

Potential Implication of Treatments for Alzheimer's Disease: Current and Future

Diatri Nari Lastri, Tiara Aninditha, Yetty Ramli, Jan Sudir Purba*

Department of Neurology, Dr. Ciptomangunkusumo General Hospital, Faculty of Medicine, Universitas Indonesia, Jalan Diponegoro No 71, Jakarta, 10430, Indonesia.

*Corresponding Author: Jan Sudir Purba, Department of Neurology, Dr. Ciptomangunkusumo General Hospital, Faculty of Medicine, Universitas Indonesia, Jalan Diponegoro No 71, Jakarta, 10430, Indonesia.

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Abstract

Alzheimer disease (AD) is a long-term and progressive neurodegenerative disorder, characterized by both structural abnormalities and inflammation in the brain. Patients suffering from AD lose autonomy in their daily normal activities that steadily worsens memory and communicating skills, often accompanied by visual disturbances, eventually leads to a disabled person of performing simple daily tasks. Pathologic characteristics of AD are β -amyloid ($A\beta$) plaques, neurofibrillary tangles. Current therapies till now only target the relief of symptoms using various drugs and psychotherapy and do not cure the disease. Unfortunately, few chemical drugs designed for clinical applications have reached the expected preventive or therapeutic effect so far, and combined with their significant side-effects. Traditional Herbal Medicine has accumulated many experiences in the treatment of dementia during thousands of years and modern pharmacological studies have confirmed the therapeutic effects of many active components derived from herbal medicines. Recently, stem cell therapy holds a great promise and provides a great research opportunity and has been shown to be a potential approach to various diseases, including neurodegenerative disorders. Here we review several stem cell transplantation studies with reference to both preclinical and clinical approaches. In this review, we focus on the need for developing herbal medicines and stem cell therapies for AD.

Keywords: alzheimer's disease; amyloid beta protein; visual disturbances; inflammatory process and herbal medicine; Stem cell therapy

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease associated with various disruptions such as language, executive, attention, and visuospatial function with progressive decline in cognitive function [1]. This disease was first discovered in 1901 by Alois Alzheimer, a German psychiatrist, in a woman 51 years old. This patient's condition is referred by Alzheimer's as "amnesic writing disorder" with the patient's psychosocial abnormalities including aphasia and memory disorders [2]. Impaired cognitive function is actually part of the aging process. To distinguish it from AD must go through a series of anamnesis against the patient along with information from family members. In this patient a physical examination, cognitive examination using Mini-Mental State Examination (MMSE) and other supporting examinations. Petersen et al. (1999) ³ found in his study a transition stage between dementia in the elderly and dementia with AD. This transitional stage is called mild cognitive impairment (MCI). Patients with MCI found a decline in cognitive function that is not found in other people of the same age. Daily activities at MCI are still normal even though memory complaints have started to appear. In the normal aging process complaints of dementia can

get worse at around 1-2% within 1 year [3,4] while about 10-15% in patients with amnesic type MCI can progress to the next stage namely AD prodromal stage. The prodromal stage is the very early form of AD when memory is deteriorating but a person remains functionally independent, a person must have an MCI also have a positive biomarker test. The biomarker tests can be a protein that is measured in cerebrospinal fluid (CSF) or a new type of scan with positron emission tomography (PET scan) that can detect the amyloid protein ($A\beta$) that accumulates in the brain in people with AD. In patients with AD with prodromal stage within a period of 3 years can increase to 20% [5] and can continue to reach about 50% in the next 5 years [3]. Neuropsychiatric disorders that appear on the MCI range from 43-59% [6], where the same symptoms can also appear in sufferers of early stages of AD. Another prominent symptom that is often found is visual disturbance. This disorder arises due to local pathology in the parieto-occipital region so that it is often referred to as a visual variant of Alzheimer's disease (VVAD) [9]. Deficits in visual function greatly affect daily functioning and quality of life and can explain the increased risk of falls and fractures. AD can affect visual pathways and visual cortex and result

in various visual changes and problems. However, how early the visual dysfunctions occur in AD is still a matter of discussion.

