Review Article

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Pathobiolgy and Management of Alzheimer's Disease

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Amyloid and tau protein abnormalities have been identified as the main causes of Alzheimer's disease but exact mechanisms remain to be revealed. Especially, amyloid beta and tau protein coupling and neuroinflammatory and neurovascular contributions to Alzheimer disease are quite mysterious. Many animal models and basic biological research are trying to solve these puzzles. Known as aging processes, autophagy, mitochondrial degeneration with generation of reactive oxygen species, and age-related epigenetic modifications are also known to be associated with development of Alzheimer's disease. Environmental factors such as bacterial and viral infections, heavy metal ions, diet, sleep, stress, and gut microbiota are also risk factors of Alzheimer's disease. Future development of preventive and therapeutic modalities may be dependent on the pathobiology of Alzheimer's disease.

Key Words: *Alzheimer Disease; Amyloid; tau Proteins; Apolipoproteins E*

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INTRODUCTION

Alzheimer disease is a serious disease in the era of the aged society. Aged society means people over age of 60 make up over 14% of total population and a super-aged society is over 20%. At present, aged society nations include all the developed countries and by 2030 they will be all super-aged societies.[1] According to current statistics nearly 50 million people suffer from Alzheimer associated dementia worldwide.[2] Dementia is a general term for loss of memory, language, problem-solving and other thinking abilities that are severe enough to interfere with daily life.[3] Alzheimer's disease (AD) is the most common etiology of the diseases causing dementia. Pathological hallmarks of AD include amyloid beta (Aβ) plaques, neurofibrillary tangles (NFTs), gliosis, and neuronal loss accompanied by cerebrovascular amyloidosis, inflammation and major synaptic changes.[4-7]

Recent advances in dementia research have revealed many secrets but still much needs to be elucidated about the biology, pathophysiology, clinical courses, prevention, and treatment. Among the theories of neurodegenerative mechanism causing Alzheimer's disease, the amyloid pathway is most well-known and widely accepted, but recent drug failures of amyloid reducing agents such as active and passive immunotherapies against amyloid beta have stoked controversy about their role in Alzheimer's disease. Besides, patterns of regional cerebral amyloid deposition do not correlate with patterns of regional cerebral hypometabolism on functional neuroimaging, which means amyloid deposition does not correlate with these patterns of brain dysfunction and cognitive dysfunction.[8,9] Other mechanisms besides the amyloid hypothesis are the tau hypothesis, the oxidative and mitochondrial dysfunction with autophagy abnormality theory, the inflammatory hypothesis, vascular dysfunction, aging with increased epigenesis, and other environmental factors such as viral and bacterial infections, heavy metals, and gut microbiota. According to such theories, many preventive and therapeutic modifications are under development.

HERITABILITY AND GENETIC INFLUENCE ON ALZHEIMER PATHOLOGY

The majority of Alzheimer's dementia patients onsets occur after age 65, constituting late-onset AD (LOAD), but rarer cases occurring earlier than age 65 are called as early onset AD (EOAD).[10] About 1-2% of AD is inherited in an autosomal dominant fashion and these patients show very early age of onset and a more rapid rate of progression. Highly penetrant mutations in Amyloid Precursor Protein (APP), Presenilin 1 (PSEN1) and 2 (PSGN2) are seen in hereditary familial AD and result in increased amyloid

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production.[11] The genetic predisposition in LOAD patients is considerable, with a heritability estimate of 60-80%.[12] The most common genetic risk factor is the apolipoproteinE (Apo E) gene, which is encoded by 3 common alleles: ε2, ε3, and ε4. The ε4 allele is associated with an increased risk for LOAD and one copy of the ε4 allele increases risk 3-4-fold and two ε4 copies increase by as much as 12-fold. Homozygous APOE4 carriers who develop AD also have a lower average ages of clinical onset of 68 years of age compared to an average age of onset of 84 for an individual with two copies of APOE3. One copy of APOE4 lowers the average age of onset to 76 years of age.[13] A wide range of compelling studies indicate that APOE4 affects the production, clearance and aggregation of Aβ. There is emerging data suggesting that APOE may also influence neuroinflammation and tau-mediated neurodegeneration.[14]

