide represents a positive feedback loop in terms of patophysiology. Aβ can activate NADPH-oxidases that produce superoxide radicals. Superoxide radicals are involved in the activation of neutral sphingomyelinases (N-SMases) that produce ceramides from sphingomyelin.

The role of nitric oxide

Nitric oxide (NO) is a diffusible free radical that has many physiological and pathological roles – from vasodilatation and neurotransmission to antimicrobial activity and neurodegeneration. NO is produced from arginine by nitric oxide synthase (NOS). There are several isoformes of NOS, with constitutional expression like endothelial NOS (eNOS), neuronal NOS (nNOS), or inducible expressed NOS (iNOS) in astrocytes and microglial cells.

There is a study[7] that discusses immunocytochemical distribution of nNOS compared to neuropathological changes in the hippocampal formation and entorhinal cortex of AD-affected patients as well as in age-matched control subjects. Several lines of evidence suggest an upregulation of NO production in the AD brain as shown by the activation of nNOS expression. Aβ stimulates the release of NO by forming calcium permeable channels in the membrane. It is postulated that NO mediates NMDA receptor-linked neurotoxicity and more recently, it has been suggested that nNOS expressing neurons of hippocampal formation and entorhinal cortex are highly susceptible to degeneration in AD. In that study, it was demonstrated that immunopositive nNOS areas surround Aβ plaques and in these areas a clear and overt neuronal loss is present. In earlier stages of AD, reactive astrocytes are present around the plaques. This suggest that neurotoxic effects of NO derived from large number of astrocytes may be an important mediator of the disease

