TEST Engineering & Management

May – June 2020
ISSN: 0193-4120 Page No. 8361 - 8367

Current Understanding of Diagnosis and Treatment of Alzheimer's Disease

Jintong Hu,
Wuhan Britain-China School
2945170964@qq.com

Article Info
Volume 83
Page Number: 8361 - 8367
Publication Issue:
May - June 2020

Article History
Article Received*: 19 November 2019*
Revised*: 27 January 2020*
Accepted*: 24 February 2020*
Publication*: 18 May 2020*

Abstract:

Alzheimer's disease, a progressive neurodegenerative disease, remains a major health issue worldwide. For aetiology, plaques and neurofibrillary tangles occur widely in patients' brain tissue. Whereas ageing is the most significant risk factor, divergent groups of factors, including heredity and lifestyle, can contribute to Alzheimer's disease development. Diagnosis includes psychological interview, testing with the presence of typical biomarkers, brain imaging, genetic tests, and other cognitive tests. Categories of different medicines are utilized to treat Alzheimer's disease or concurrent diseases. Common surgery therapies for Alzheimer's disease include Deep Brain Stimulation and Neural Stem Cell Therapy. Some researchers report that certain currently underestimated treatments like intake of vitamin E can also help to control Alzheimer's disease development. Researches of Alzheimer's disease are still underway for developing affordable cure for Alzheimer's disease.

Keywords: *Alzheimer's disease, Alzheimer's disease diagnosis, Alzheimer's disease treatment, amyloid β-protein, dementia, tau*

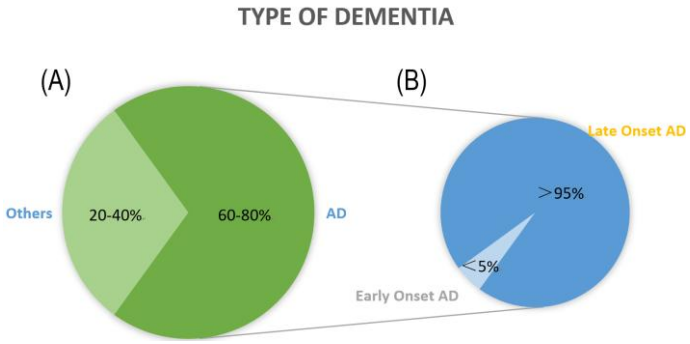
I. INTRODUCTION

A. Dementia

Dementia is recognised as a set of serious multifactorial progressive neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease and Huntington's disease [1]. Currently, it is worried and believed by 95% people that they may have dementia at some age [2]. AD is the dominating cause of dementia worldwide, attributing to 60-80% of dementia cases, and it remains a major cause of death in elderly people (Figure 1A) [3]. Compared with normal people, patients with AD usually have abnormal tau protein deposits in neuronal cell bodies [4]. Common symptoms of AD include memory instabilities, problems with motor skills, cognition, creation and comprehension of languages [5]. Distinctive symptoms in AD can occur since different brain regions may be involved in degeneration, causing further disabilities in the interaction between functional areas of the brain.

B. Early onset and late onset AD

AD can be differentiated into early and late onset. AD patients diagnosed under 65 years of age are regarded as early onset, whereas AD patients diagnosed above 65 years of age are regarded as late onset. Early Onset AD is much less common; less than 5% of the AD patients have early onset AD (Figure 1B) [5]. Comparatively, early onset AD is more likely caused by genetic mutations while late onset AD is more likely caused by other factors, although genetic predispositions can play an important role.



TEST Engineering & Management

May – June 2020
ISSN: 0193-4120 Page No. 8361 - 8367

Figure 1. A) Proportions of different types of dementia worldwide. AD is the main type of dementia which constitutes 60-80% of cases. B) Distribution of early and late onset AD. Late onset AD is much more common. The graph is generated based on the data obtained from [3], [5].

C. AD incidence and prevalence

AD is associated with ageing. The incidence of dementia doubles with an average increase of 6.3 years in age (3.9 % in 60-90 years old and 104.8 % in more than 90 years old) [6]. Prevalence of AD is around 10% for people above 65 worldwide and is about 30% in those over 80 (Figure 2) [7].

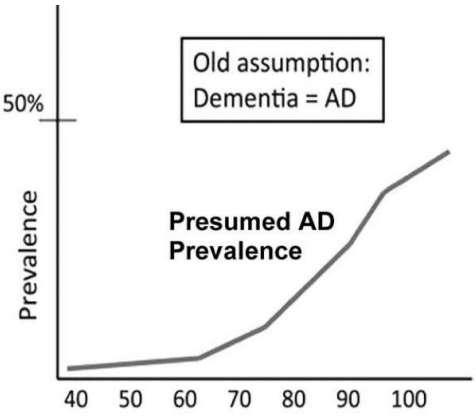


Figure 2. Prevalence of AD increases significantly with age. The figure is obtained from [8] with modification.

With increasing life expectancy and gradually ageing population, especially in the circumstances of developing countries, AD prevalence is increasing, which requires more resources to tackle it. People from lower socioeconomic backgrounds may have poor physical and mental health with insufficient funding for treatments, exacerbating the problem.