Epidemiology

Epidemiological studies in a number of countries in Asia in 1998 found that around 24.3 million people were suffering from dementia where women had a higher risk of AD than men [10]. This number of sufferers continues to increase so that in 2015 "Alzheimer's Disease International" estimates the number of AD sufferers worldwide to reach 46.8 million, with a global cost of around US \$ 818 billion [11]. In line with the increasing in life expectancy in various countries in the world this number is expected to increase fourfold in 2050 reaching up to 115 million AD patients [12,13,14].

Etiology

The etiology of Alzheimer's disease has not been known with certainty. However, through a number of studies both epidemiologically and biologically suspected to be caused by various causes including the aging process, the influence of toxic substances such as aluminum, heavy metals, hyper - and / or hypo thyroid, diabetes, auto immune and inflammatory processes in the form of A β protein accumulation [15,16]. In addition free radicals, capitis trauma and prolonged stress and severe depression are also thought to be stimuli for the occurrence of this disease [17]. Genetic disorders related to abnormalities on chromosomes [14,19,21]. are often associated as causes of AD [18,19]. The E4 variant of the apolipoprotein (ApoE) gene on chromosome 19 was identified as a susceptibility gene to late-onset Alzheimer's disease, which tends to decrease age at the onset of disease [20]. However, in general direct pathogenesis of AD has not yet been discovered by researchers. Concerning the onset at a certain age, it was found that the onset patients with older age had a better prognosis compared to their onset at a young age [21].

Neuropathology

Cognitive decline in AD results from loss of neurons and neuronal processes, which results from various factors. The pathway for the synthesis and degradation of toxic proteins in AD has been carefully studied to determine the most effective disease management [22].

Imaging

Magnetic resonance imaging (MRI) examination of the brain of Alzheimer's patients shows atrophy in the form of widening of the sulcus and the ventricles and thinning of the gyrus resulting in a decrease in brain weight. The size of brain atrophy correlates with neuropathological development [23,24] and the level of cognitive impairment [24,25]. This reduction in brain weight can reach more than 35%.

Histopathology Biomarker and Neuroinflammation

Histopathological examination found extracellular accumulation of A β protein, neurofibrillary tangles (NFT) in the hippocampus [26,27,28] which could damage neurons such as cholinergic neurons in the Nucleus Basalis of Meynert (NBM) as a producer of acetylcholin neurotransmitters resulting in memory disorders [29]. The human brain exists and functions with a degree of immunologic isolation. The blood brain barrier (BBB) chiefly serves this purpose by limiting access of blood-derived products to the CNS. In healthy individuals, the BBB limits the entry into the CNS of A β from the serum. The structural changes characterizing AD comprise an accumulation of A β that should not otherwise be present in the CNS, indicating a loss of BBB functionality [30]. Stacking of plaque A β protein in brain tissue can be caused by impaired secretion of A β / production of neurons accompanied by disruption to blood circulation due to malfunction of the BBB [31].

Excessive A β formation can be due to genetic mutation of amyloid peptides derived from amyloid precursor protein (APP) [32,33]. Increased A β production can be a stimulus factor for the inflammatory process in AD [31]. Basically A β is a group of endogenous proteins in neurons and secreted as the production of neuronal metabolism. Physiologically, A β as a group of other neuromodulatory proteins is important to guarantee the brain's function in transferring information between synaptic neurons for example in terms of learning and memory [34]. This is evident from research data which shows that A β secretion results in increased synaptic activity. This can also be proven if the production of A β is inhibited or eliminated, for example through the administration of anti-A β drugs, the communication between neurons will be disrupted [34]. The formation of amyloid plaque in the brain is thought to begin before the onset of dementia, and the process involves low-density lipoprotein (LDL) lipid profiles, ApoE4, A β which can be examined in plasma, blood, eye fluid and eye piece. In healthy people the level of A β secretion is regulated through a feed back process. Therefore one possibility that occurs in patients with Alzheimer's disease is a feed back reaction disorder so that the production of A β takes place without any inhibition that causes buildup as amyloid plaque. This amyloid plaque buildup by the immune system in this case microglia is seen as toxic [35, 36]. Microglia are part of the immune system in the central nervous system [35], playing a role similar to macrophages. In a healthy brain, microglia are at rest and become active if there is infection or nerve tissue damage [35,36,37]. Microglia also have the ability to secrete reactive oxygen species (ROS), nitric oxide (NO), interleukin-1-beta (IL-1 β), and tumor necrosis factor-alpha (TNF α) function in dealing with the entry of pathogenic objects in the brain. However, these substances can also be neurotoxic causing neuron damage such as the formation of plaque which also acts as an immunologic trigger which then re-activates microglia [36,38].