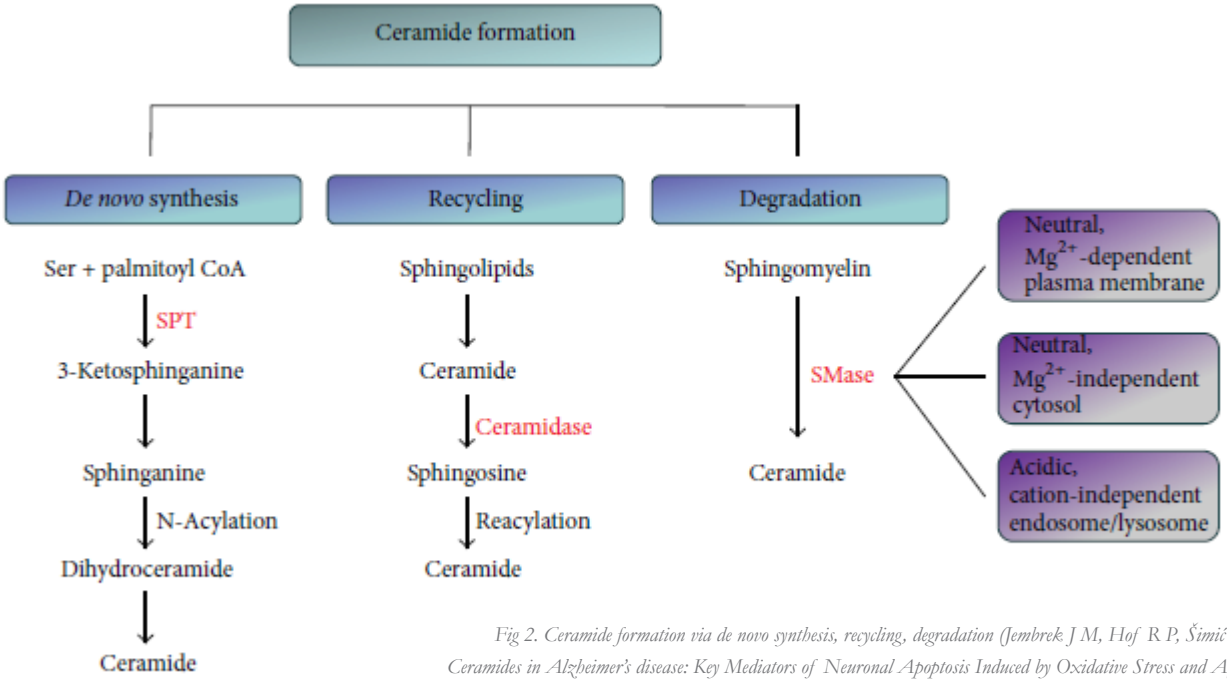

Fig 2. Ceramide formation via de novo synthesis, recycling, degradation (Jembrek J M, Hof R P, Šimić G (2015) Ceramides in Alzheimer's disease: Key Mediators of Neuronal Apoptosis Induced by Oxidative Stress and Aβ Accumulation. Oxid Med Cell Longev 2015: 1-17)

progression.

AD remains an incurable disease. One of the reasons for this is the sheer nature of the disease. AD is a complex neurodegenerative disorder with late-onset symptoms. Neurodegenerative changes are irreversible and the cure, when the symptoms are already clinically evident, still isn't in sight. Curing AD would have a better chance if there were early-onset biomarkers characteristic for this pathological entity. Through an early diagnosis, there would be a chance to stop or decrease the intensity of neurodegenerative progression which would lead to fewer AD symptoms. They could be avoided entirely or at least delayed for some time. These AD markers must have a sensitivity and specificity above 85 %. Additionally, other important factors which should not be neglected are: availability, non-invasiveness, reasonable pricing etc. Cerebrospinal fluid (CSF) could be used as a sample for searching biomarkers. As core biomarkers for AD[8], one can use the concentration of Aβ or TAU-protein (t-TAU, p-TAU) in CSF. Besides core biomarkers, other biomarkers could reflect AD pathological processes. These novel biomarkers are mostly related to Aβ metabolism, degeneration, inflammation and lipid metabolism.

These discoveries could provide us with a better understanding of AD pathogenesis and risk factors. As it was mentioned, a better prognosis could be achieved with an earlier diagnosis. Dementia is an irreversible state, so focusing researches and trying to find early-onset biomarkers for AD could ultimately lead us to a decreasing intensity of this particular disease. The number of people affected with AD is going to grow four times by the year 2050, which implies that AD will become a more and more well-known problem that will demand hard work and future research in order for better treatments regarding this disease.

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Kratki pregled patogeneze Alzheimerove bolesti

SAŽETAK:: Alzheimerova bolest je degenerativna neizlječiva bolest čija je glavna karakteristika demencija. Neki od simptoma bolesti su poremećaj u pamćenju, prosuđivanju, usmjeravanju pažnje i sposobnosti rješavanja problema. Obdukcijom se dokazalo da mozak zahvaćen Alzheimerovom bolesti izgleda kao i ostale demencije, na primjer: smanjena debljina kortikalne sive tvari, povećan obujam moždanih komora itd. Neuropatološki, Alzheimerovu bolest karakterizira poremećaj u akumulaciji i odlaganju pogrešno geometrijsko strukturiranih proteina. Otkriveno je da su ceramidi u membrani uključeni u patogenezu Alzheimerove bolesti aktivirajući enzim β-sekretazu (enzim koji katalizira akumulaciju Aβ). Također je primjećena specifična distribucija neuronalne NO-sintetaze u hipokampalnoj formaciji i entorinalnom korteksu u pacijenata oboljelih od Alzheimerove bolesti u usporedbi s kontrolnom grupom. Budući da je napredna neuronalna degeneracija ireverzibilno stanje, terapija bi imala smisla kada bi se liječilo u ranim stadijima. Stoga za istraživanje terapije trebalo bi gravitirati najprije otkriću pouzdanih biomarkera i razvoju tehnike za rano dijagnosticiranje Alzheimerove bolesti.

KLJUČNE RIJEČI: Alzheimerova bolest, TAU proteini, dušikov oksid;