Large-scale collaborative GWAS and the International Genomics of Alzheimers Project have significantly advanced the knowledge regarding the genetic underpinnings of LOAD by identifying at least 20 additional genetic risk loci.[15] Several of these genetic risk factors encode proteins involved in microglial function and inflammation including TREM2, CD33, CR1, ABCA7 and SHIP1. Particularly the TREM 2 gene have been found to increase LOAD risk by 2-4-fold, similar to that in patients with one copy of APOE ε4.[16] Others, such as SORL1, BIN1, PICALM, CD2AP are associated with endosomal vesicle cycling and FERMT2 and CASS4 are involved in cytoskeletal function and axonal transport. The mechanisms related with the above risk genes can be summarized into the Aβ metabolism, neuroinflammation and intraneuronal vesicle, and tau-related cytoskeletal and axonal transport system.

AMYLOID HYPOTHESIS

Amyloid plaques, extracellular aggregates of amyloid beta (Aβ) proteins formed through abnormal proteolytic cleavage of APP have been reported to play a dominant role in the pathogenesis of AD. APP is a type 1 membrane protein with a short cytoplasmic region and extracellular domain which is synthesized in the endoplasmic reticulum, transported through secretary vesicles, and cleaved in the Golgi complex. Within the Golgi complex, APP is cleaved through either of two distinct metabolic pathways. The first cleavage is reportedly driven by α-secretase, resulting in the formation of a soluble ectodomain of APP (sAPPα), which may have neuroprotective effects. Whereas, β-secretase (BACE1) and γ-secretases dependent proteolytic cleavage of APP give rise to the formation of Aβ peptides fragments ranging in length from 39 to 43 amino acids. Among them 40 (Aβ40) and 42 amino acid (Aβ42) fragments are the most predominant forms. Aβ40 is soluble, less neurotoxic, and predominantly found in the healthy brain, while Aβ42 is highly neurotoxic, has a greater propensity to aggregate, and is predominantly found in brains with AD pathology.[17] Aβ peptides are prone to aggregate into β sheet conformations in the form of higher-order oligomers, protofibrils, and fibrils, which are detectable in AD brain. Owing to increased hydrophobicity of its expanded C terminus, Aβ42 has a greater propensity for aggregation.

Release of Aβ from neurons is modulated by synaptic activity, both presynaptically and postsynaptically.[18] The effects of Aβ on synapse activity vary with its extracellular concentration: low levels of Aβ promote excitatory activity and higher levels depress it. Small increases in amyloid-β levels promote activity through presynaptic acetylcholine receptors, which elevate internal calcium concentrations to increase the probability of glutamate release.[19,20] Although the postsynaptic excitation could lead to positive feedback in which the further release of Aβ increases synaptic excitability, increasingly high levels of Aβ actually depress synapse activity through several mechanisms that modify synapse strength, including the internalization of glutamate receptors.[21,22] Chronic elevations can weaken connectivity, alter the dynamics of dendritic spines, promote synapse loss and impair circuit-shaping processes that underlie learning and memory (especially in the area such as the hippocampus).[23-25] Amyloid-β-induced loss of dendritic spines can lead to hyperexcitable neurons that fire more easily, and amyloid-β also alters the balance between excitatory and inhibitory activity by influencing inhibitory interneurons. Loss of synaptic inhibition occurs through numerous pathways, including the downregulation of cell-surface voltage-gated sodium channels.[26]

The deposition of amyloids affects circuit connectivity and network activity. Initial cross-sectional studies of postmortem tissue showed amyloid-β deposition beginning in neocortical regions involved in cognition spreads to the neural hubs that underlie learning and memory, and finally progresses to the motor and sensory structures.[27] Some studies suggest Aβ propagates in a prion-like manner and undergo cell-to-cell transmission.[28,29] However, other studies propose the Aβ-induced circuit dysfunction affects networks and that local aberrant activity could lead to the accumulation of Aβ at downstream projection structures, becoming the sequential appearance of Aβ in the regions of connected networks.[30]

