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REVIEW ARTICLE **Open Access**

Deep Brain Stimulation for Alzheimer's Disease: A Review of a Potential Treatment in Neurosurgery

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ABSTRACT

Background: Alzheimer's disease (AD) is still a disease with abundant enigma. Moreover, the prevalence of AD increases every year by about 10 million new cases. This disease is well known for its degenerative feature with age being the most influencing factor. Pathophysiologically, the deposition of beta-amyloid and tau proteins is the culprit for disrupting the neural connections in the brains of AD patients. Some studies have stated that drug medications are not effective in treating AD patients.
Content: Currently, there is no drug to cure the disease. In conditions in which drugs fail to take effect, there is a therapy called deep brain stimulation (DBS), which allows the brain to be stimulated electrically using electrodes that are implanted into certain brain areas as targets. The fornix and nucleus basalis of Meynert (NBM) are commonly chosen as targets in DBS in AD patients. This intervention is performed surgically by the neurosurgeon. Several potential mechanisms of this treatment include controlling connections among neurons, decreasing beta-amyloid and tau protein levels, and inhibiting the inflammation process in the brain.
Conclusion: DBS can improve AD patients, both clinically and molecularly. Despite the promising effects of DBS, this treatment has limitations, so it cannot be applied to every patient with AD.

Key words: Alzheimer's disease, cognitive impairment, deep brain stimulation, neurosurgery, neurofunctional

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Introduction

Globally, the prevalence of Alzheimer's disease is rising quickly. It is currently estimated about 46.8 or 50 million people diagnosed with dementia in the world, while in the Asia Pacific the prevalence reaches 20.9 million. The World Health Organization (WHO) also predicted that there are approximately ten million new cases annually.[1] As of 2016, there were about 1.2 million dementia sufferers in Indonesia; by 2030, that number is expected to rise to 2 million, and by 2050, it will reach 4 million.[2]

Dementia has several types based on etiology and pathophysiology of the disease. Alzheimer's disease (AD) is the most common type of dementia.[3] AD occurs due to the buildup of abnormal proteins that disturb the brain and nerve cells function. The proteins which contribute to AD development are β-amyloid and tau proteins. In the long term, various functions, such as controlling thoughts, memory and language, will decrease.[4]

Until now, the disease known as Alzheimer's cannot be cured. However, several medications can reduce the worsening of symptoms experienced by patients with AD[3]. There are only a few AD patients who obtain the benefit of short-term treatment effects of AD drugs. Research on non-drug treatments has developed as a result of the limits of medication therapy effect and the severity of AD.[5] One of the promising treatment options for AD is deep brain stimulation (DBS). DBS is a treatment in neurosurgery, especially neurofunctional division, which modulates activity on neurons in the brain by placing internal generators as stimulators to electrodes in distinct target parts.[6] Some studies reported that DBS treatment improved the cognitive function, spatial memory and recognition. This treatment also could slow down the disease progression

This paper will discuss the potential treatment for AD in neurosurgery using deep brain stimulation (DBS). We will conclude the effectiveness and the efficacy of DBS for managing AD.

Etiology and Pathophysiology

The etiology of AD is not clearly understood. Many theories have been described about disease progression of AD. It is well known that AD occurs when plaques of abnormal proteins accumulate and tangles of neurofibrillary form in the brain. There are two proteins which are familiar in contributing to AD progression, they are beta-amyloid and tau proteins.[7] The beta-amyloid protein originated from the amyloid precursor protein (APP), a transmembrane protein. Proteases such as alpha, beta, and gamma-secretases cleave the beta-

amyloid peptide from the amyloid precursor protein (APP). When alpha- or beta-secretase is functioning normally, APP will be broken down, and the resulting pieces won't damage neurons. Nevertheless, 42 amino acid peptides known as beta-amyloid 42 are produced by gamma-secretase and beta-secretase cleavages. An elevation in beta-amyloid 42 causes amyloid aggregation, which damages brain neurons.[6] Beta-amyloid 42 induces the accumulation of aggregated fibrillar amyloid protein over normal APP degradation. The APP gene is located on chromosome 21, which is linked to familial Alzheimer's disease. Amyloid is deposited in the grey matter, cerebral arteries, and the area around the meninges.[7]