This activation is actually needed for the purpose of clearing the accumulation of A β through phagocytic processes using Toll-like receptor 4 (TLR4) [39]. This hope is supported by a number of epidemiology studies demonstrating that patients who took nonsteroidal anti-inflammatory drugs (NSAID) had lower risk of developing AD. However, clinical trials of anti-inflammatories have not shown effectiveness, and in recent years, the concept of immune therapy has become a treatment option as animal studies and clinical trials with A β vaccines have demonstrated enhanced amyloid removal through stimulation of microglial phagocytosis [40].

Neuropathology and visual disruption

In addition to cognitive and memory disorders sufferers of AD also often found impaired visual function. This visual disturbance is often found in the form of decreased visual acuity and impaired perception of three-dimensional objects and perception of motion [41,42,43]. This disorder is thought to occur due to local pathology in the parieto-occipital region which is often referred to as a visual variant of Alzheimer's disease (VVAD) [9].

From the neuro-ophthalmological examination by Rizzo et al., (1992) [44] it was found that visual disturbances in AD are dominated by pathological events in the associated cortex compared with disorders in the retina or n. opticus. Armstrong, (1996) [45] found in AD patients specific densities of plaque and tangles in the area of the primary visual cortex (lingual gyrus and cunealis) where the density of plaque and NFT in the cuneal gyrus was denser than in lingual gyrus [46]. Goldstein et al. (2003) [47] identified the accumulation of A β in supranuclear lens cataracts which is an early sign of AD pathology [48,49,50]. Furthermore, the clinical and biochemistry examination shows the similarity of the process of cataracts with AD in terms of etiology and mechanism of disease. AD sufferers in addition to suffering from glaucoma also often show degeneration of the optic nerve and cell loss in the retinal ganglia [51,52]. In the initial phase of AD it is found that it loses character from

the lining of the retinal nerve tissue and constriction of the veins which is thought to cause a decrease in blood flow from the retina to the vein [48]. Wostyn et al. (2009) [52] found decreased cerebrospinal fluid pressure (CSFP) in trans-laminar cribrosa which could reach about 33% lower than normal. It is suspected that a decrease in CSFP in AD gives an opportunity for glaucoma [52].

General Treatment for Alzheimer's Disease

Until now, efforts to develop target-specific drugs have not been successful. The progressive and destructive nature of AD requires breakthrough therapy to meet unmet patient needs. Cell-based therapy can offer a promising solution to this need. They may not only be able to reverse the development of AD but also improve cell function.

Non-Pharmacological Therapy

The goal is to help maintain or improve cognitive function by increasing daily activities such as doing light work. This can improve behavioral symptoms such as sleep disorders, stress and depression [53].

Pharmacological Therapy

At present to improve cognitive abilities, patients diagnosed with AD are currently treated with acetylcholinesterase inhibitors (donepezil, rivastigmine or galantamine) to improve cognitive abilities. Furthermore, memantine (NMDA receptor antagonist), being an additional treatment option for more severely-affected AD patients. These drugs, as measured by different psychometric parameters have been demonstrated to have an effect on slowing the progression of the disease, however, it is widely accepted that their effectiveness is limited [54,55].

Herbal Therapy

It is already known that the aggregation of A β into fibrillary amyloid plaques is a key pathological event in the development of the AD. Amyloid-beta plays an important role by inducing microglia activation. Once activated, microglial cells promote the release of reactive species and cytokines that are known to enhance immune responses in AD brain [56]. It is known that the entry and exit of substances from peripheral circulation to the brain tissue depends on the BBB. One problem for AD-targeted drugs is whether they can cross the BBB [30,57].