TAU HYPOTHESIS

Tau is a soluble microtubule-associated protein working as an anchor maintaining the stability of microtubular assembly in axons. Under normal conditions, there has been reported a balance between microtubule-associated phosphatase and kinase affecting phosphorylation-dephosphorylation states of tau. Under pathologic conditions, upregulation of kinases and down regulation of phosphatases give rise to increases in hyperphosphorylated tau proteins that are aggregation-prone and show less affinity for microtubules. Disassembly of tau proteins increase cytoplasmic pools of tau and further aggregation progresses to develop intracellular insoluble filaments and tangled clumps, known as neurofibrillary tangle (NFT).[31] Hyperphosphorylated tau is redirected from the axonal compartment to soma-

to-dendritic compartment and impairs synaptic function by inhibiting glutamate receptor trafficking or synaptic anchoring.[32]

The pathological tau propagation hypothesis is supported by numerous studies using mouse models, in which seeded synthetic tau fibrils of brain extracts from mice or human subjects of tauopathy were injected into the brain of tau transgenic or wild type mice and were found to induce pathological tau spreading at sites distal to the injection site (prion-like manner).[33-36]

Aβ can induce tau pathology in multiple APP transgenic animal models, whereas tau does not induce amyloid pathology or mutation in tau genes that have not been associated with AD, suggesting tau pathogenesis may be the downstream of Amyloid accumulation.[37,38] Aβ may contribute tau pathology with tau phosphorylation through the activation of tau kinase or Aβ-induced microglial activation and releasing inflammatory cytokines.[39,40] Longitudinal and cross-sectional studies of tau- and amyloid-PET imaging suggests that amyloid accumulation predicts the onset of tau accumulation whereas the rate of tau accumulation predicts onset of cognitive impairment.[41,42]

The mechanism of Tau pathology propagation from initial age-related accumulation in the entorhinal cortex and medial temporal lobes, even in the absence of cognitive decline (termed as primary age-related tauopathy: PART) into the neocortex is still need to be elucidated.[43] Network susceptibility is a putative theory which tau pathology develops in specific vulnerable networks and is possibly facilitated by amyloid pathology, which spreads transneuronally to closely related networks. This network vulnerability theory may explain the reason for different clinical phenotypes in AD such as typical amnestic, behavioral frontal, aphasic, and posterior cortical atrophy types. Hypometabolism, measured by FDG-PET in the dorsal default mode network and atrophy, measured by MRI in parietotemporal regions and posterior cingulate may be supportive of network propagation.[44-46]

NEUROINFLAMMATION

Neuroinflammation in Alzheimer's disease is described as a reactive gliosis with astrocytes and microglia accompanied by low to moderate levels of inflammatory mediators in the parenchyme. This reaction, both cellular and molecular, is not distinguishable between one disease and other conditions such as Parkinson's disease, amyotrophic lateral sclerosis (ALS), stroke, or traumatic injury. Given this lack of specificity, it is easy to conclude that the glial reaction is secondary to neuronal death or dysfunction and is accordingly unlikely to provide useful targets for therapeutic intervention or topics for intensive investigation.[47]

The neuroinflammatory hypothesis is supported by pathologic findings of autopsy brain sections and a population-based prospective study that used pharmacological records and showed a dose-related negative correlation between the use of nonsteroidal anti-inflammatory drugs (NSAIDs) during midlife and the likelihood of later developing AD.[48-50] In addition, recent genetic studies including genome-wide association studies (GWAS) have identified about 20 well-validated genes harboring risk alleles, of which about half are predominantly or completely expressed in the microglia.[51] TREM2 belongs to a family of receptors referred to as the triggering receptors expressed on myeloid cells (TREM). The TREM2 gene is exclusively expressed by microglia in brain.[52] TREM2 enhances the rate of phagocytosis and modulates inflammatory signaling. Also, it has been shown to modulate microglial number, proliferation and survival. Several rare variants in TREM2 have emerged that significantly increase AD risk but how TREM2 variants exactly alter AD remains unclear.[40]