Tau proteins have a role in stabilizing microtubules. Tau protein binds the microtubules together, which are located along neuronal axons and its function in intracellular transport.[7] In the pathologic condition of AD, abnormal alteration of beta-amyloid causes tau hyperphosphorylation that leads to separation of tau from microtubules, then accumulation of tau aggregates happen. This tau aggregates formation which generates twisted coupled helical filaments are called neurofibrillary tangles. Due to this condition, the synaptic communication between neurons is blocked by neurofibrillary tangles.[8]

Other theories regarding AD have been hypothesized, such as granulovacuolar degeneration, hirano bodies, synaptic loss, genetic mutation, and inflammatory responses.[7,8] Granulovacuolar degeneration is the accumulation of membrane-bound vacuolar structures with a dense core in the brain. The Granulovacuolar increases in the hippocampus of AD patients, which indicates a significant correlation with tauopathy condition.[9] Hirano bodies are described as refractile eosinophilic rod-like structures which run in neuronal dendrites. Their structures are rich in actin and actin-associated proteins. Although this feature is highlighted in AD, its role in AD pathophysiology is still poorly recognized.[8] Synaptic loss is observed at the early progression of AD. The characteristics of synaptic loss in AD are disorder in axonal transport, destruction of mitochondria, and oxidative stress. Neurogranin, visinin-like protein-1, and synaptotagmin-1 are proteins which can be used as biomarkers of synaptic loss.[10] Some genes which are linked to AD are AAP gene on chromosome 21, Presenilin1 (PSEN1) on chromosome 14, Presenilin 2 (PSEN2) on chromosome 1 and apolipoprotein E (ApoE) on chromosome 19.[7,10] Inflammatory response in the brain, especially due to microglial cells, contributes to the AD process. When these cells are activated in AD patients, their numbers increase but they fail to clear pathologic debris such as neurofibrillary tangles and beta-amyloid deposition.[10] On the other hand, these microglial cells might cause neuronal damage.[8]

Despite the condition that pathophysiology of AD remains unclear, there are several risk factors that contribute to AD progression. Unmodifiable and modifiable risk variables make up the main category of AD risk factors. Age, gender, and genetic characteristics are the unchangeable risk factors. Genetic factors have been described in previous paragraphs. While age is the most important risk factor for AD development. Individuals over the age of 65 are twice as likely to develop Alzheimer's disease.[11] It is stated that women are at greater risk than men, but the understanding of this condition is imprecise. Because women typically live longer than men do, they are more likely to develop AD dementia over their lifetime, just like they are more likely to get other aging-related disorders.[11] Several acquired risk factors of AD are cerebrovascular disease, hypertension, stroke, diabetes melitus, obesity, dyslipidemia, history of psychiatric disease (depression and insomnia), smoking, lack of exercise, and vitamin D deficiency.[12]

Diagnosis

Alzheimer's Disease (AD) is a pathologic condition which can be cured but It is important to diagnose it early to improve the symptoms of patients with AD. History taking and clinical examination are crucial examinations to make prompt diagnosis of AD. Some red flag conditions to suspect an individual developing AD are gradual memory loss, behavior changes, difficulty of speech and nonsense decision-making.[13] A physician also should look for risk factors that precipitate the AD in patients. These assessments are aimed at ruling out other disorders instead of AD. Mini mental state examination (MMSE) is a tool that can help in screening patients with AD, because MMSE can determine that an individual has any cognitive disorder.[10]

Definitive diagnosis of AD is difficult to establish. National Institute of Aging and Alzheimer's Association (NIA-AA) make some recommended tests which can be used in diagnosing AD. In the 2018 NIA-AA revised the diagnostic criteria, which identified imaging and CSF biomarkers as valid diagnostic tools (Table 1).[14] The US Food and Drug Administration (FDA) recommended staging approach for the Alzheimer's spectrum and the clinical phases correspond. The clinical stage, the assessment tools, and the ATN categorization are evaluated. There are some laboratory and radiology examinations can be utilized to diagnose Alzheimer's disease. Computed Tomography (CT) scan is used to rule out other underlying diseases, such as vascular dementia, stroke or fahr's disease. Neurofibrillary tangles and the level of tau protein and beta-amyloid in AD patients can be assessed using a PET scan or a cerebrospinal fluid (CSF) test. These instruments revealed

that the symptoms weren't derived from concomitant illnesses, but were mainly associated with AD pathophysiological pathways. However, because of the lack of evidence linking biomarker concentrations with AD pathology, the limited availability of the tools, and the insufficient standardization of the analytical results, biomarkers could only be used as supportive diagnostic tools in clinical research and could not be implemented in clinical diagnostic settings.[15]