As is known that herbal medicine is the oldest and still the most widely used system of medicine in the world today and phytochemicals are the chemical molecules contained in plants not usually processed for pharmacological purposes. Phytochemicals and other herbal medicines are found to be useful in preventing or treating many neurodegenerative conditions, especially Alzheimer's disease [58]. Phytochemicals influence the function of various receptors for both excitatory and inhibitory neurotransmitters in the brain and thus can maintain or alter the chemical balance of the brain [59]. Several studies have shown that the herbal medicine contain many potential alkaloids, and they can counteract oxidative stress on the nervous system and act as anti-inflammatory drugs on aging brain [60]. It is also mentioned that some of the monomers extracted from Chinese herbal medicines can cross the BBB and exert therapeutic effects directly in the brain. Others cannot, and may act as prodrugs that can be cut into smaller molecules by enzymes, and can subsequently cross the BBB [61]. Other studies have also found that some monomers extracted from *Radix Salviae miltiorrhize* (Danshen) can cross the BBB. Tanshinone IIA can be detected in blood in the brain within 5 minutes after intraperitoneal injection in rats, which indicates that it can cross the BBB directly in rats [62]. Danshensu, another monomer extracted from Danshen, can also cross the BBB of the Sprague Dawley Rats and reach a relatively high level in 15 min in the brain intravenously [63]. Ginsenoside Rg1, one compound of *Radix Ginseng*, can barely transport through the BBB [64], and compound K and 20 (S)-

protopanaxatriol (PPT) metabolites of ginsenosides, exert biological activities in brain [65].

As is known that A β deposits are a pathological feature of AD, and therefore A β depletion can be a useful therapy to develop. One type of cysteine protease from the papain superfamily, which is able to degrade peptides and proteins, is cathepsin B. Cathepsin B can enter the endolysosomal system through endocytosis or phagocytosis. Hook et al. [66] and Mueller-Stein et al [67], reported that extracellular cathepsin B is associated with amyloid plaque, collocalizing with A β in the brain chromaffin cell secretory vesicles and can reduce A β production by limiting proteolysis activity, so that it can be classified as a therapeutic candidate for AD [67]. Another type of herbal drugs is Glutathione which acts as an antioxidant against neurons that react with reactive oxygen species (ROS) and forms glutathione disulphide [68]. Vitamin E as another endogenous antioxidant with high levels can protect the lipid peroxidation process, has been shown to reduce the risk of AD [69]. Vitamin C is a water-soluble antioxidant that is needed to reactivate vitamin E. Although vitamins C and E have been used in clinical applications to prevent AD but do not show a clear therapeutic effect [68]. Amyloid β plays an important role in AD by inducing microglia to enhance immune responses in AD brain. Therefore, drugs that can function as negative regulators of microglia activation are considered as potential therapeutic candidates for AD. Curcumin, the major yellow pigment in turmeric (*Curcuma longa*), is proposed for its anti-inflammatory properties [71]. Several studies have indicated the suppressive effects of curcumin on lipopolysaccharide (LPS)-induced microglia activation and Mitogen Activated Protein Kinase (MAPK) activities. Curcumin has demonstrated beneficial effects on brain health through several mechanisms such as antioxidant, amyloid β -binding, anti-inflammatory, tau inhibition, metal chelation, neurogenesis activity, and synaptogenesis promotion [70,71].

As mentioned above, phytochemicals from herbal medicines have become a major source and main stream for future drug development and for human health care. These herbal medicines are able to target other salient systems such as cerebral blood flow, free radical scavenging, anti-inflammation, inhibition of amyloid- β neurotoxicity, glucoregulation and interaction with other neurotransmitters (such as γ -aminobutyric acid) and signaling pathways e.g. via kinase enzymes [72].

In this review, the authors cannot mention various types of herbs that have the potential for AD therapy. The author wants and pleads for herbal researchers in the future to increase their activities in developing research that is more specific to therapeutic goals in this case for Alzheimer Disease.

Stem cell therapy

Stem cells are undifferentiated cells that are capable of self-renewal and differentiation. Most human tissues are composed of a majority of differentiated cells with a limited life span. These cells die and the tissue shrinks, unless replenished by new cells. A crucial source of these new cells is tissue stem cells, which compose only a small minority of a tissue's cells. These cells are termed adult stem cells and are multipotent (capable of differentiation into several cell types, but not all three germ layers). Nevertheless, they are required for the maintenance of adult tissues. Alzheimer's disease is a disease that involves damage to neurons in several locations in the brain. The location of neuronal damage in these different areas makes each case unique and very difficult to treat. Stem cells have a therapeutic effect through the process of regeneration and cell substitution from the tissue itself. Stem cell therapy strategies have two mechanisms. One of them is to induce endogenous stem cell activation and the other is to support the regeneration of injured cells or tissues through stem cell transplantation [73].