Aβ oligomer can stimulate microglial proliferation and activation. Activated microglia can release proinflammatory cytokines such as interleukin 1β, 6, tumor necrosis factor 6 and enhance oxidative stress through induced reactive oxygen species (ROS) generation. Further hyperactive microglia may impair synaptic function by stimulating synaptic pruning. In addition, neuroinflammation may increase Aβ accumulation through disturbance in phagocytic Aβ uptake and clearance.[53]

NEUROVASCULAR THEORY

The vascular theory of AD can be divided into 2 mechanisms. One is Aβ dependent vascular dysfunction and the other is vascular dysfunction can induce Aβ accumulation and downstream tau pathology and neuroinflammation. According to the results in animal models, Aβ dependent vascular changes include reduced cerebrovascular reactivity to endothelium-dependent and increased response to vasoconstrictors acting directly on vascular smooth muscle cells, as well as Aβ-mediated oxidative stress in cerebral blood vessels and diminished neurovascular coupling.[54]

Hypertension (HTN) is a risk factor for AD. A number of studies have shown that HTN alters functional hyperemia and endothelial function. Angiotensin II-induced HTN in mice worsens Aβ-induced neurovascular dysfunction and promotes β-secretase activity increasing amyloidogenic APP processing, which may contribute to the pathogenic interaction between HTN and AD.[55]

CBF reductions and vascular dysfunction were also found in apolipoprotein E4 (APOE4) transgenic mice with targeted replacement of murine APOE with human APOE4 gene.[56] Using CO2 inhalation challenges in cognitively normal APOE4 carriers compared to APOE4 non-carriers confirmed impaired CBF responses, suggesting that early CBF dysregulation contributes to cognitive impairment in APOE4 carriers.[57]

Cerebral blood flow (CBF) in vivo can be measured by single positron emission computed tomography (SPECT) or Arterial spin labeling (ASL) MRI. Individuals with mild cognitive impairment and probable AD showing regional CBF reductions in posterior cingulate gyrus, precuneus,

inferior parietal area, and lateral prefrontal cortex.[58,59] The resting state fMRI, also called brain "default-mode network" (DMN), typically includes the medial prefrontal cortex, the posterior cingulate and precuneus, inferior parietal lobe, lateral temporal cortex, and hippocampus. Due to the tight relationship between blood flow and neuronal activity, decreased BOLD (decreased blood oxygen-dependent)-fMRI signals indicate decreased regional cerebral flow and regional cerebral dysfunction, suggesting disrupted connectivity in the network. A decreased resting-state activity in the posterior cingulate and hippocampus was reported in subjects during early stages of AD when compared to age-matched elderly controls. In addition, disrupted hippocampal connectivity was also confirmed in the medial prefrontal cortex and cingulate cortex in AD compared to cognitively normal controls.[60,61]

AGING, AUTOPHAGY, AND EPIGENETICS

Given the higher the incidence of neurodegenerative diseases in older subjects, it tends to regard neurodegenerative diseases as clinical expressions of accelerated aging. However, many neurodegenerative diseases such as AD, PD, Huntington's disease, and ALS are so different from each other that a universal aging mechanism cannot explain each disease process.

Biologic Ageing of cells can be dissected into 1) a loss of protein homeostasis that leads to the development of aggregates and inclusion bodies, 2) DNA damage, 3) lysosomal dysfunction, 4) epigenetic changes and 5) immune dysregulation. The genetic predisposition of an individual, together with his or her exposure to the environment, determine the incidence and prevalence of the lesions that result from such processes, probably in a cell-specific manner.[62]