Table 1. The diagnostic criteria of AD based on NIA-AA.[14]

Clinical phase	Assessment			ATN Classification		
	Cognitive deficit	Functional deficit	Behavioural deficit	A	T	N
Normal cognitive without decline indication	PACC; APCC	Absence	Absence	+	-	-
Normal Cognitive with decline indication	PACC; APCC	Absence	Absence	+	+	- / +
Prodromal AD	CDR-sb; ADCOMS; iADRS; NTB	ADCS-ADL (MCI version)	MBI/NPI	+	+	+
Mild AD dementia	ADAS-cog; NTB; CDR-sb	ADCS-ADL	NPI	+	+	+
Moderate AD dementia	ADAS-cog; NTB; CDR-sb	ADCS-ADL	NPI	+	+	+
Severe AD dementia	SIB; CDR-sb	ADCS-ADL (severe version)	NPI	+	+	+

Medication Treatments

There are currently only symptomatic therapies for AD, which have no effect on the disease's progression. Acetylcholine or glutamate are the neurotransmitters that are modulated by all medications to treat AD that have been approved by the FDA. The usual medical treatment for AD includes cholinesterase inhibitors (ChEIs) and a partial N-methyl-D-aspartate (NMDA) antagonist[16]. Furthermore, several drugs which target amyloid have been approved, such as monoclonal antibodies (e.g., aducanumab, bapineuzumab, lecanemab). However, tau-targeted drugs are still in clinical trials.[17]

Some studies about AD progression suggested that a cholinergic system is impaired in AD whereas it modulates neuronal information in the hippocampus and neocortex.[18] Those

studies also reported that clinical signs and symptoms of AD are caused by loss of cholinergic innervation to the cerebral cortex. Cholinesterase inhibitors (ChEIs) block acetylcholinesterase (AChE) at the synapse (specific cholinesterase) to improve cholinergic paucity. Several ChEIs drugs which are currently approved are donepezil, rivastigmine and galantamine.[16] Although AD cannot be cured by ChEIs drugs, these drugs are supposed to restrict neurodegeneration in patients.[18]

N-methyl-D-aspartate (NMDA) antagonist drugs act by inhibiting NMDA receptors uncompetitively in the brain. Some benefits of NMDA antagonist drugs are neuroprotective effects by blocking the deprivation of neurons and restoring the function of injured neurons in the brain.[16] Memantine is one of NMDA antagonist drugs which has been approved by FDA to treat AD patients since 2003. A study conducted by McShane *et al*. stated that memantine had a small clinical benefit in patients with moderate-to-severe AD, nonetheless taking ChEIs drugs or not. On the other hand, memantine was not effective in treating mild AD patients.[19]

Monoclonal antibodies have been developed to target beta amyloid and bind to beta-amyloid aggregates to lessen the plaques associated with AD. Aducanumab is one of immunoglobulin G monoclonal antibodies that targets beta amyloid and has promising results in improving AD patients at pre-clinical and mild stage.[16] Although bapineuzumab was reported to decrease amyloid aggregation in Apoe4 carriers, this drug does not change either cognitive or functional outcomes. A humanized immunoglobulin gamma 1 (IgG1) monoclonal antibody, lecanemab also functions by preventing beta amyloid aggregation from forming. Lecanemab should be considered for the treatment of individuals with moderate AD.[20]