An important step in developing any stem cell therapy is to choose the appropriate cell source. The most commonly utilized cells in recent AD studies are embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), brain-derived neural stem cells (NSCs), and induced pluripotent stem cells (iPSCs), each has unique properties that could be used in stem cell therapy strategies in various ways [74].

ESCs are derived from the inner cell mass of the developing blastocyst and are classified as pluripotent because they possess the ability to generate cell types from the ectodermal, mesodermal, and endodermal germ layers. MSCs are involved in the development of mesenchymal tissue types and can be harvested from umbilical cord blood (UCB-MSCs) or Wharton's jelly, and also remain present in several adult stem cell niches including bone marrow and adipose tissue. A subspecies of stem cells are embryonic stem (ES) cells, which can be obtained from early stage embryos (blastocyst). ES cells are pluripotent, which means they can differentiate into all three primary germ layers [75,76]. ES cells are critical to organism development. A defect in ES cell differentiation may have a pleiotropic effect on the organism. ES cells recently gained tremendous attention due to the reprogramming of adult somatic cells into induced pluripotent (iPS) cells [75]. iPS cells possess ES cell properties and were developed with the long-term objective to gain a new therapeutic tool.

Treatment of AD with stem cell technology depends on the neurogenesis capacities of stem cells. The strategy is to utilize stem cells to physically replace the neurons that are lost of cell in the degenerative stages of AD. In recent findings, the importance of glial cells and intercellular binding proteins in shaping the external environments of neurons have been suggested. The decline of microglia, astrocytes and oligodendrocytes that support the neuronal networks in the CNS through immune, nutritional and homeostatic mechanisms are correlated with the neuro inflammatory biochemistry of AD [77,78]. Through transplantation or in situ regeneration of lost neurons and key proteins that support them, there is hope to rebuild the integrity of the CNS and to alleviate the decline in cognitive functions in AD patients. ESC obtained from cell mass in a blastocyst, is pluripotent capable of developing three embryonic layers into ectoderm, mesoderm, and endoderm [79]. ESC is an excellent candidate for cell replacement therapy approach, where pluripotency is directed to develop properly into the growth of nerve tissue [80,81]. From the results of this recent research found the importance of glial cell bonding with protein as a binding between cells in forming the external environment of neurons [82]. Stem cell therapy through regeneration of *in situ* from damaged neurons is the formation of major proteins, raising hopes for rebuilding the integrity of the central nervous system in AD sufferers.

Conclusion

Alzheimer's disease (AD) is one of the most serious health issues for the elderly leading to neuronal dysfunctions with cognitive impairment. Pathologically, AD is characterized by two hallmark protein aggregates, amyloid- β (A β) plaques and neurofibrillary tangles, that are accompanied by neuroinflammation, including microgliosis, elevated cytokine production, and activation of complement pathways. It is clear that cerebral or peripheral inflammation can be an early AD and can affect visual pathways, visual cortex, result in various visual changes and problems. However, literature on the presence of A β and phosphorylated tau (pTau) in AD retinas is inconclusive visual dysfunction has long been recognized as a manifestation of Alzheimer's disease (AD), particularly in the form of visuospatial impairment during all stages of disease. However, investigations have revealed findings within the anterior (i.e., pregeniculate) afferent visual pathways that rely on retinal imaging and electrophysiologic methodologies for detection. It is still not possible to conclude if anti-inflammatory treatment alone is no longer treating AD. Phytochemicals from medicinal plants have been used in different

systems of medicine. Most of herbals medicine have been chemically evaluated and their efficacy has also been proven in clinical trials. However, the underlying mechanisms of actions are still on the way.

Stem cell-based therapies may become an effective therapeutic alternative (to conventional therapies) due to their regenerative potential. Although the mechanism of action of stem cell therapies remains incompletely elucidated, a number of preclinical studies have provided promising results. However, human clinical trials are still in their infancy. For the successful clinical translation of this technology, further relevant animal studies and clinical trials (with standardized protocols) are needed. However, there are many questions left unanswered regarding the safety, efficacy, ethical issues, and regulatory framework of stem cell-based therapies but there is a growing hope for patient-specific individualized stem cell based therapy.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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