Most neurodegenerative diseases are associated intracytoplasmic deposition of aggregate-prone proteins in the neuron. For example, tau in Alzheimer's disease, frontotemporal dementia, ALS, and alpha-synuclein in Parkinson's disease. Autophagy ("self-eating") is the process through which parts of cell are degraded in the lysosome. Physiologic role of autophagy may be recycling of cellular components, which is removing unnecessary or dysfunctional components. Three types of autophagy involving different modes of cargo delivery to the lysosome are commonly described as macro-autophagy, micro-autophagy, and chaperone-mediated autophagy. In macro-autophagy, the most common form, cytoplasmic components (damaged mitochondria known as "mitophagy", ruptured lysosome known as "lysophagy", infectious particles known as "xenophagy") are targeted and isolated from the rest of the cell within a double-membraned vesicle known as an autophagosome.[63] Autophagy is up-regulated during starvation and aerobic exercise, degrading macromolecules to produce the nutrients that are required as building blocks or energy sources. Autophagy plays homeostatic roles, particularly in long-lived populations of cells such as neuron or muscle cell, in which obsolete material cannot be diluted by cell proliferation. Autophagic activity is reduced during aging and mutations in autophagy-related genes have been linked to numerous human neurodegenerative diseases.[64]

Mitochondrial biogenesis occurs on a regular basis in healthy cells where mitochondria constantly divide and fuse with each other and also occurs in response to oxidative stress, increased energy demand, exercise training and certain diseases. Mitophagy is the process by which damaged or dysfunctional mitochondria and an excess of reactive oxygen species (ROS) may function as an autophagy trigger. ROS is the main source of DNA or intracellular organelle damage. However, Increased formation of ROS within the mitochondria may cause an adaptive reaction which produces increased stress resistance and a long-term reduction of oxidative stress. This kind of reverse effect of the response to ROS stress has been named mitochondrial hormesis or mitohormesis and is hypothesized to be responsible for the respective lifespan-extending and health-promoting capabilities of glucose (calory) restriction and physical exercise.[65]

Epigenetics is the study of heritable phenotype changes that do not involve alterations in the DNA sequence. Epigenetics most often involves changes that affect gene activity and expression. Changes in the epigenome during aging lead to alterations in gene regulation and genomic instability, mainly contributing to the appearance of age-related diseases such as cancer and neurodegenerative diseases. Aberrant gene expression, genomic instability, and the loss in chromatin structures are three of the characteristics associated with both aging and multifactorial or complex diseases. Epigenetic mechanisms include methylation or hydroxymethylation of DNA, chromatin remodeling and histone modifications, histone acetylation and deacetylation, histone methylation, and non-coding RNAs and microRNAs.[66]

ENVIRONMENTAL: INFECTION, TOXIN, LIFESTYLE, GUT MICROBIOTA

Meta-analysis from various literature databases indicate that AD risk increased 1.3 times with HSV in the brain, and risk increased 2.7 times in concurrent HSV-1/APOE4 carriers compared to controls.[67] Epidemiological studies indicate that HSV-positive individuals feature markedly higher risks of developing AD compared to seronegative subjects, and antiviral therapy reduced AD onset.[68] Periodontal bacterial infection by pathogens such as Porphyromonas gingivalis may also play a role in AD. Specific proteins and DNA from P. Gingivalis have been identified in the AD brain. Oral P. gingivalis infection increases Aβ42 generation, where Aβ42 can also be toxic to P. Gingivalis.[69] This antimicrobial property of Aβ suggests intracerebral infection by certain pathogens may induce Ab fibrillization as an antimicrobial defense mechanism, leading to amyloid seeding and deposition and thereby initiating the amyloid cascade.[70]

Post-mortem analysis in AD patients reveals the accu-

mulation of metal ions such as copper, iron, and zinc (5.7, 2.8 and 3.1 times, respectively) over levels observed in the normal brain, demonstrating a close correlation between AD and redox metal dysregulation.[71]

Vulnerability to stress and higher levels of anxiety are significantly associated with the incidence of dementia. Environmental and external stress can lead to psychological stress and the subsequent cellular stress exacerbated by inflammation and oxidative damage, through the mainly glucocorticoid cascade hypothesis.[72,73]

Sleep disorders increase AD risk and about 15% of AD cases may be attributed to sleep problems.[74] In humans, SD increases CSF levels of Aβ38, Aβ40, and Aβ42 through the enhancement of Aβ production. In animal models of AD, chronic mild sleep restriction aggravates contextual memory impairment, cortical Aβ accumulation and tau hyperphosphorylation.[75,76]