Deep Brain Stimulation

Deep Brain Stimulation (DBS) is a surgical procedure that stimulates particular brain regions by sending electrical impulses through electrodes. Some diseases, such as Parkinson's disease, dystonia, and depression, which are resistant to drugs, can be treated by DBS.[21] The difference in DBS treatment among diseases depends on the target areas to be electrically stimulated. In AD patients, areas that are used to be triggered are the fornix (hypothalamus) and the nucleus basalis of meynert (NBM).[22] The vagal nerve can also be chosen to be the stimulation area, but this nerve is outside the brain area and not specific, thus vagal nerve stimulation (VNS) is not included as DBS. The application of VNS modality is wide, such as depression, epilepsy, and others.[23]

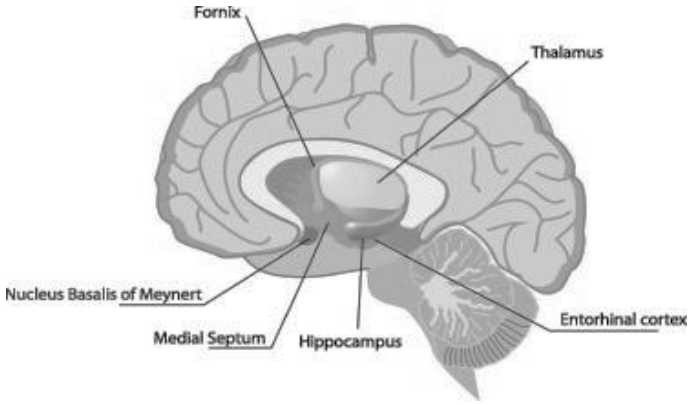

Figure 1. Some brain areas targeted in deep brain stimulation.[28]

Table 2. The target areas of DBS for some conditions.[22]

Condition	Target Areas	Advantages/Mechanism	Disadvantages/ Adverse Effects
Parkinson's disease	Subthalamic nucleus Globus pallidus internus	Improve motor symptom Ameliorate tremor Reduce medication	Depression Personality change Fatigue
Epilepsy	Anterior Nucleus of the Thalamus Hippocampus Medial septum	seizure frequency reduction longer seizure-free interval improved quality of life	Paresthesia in the limb or face Disturbance in speech or vision Balance problems
Obsessive-compulsive disorder	Anterior limb of Internal Capsule Nucleus Accumbens Ventral caudate/striatum	Decrease obsessive symptoms	Hypomania Sleep disturbances Weight gain Fatigue
Essential tremor	Ventral Intermedius Nucleus	Decrease tremor symptom	Depression Paresthesia Fatigue
Major Depressive disorder	Subcallosal cingulate Nucleus Accumbens Medial forebrain bundle	Improve depressive symptoms Improve mood of the patient Increase Serotonin and brain-derived neurotrophic factor	Paresthesia Increase dizziness frequency Uncontrollable jerking movements of arms or legs
Alzheimer's Disease	NBM Fornix Entorhinal cortex	Improve cognitive function Increase memory Slow the disease progression	Palpitations Paresthesia Fatigue

In the brain, NBM was a former target area for stimulation in AD patients. The neocortex and hippocampal regions are innervated by the vast cholinergic projections found in NBM. The NBM cholinergic pathway has a significant decline in AD patients.[22] Acetylcholine (ACh) is an important substance for memory and cognitive function. ACh mostly originates from the NBM cholinergic pathway. As shown in the Figure 1, this area is located on the anterior lateral part of the hypothalamus and below the anterior commissure and globus pallidus.[28] Damage to the NBM can affect cholinergic transmission reduction and degenerative changes of the hippocampus. In AD, DBS in the NBM has demonstrated good effectiveness. On the evolution of AD and cognitive function, DBS in the NBM conducted in the early stages of AD may be advantageous.[24] Additionally, DBS to NBM can lower the amount of beta amyloid protein, control the gamma-aminobutyric acid (GABA), glutamate system, and cholinergic systems, enhance spatial learning and memory in AD model mice, and have neuroprotective effects.[25]