Alterations in the gut microbiota composition induce increased permeability of the gut barrier and immune activation leading to systemic inflammation, which in turn may impair the blood-brain barrier and promote neuroinflammation, neural injury, and ultimately neurodegeneration. Bacterial amyloids through molecular mimicry may elicit cross-seeding of misfolding and induce microglial priming. Aβ seeding and propagation may occur at different levels of the brain-gut-microbiota axis.[77]

A high fat diet is thought to contribute directly to several key aspects of AD, including increased accumulation of Aβ, tau hyperphosphorylation, and inflammation of peripheral organs and brain. Also, high dietary salt is a risk factor for dementia. A very recent study shows that high dietary salt leads to cognitive dysfunction of mice by promoting tau hyperphosphorylation through the activation of tau kinases.[78-80] Above all the etiological agents are summerized in Table 1.

PREVENTIVE AND THERAPEUTIC MODALITIES TAILORED TO ALZHEIMER'S DISEASE STAGE

1. Preclinical Alzheimer's disease

A hallmark of AD is a typical neuropathological finding characterized by amyloid beta and tau depositions. The beginning events of AD may be the amyloid deposition because amyloid plaques have been known to precede intracellular neurofibrillary tangles. Amyloid deposition in the brain of cognitively normal individuals is commonly observed in postmortem studies, CSF and amyloid PET studies. The prevalence of positive Aβ increases with older age as well as APE4 genotypes, but is rare before age 60.[81] Comparing several epidemiologic studies and a large autopsy series, temporal lag between the deposition of Aβ in an autopsy and clinical AD dementia has been disclosed to be about 10-15 years.[82-85]

In 2018, the National Institute on Aging and Alzheimer's Association (NIAA-AA) working group published a research framework which defines separate diagnostic rec-

TABLE 1. Summary of pathobiology and management in Alzheimer's disease

Etiological agents	Pathobiology	Prevention and management
Amyloid	Direct Aβ neurotoxicity	Monoclonal Ab therapy for Aβ removal
	Aβ-related synaptic/circuit/network dysfunction	BACE inhibitor reducing Aβ production
Tau	Direct tau neurotoxicity	Tau aggregation inhibitor: TRx0237 (LMTX)
	Disruption of neuronal cytoskeleton	Active tau vaccine: AADvac1
	Pathologic tau trans-synaptic spreading	Anti-tau antibody: Zagotenemab (LY3303560)
Neuroinflammation	Microglial proliferation and activation	Target specific anti-inflammatory drugs such as the cytokine-suppressive anti-inflammatory drugs (CSAIDs)
Neurovascular injury	Aβ-induced neurovascular dysfunction	Control of vascular risk factors such as hypertension, diabetes, hyperlipidemia, obesity, smoking, alcohol consumption
	APOE4-related cerebral blood flow reductions and vascular dysfunction	
Aging	Autophagy	Free radical scavengers (antioxidants)
	Increased mitochondrial ROS production	Mitohormesis
	Change in the epigenomes	
Infection	Herpes simplex virus infection	Aggressive treatment of herpes virus
	Periodontal bacterial infections	Zoster vaccination
		Oral hygiene
environmental toxins	Heavy metals such as copper, iron, zinc	Avoiding exposure to heavy metals, air pollution
	Air pollution	
Lifestyle	Stress and anxiety	Lifestyle modification
	Sleep deprivation and sleep disorders	Sleep hygiene and enough sleeping
	High fat diet	Mediterranean diet, DASH (Dietary Approaches to Stop Hypertension) diet
	High dietary salt	
Gut microbiota	Alterations in gut microbiota composition	Oligomannate, derived from a compound in seaweed, suppresses neural inflammation caused by gut bacteria in mice: GV-971, approved in China
	Bacterial amyloids	

ommendations for the preclinical, mild cognitive impairment, and dementia stages of Alzheimer's disease. They declared that The term "Alzheimer's disease" refers to an aggregate of neuropathologic changes and thus is defined in vivo by biomarkers and by postmortem examination, not by clinical symptoms.[86] According to their definition, the preclinical AD stage means Aβ deposition in cognitively normal subjects without any evidence of neurodegeneration or neuronal injury such as cortical atrophy by MRI, pathologic tau by CSF phosphorylated tau or positive tau PET, and hypometabolism by FDG PET. The clinical AD stage defines MCI or dementia with Aβ pathology, pathologic tau, and neuronal injury. Fig. 1 shows the stages of AD and the correlation pattern of biomarkers such as cognition, Aβ deposition, pathologic tau and neuronal injury (brain atrophy).

A common concern is why so much time (as long as a decade or more) is needed to develop clinical symptoms. The "Cellular phase of AD" proposed by Bart De Strooper and Eric Karran may be a possible answer. They propose that accumulation of cerebral amyloid and tau pathology (the "biochemical phase") is a slow, gradual process that is tolerated by CNS cells early in the course of disease, serving as a risk factor for development of clinical disease, but that the disease only manifests clinically when cellular homeostatic mechanisms fail, leading to impaired clearance of aggregated pathologic protein (proteopathy), increased cellular stress, and a complex breakdown of finely tuned intercellular physiologic functions that ultimately lead to neurodegeneration.[87] Another mechanism may be a resilience factor. There are individuals who are inherently resistant to the initiation or spread of neurodegeneration. Or some external preventive mechanisms may be contributed.

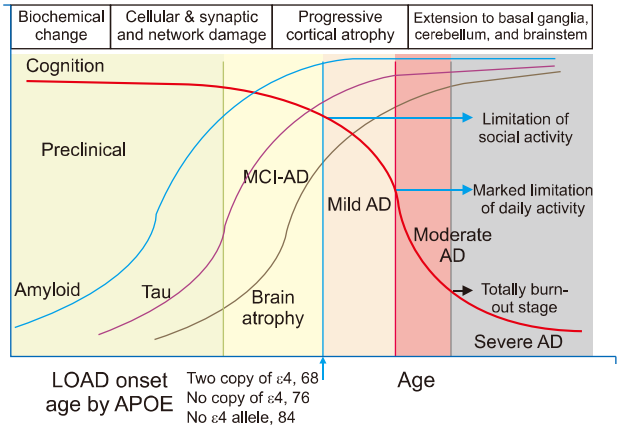

FIG. 1. Stages of Alzheimer's disease and changes of biomarker. As cognition decreases, the continuum of Alzheimer's disease is divided into the preclinical stage, MCI, mild AD, moderate AD, and severe AD. Biomarkers are cognitive tests, amyloid tests such as level of CSF amyloid beta or amyloid PET CT, tau tests such as level of CSF phosphorylated tau or tau PET, and structural changes in brain MRIs. MCI: mild cognitive impairment, AD: Alzheimer's dementia, LOAD: late-onset Alzheimer's disease, CSF: cerebrospinal fluid, PET CT: positron emission tomography computed tomography, MRI: magntic resonance image.

So, this stage seems to be the exact time to do preventive modalities. According to APOE gene risk results, high risk patients develop clinical symptoms around age 68. So, the time to do prevention may be as early as the mid-50s. According to above mentioned environmental risk factors, control of midlife hypertension, reducing salt intake, decreasing body weight, a low-fat diet, sleeping enough, decreasing anxiety and stress, and avoiding the intake heavy metals are the relatively easy rules to follow. A little more difficult ones may be calorie restriction such as intermittent fasting or heavy exercise for increasing autophagy or mitohormesis. In addition, aggressive treatment of herpes simplex or zoster infections and zoster vaccination may be helpful. Clean care of oral flora and making good gut microbiota through lactobacillus products and fermented foods may be also beneficial.

2. Clinical Alzheimer's disease

Mild cognitive impairment (MCI) is a quite ambiguous term which is the stage between the expected cognitive normal for an age and the more serious decline of dementia. It is divided into memory dominant impairment, amnestic MCI and non-memory dominant, non-amnestic MCI. Amnestic MCI is considered as transitional stage of AD. Annual conversion rates of MCI to AD often range from 10% to 15% in clinical samples. Conversion rates in community-based studies are often substantially lower (i.e., 3.8%-6.3% per year).[88]