The fornix, an essential part of limbic circuits, is responsible for memory processing and transports cholinergic axons from the septal area to the hippocampus. The fornix resembles an arcuate fiber bundle that connects the mammillary bodies to the hippocampal region. Any damage to the fornix can cause memory impairment.[6] In 2008, DBS in the fornix was reported firstly to improve the memory of the patient. Due to its successful result in improving memory, DBS in the fornix began to be applied in to AD patients. A study by Sankar *et al.* showed that DBS in the fornix had a bilateral increased hippocampal volume in AD patients. This result suggests that fornix DBS may improve brain volume, while the brain condition in AD patients is atrophy.[26] Another study conducted by Lozano *et al.* found that DBS surgery and stimulation processes were safe and well tolerated in mild AD patients. The glucose metabolism of the brain is increased in AD patients who received the fornix DBS.[27] In animal studies, Fornix has the potential to stimulate the brain area electrically in AD model patients to improve memory function, decrease beta amyloid deposition in the hippocampus and cortex, inhibit microglial activation and lessen neuronal damage.[28,29] According to these findings, fornix is the potential target area for DBS treatment in AD patients.

DBS treatment requires some equipment, such as a lead with electrodes, a wire, an implantable pulse generator (IPG), a set of brain surgery instruments, and a set of chest wall implantation instruments. It is important that the hospital which performs DBS surgery also supports stereotactic procedures.[30] Using a stereotactic head frame, the head of the patient will be immobilized during surgery. DBS treatment begins with creating skin incisions at the skull to make small holes in the skull. The electrodes of the DBS treatment are implanted into

the skull, passing through the holes.[31] DBS surgery is carried out under general anesthesia or local anesthesia while the patient is awake. In awake brain surgery, an anesthesia is administered to numb the scalp and the brain does not need to be given an anesthesia since it lacks receptors of pain.[32] Small electrodes which have been implanted to certain brain areas then are connected to the wire which runs superficially to the skin towards the IPG. During surgery, brain function is monitored to ensure the position of electrodes and the function of stimulation.[31] For the IPG placement under the skin, the surgery requires general anesthesia. The chest wall surgery is performed to implant the device of DBS treatment under the skin, usually near the clavicle. There is an exclusive remote control that connects to the IPG.[30]

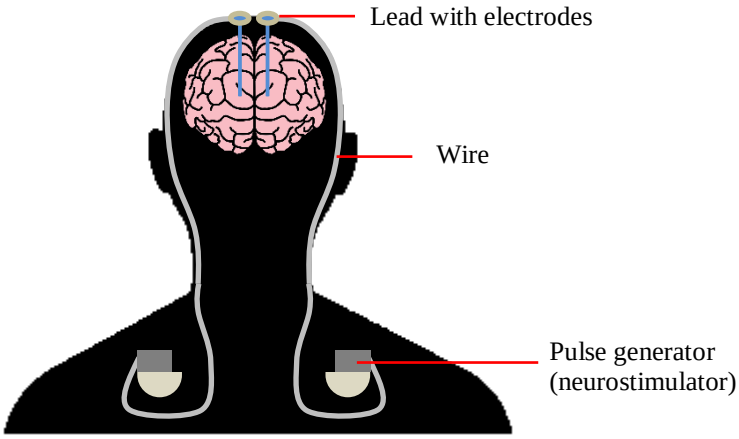

Figure 2. Illustration of DBS treatment in Alzheimer's disease.

Practically, electrical stimulation of DBS is regulated by its frequency and duration. There are two types of frequency stimulation: high-frequency stimulation (HFS) and low-frequency stimulation (LFS). HFS has a frequency range of 25 to 1000 Hz, and it is commonly used for mental illness, movement disorders, and cognitive impairment.[6] While LFS has no effect on AD patients.[33] Huang *et al.* carried out in vivo research to measure the optimal frequency for DBS with NBS as a target area. In mice, cognitive function improved significantly (parameters used were learning period and occupation time) in mice with HFS of DBS (50 Hz, 100 Hz, and 130 Hz). It can be concluded that a higher frequency is better than a lower frequency for DBS in AD patients. However, the optimal DBS frequency remains unclear.[28] The duration of DBS in patients is also related to the slowing progression of the disease. Several studies about DBS treatment in animal models showed that both acute and chronic stimulation can lead to long-term brain remodeling.[34] For daily duration, some studies suggested that one hour, seven hours, and 24 hours of duration already affected the improvement of spatial memory and recognition. However, it is recommended to use DBS in

the long term to allow long-term alteration in brain function.[35] Based on the duration of the day, DBS for 14, 21, and 28 days has been proven to improve the memory of animal models and decrease beta-amyloid levels in the brain, especially in the cortex and hippocampus. On the other hand, 7 days of DBS had no good impact.[33]

Although the mechanism of DBS as a treatment in AD is unknown, it is generally accepted that DBS acts by stimulating or inhibiting the neuronal cell bodies that are close to the electrodes and the axons that pass nearby high-frequency stimulation has the potential to produce a reversible functional lesion by reducing local activity. On the other hand, nearby neurons seem to be generally activated by low-frequency stimulation.[21] There are some theories of the potential mechanisms of DBS as an AD treatment, such as controlling related neural connections, inducing nerve oscillation, decreasing beta-amyloid levels, decreasing tau levels, reducing inflammation in the brain, modulating the cholinergic system, and inducing nerve growth factor (NGF) synthesis.[21]

DBS treatment cannot be applied to all AD patients. Research by Lorenzo *et al.* revealed that DBS treatment in AD patients may benefit patients aged 65 years or older, while patients aged under 65 years showed no benefit effect instead of worsening condition.[27] The risks and complications that can develop in patients with DBS treatment include infection, malposition of IPG or electrodes, disconnection of wire, and intracerebral hemorrhage (ICH). A study by Jung *et al.* showed several complications after DBS treatment, with infection being the most common complication, accounting for about 2.8% of all 416 subjects. ICH and hardware-related complications were the most common complications after infection, respectively.[36] Therefore, in treating AD patients with DBS, the neurosurgeons and neurologists should choose more selectively the candidate of the patient who will undergo DBS treatment in dealing with AD.

Conclusion

Alzheimer's disease (AD) is a degenerative disorder that is currently claimed to be unable to be cured. AD occurs usually when beta-amyloid proteins are accumulated and tau proteins are deposited in the brain, which causes some brain functions to not work properly. Several drugs are prescribed to improve quality of life in cases of cognitive and memory problems, but they are not effective in slowing the disease progression. A procedure in neurosurgery, deep brain stimulation (DBS), has potential advantages for treating AD, whereas medication is not effective as an AD treatment. DBS for AD has some specified target brain areas; fornix and NBM are the most frequently selected areas because DBS in

these areas is proven to improve the quality of AD patients both molecularly and clinically.

List of Abbreviations

A: amyloid; Ach: Acetylcholine; AD: Alzheimer's Disease; ADAS-cog: Alzheimer's Disease Assessment Scale – cognitive subscale; ADCOMS: AD Composite Score; ADCS-ADL (MCI): Alzheimer's Disease Cooperative Study – Activities of Daily Living scale (mild cognitive impairment version); APCC: Alzheimer Prevention Initiative Cognitive Composite; APP: amyloid precursor protein; ATN: Amyloid, Tau and Neurodegeneration; CDR-sb: Clinical Dementia Rating- Sum of Boxes; ChEIs: cholinesterase inhibitors; CSF: Cerebrospinal fluid; CT: Computed Tomography; DBS: Deep Brain Stimulation; FDA: U.S. Food and Drug Administration; GABA: gamma-aminobutyric acid; HFS: high-frequency stimulation; iADRS: Integrated AD Rating Scale; ICH: intracerebral hemorrhage; IPG: implantable pulse generator; LFS: Low-frequency stimulation; MBI: Minimal Behavioral Impairment scale; MMSE: Mini mental state examination; N: neurodegeneration; NBM: nucleus basalis of meynert; NFG: NGF: nerve growth factor; NIA-AA: National Institute of Aging and Alzheimer's Association; NMDA: N-methyl-D-aspartate; NPI: Neuropsychiatric Inventory; NTB: Neuropsychological Test Battery; PACC: Preclinical Alzheimer Cognitive Composite; PET: Positron Emission Tomography; PSEN1: Presenilin1; PSEN2: Presenilin2; SIB: severe impairment battery; T: tau; VNS: vagal nerve stimulation; WHO: World Health Organization

Conflict of Interest

All authors declare that there is no conflict of interest in this paper.

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