Pathobiologically, MCI can be the stage of cellular failure and network dysfunction through tau pathology superimposed on amyloid deposition followed by neuroinflammation. Therefore, the main treatment target should be tau and neuroinflammation. This may be a reason why anti-amyloid therapies have failed. The earlier the amyloid treatment starts before tau pathology extension beyond the hippocampus and medial temporal region, the better outcomes can be expected. In spite of repeated failures of anti-amyloid therapies, continuous drug trials have been underway and recently a Adcanumab (Biogen and Eisai company) trial was reported to be continuing to show dose-dependent amyloid removal and slowing cognitive decline and awaits FDA approval. However, anti-amyloid immunotherapy has a disturbing common side effect, amyloid-related imaging abnormalities (ARIA) which is an MRI white spot, representing vasogenic edema, although mostly asymptomatic and transient. Unfortunately, anti-tau treatments have not been developed and anti-inflammatory treatments through drugs modifying general inflammatory processes such as nonsteroid anti-inflammatory drugs (NSAIDs), prednisone, and intravenous immunoglobulin (IVIg) did not show any cognitive benefits in mild to moderate AD.[18]

In the future, target specific anti-inflammatory drugs such as the cytokine-suppressive anti-inflammatory drugs (CSAIDs) would be preferable. CSAIDs target pro-inflammatory signal transduction pathways in microglia and as-

troglia, and thus they decrease the production of cytotoxic cytokines, such as TNF, and free radicals, such as nitric oxide.[89]

Differentiating between MCI and early dementia is very difficult because of the limitation of daily activity, a key feature of dementia, is contributed to by many other factors besides cognitive deterioration such as hearing or visual difficulty, spine and joint problems, socioeconomical factors, and psychiatric illness such as depression. Treatment targets in this stage aim at cognitive reinforcement, decreasing emotional and behavioral perturbations, stabilizing diurnal disturbances such as sleep wake cycle, appetite change, and urinary and fecal control. There are just 5 FDA approved drugs including 4 acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine, tacrine is not available) which increase acetylcholine concentration in the brain and 1 glutamate antagonist. Clinical indications of these drugs are mild, moderate, and severe (only for donepezil) Alzheimer's disease, Parkinson disease dementia (rivastigmine only), but not MCI or vascular dementia. The NMDA antagonist, Memantine is approved to treat moderate-to-severe Alzheimer's disease but it is less effective for increase in cognition but has been reported to be effective for behavioral turbulences such as agitation and irritability. When dementia progresses, Behavioral and psychological symptoms of dementia (BPSD) are common, which are cognitive/perceptual (delusions, hallucinations), motor (e.g., pacing, wandering, repetitive movements, physical aggression), verbal (e.g., yelling, calling out, repetitive speech, verbal aggression), emotional (e.g., euphoria, depression, apathy, anxiety, irritability), and vegetative (disturbances in sleep and appetite).[90] For the control of BPSD antidepressants, benzodiazepines, antipsychotics, and anticonvulsants are frequently prescribed. However, as dementia deepens, drug therapies, especially behavior-control drugs, may aggravate the patient's condition because of sedation, frequent falling, loss of appetite, and increased gastrointestinal problems. Stable and comfortable environmental conditions, behavioral modifications, and a sufficient caregiver labor force are more important and these are expensive and becoming a burden to society and national economies.

SUMMARY

Still there are many unsolved problems in the mechanism, diagnosis, prevention and treatment of AD. Now protein aggregation disease is a main etiological process in most neurodegenerative diseases. Genetic predispositions and environmental factors may intersect and influence on the onset age, speed of progression, and clinical phenotypes of theses neurodegenerative diseases. Alzheimer's disease is main problem now and is getting more serious as time goes by. Complete treatment may never be possible. Delaying the onset of the disease process or clinical manifestation should be main target at the present. Blocking of the disease process through intervention on amyloid and tau accumulation seem to be ideal, but there may significantly meaningful physiological functions in amyloid beta or tau proteins and chronic removal of these proteins may evoke serious long-term side effects. Preventive modifications disclosed by epidemiologic evidences may be the slow, but safe remedy for Alzheimer's dementia.

CONFLICT OF INTEREST STATEMENT

None declared.

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