D. The financial burden of AD and AD consequences on the society

In the USA alone, the average annual medicine care expenditure per dementia patient is around $44,000; which adds up to around $207 billion [9]. Caregivers not only shoulder financial loads but also, they might suffer from psychological and health-related conditions such as anxiety and depression [10], [11]. In 2019, more than 50% of dementia caregivers reported affected health conditions, and more than 60% of them report affected social life [2]. These further increase the impact on the society as the carers become less efficient as both labour and consumer in the market, as well as needing medication. Therefore, considerable resources are spent on medical treatment of AD patients.

II. AETIOLOGY

A. Amyloid β-protein and tau

Amyloid β-protein is circulated freely in the blood and cerebrospinal fluid (CSF) or in association with chaperone molecules [4]. While they are present in all healthy neurons, a version of amyloid β-protein, Ab42 oligomers, can be harmful by causing tau hyperphosphorylation; therefore, causing toxicity to structures such as synapses and mitochondria [4]. Normal neurons synthesize tau proteins for stabilizing microtubules, which are important for axonal morphology, cell growth and setting the polarity [4]. However, in AD patients, tau may become hyperphosphorylated and aggregate. Plaques and neurofibrillary tangles are widely observed in AD patients and are representative features of AD (Figure 3) [12].

Amyloid β-protein is the main component of plaque which is present extracellularly, while tau neurofibrillary tangles are present intracellularly [13] (Figure 3). Protein aggregation eventually results in neuron apoptosis, and as neurons do not have regenerative capacity, it causes irreversible damage to the brain.

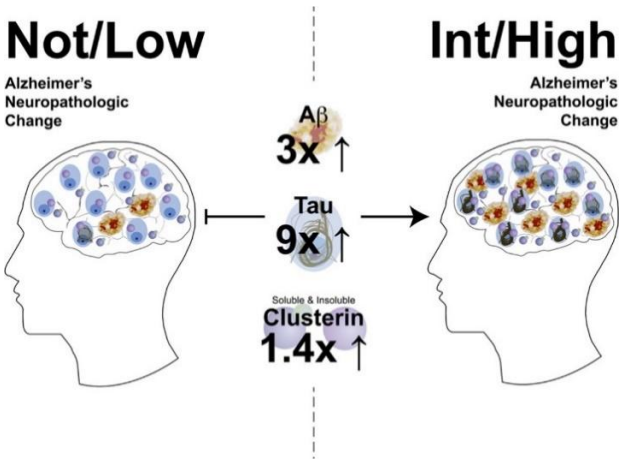


Figure 3. An overview of different proteins deposited in AD patients. Aβ deposit concentration triples in moderate/severe AD neuropathogenesis, as well as tau aggregation. Other proteins such as

TEST Engineering & Management

May – June 2020
ISSN: 0193-4120 Page No. 8361 - 8367

clusterin show some degrees of increase as well. The figure is obtained from [14].

B. Risk factors

Age remains the greatest risk factor for AD (Figure 4). Apart from that, other factors such as genetic mutations, gender and gender-related hormones, head trauma, lifestyle and environmental factors can increase the likelihood of AD formation as well (Figure 4) [15].

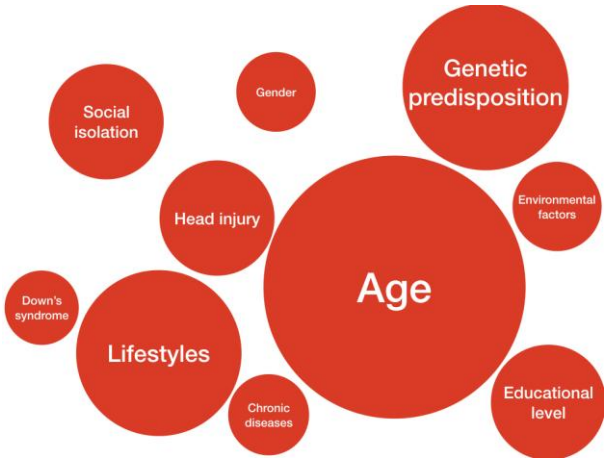


Figure 4. Different risk factors of AD, with different degrees of significance, correspond to each circle's size. Circle's sizes are representative and are illustrated arbitrarily.

People may have a high risk of AD if they have first-degree relatives with AD, or if they have Down's syndrome [1]. Females are more likely than males to have AD than males because of differences in their sex hormones as the ratio of females with AD to males is roughly 3:1 worldwide [16]. Chronic diseases and unhealthy lifestyle may also predispose people to AD [16]. Although some risk factors like ageing are inevitable, we can control other risk factors such as lifestyle changes and social interactions to decrease the chances of having AD.

C. Heredity

Genes associated with AD can be categorized into risk genes which only increase the possibility of getting AD; and deterministic genes which directly result in AD (Figure 5) [16].

Few genes are deterministic genes of AD. For example, the altered sequence of genes for amyloid precursor protein, Presenilin 1, can result in dominantly inherited familial AD in people as young as 46 years old (Figure 5) [5]. Apolipoprotein E allele (APOE) gene is a risk gene which functions in metabolism of amyloid β-protein and is the most well-known and significant genetic risk factor for late onset AD (Figure 5) [1]. Three common alleles of APOE gene are present, ε4 allele is the most common and a dangerous form, while ε2 allele is an uncommon form which is correlated with less AD pathology [17]. Apart from these alleles, alteration in chromosomal number can also increase the risk of AD; Down's syndrome patients usually have a high risk of AD as they age (Figures 4 and 5). While some genes involved in AD are identified, more research is required to illustrate the effect of genetics on AD.

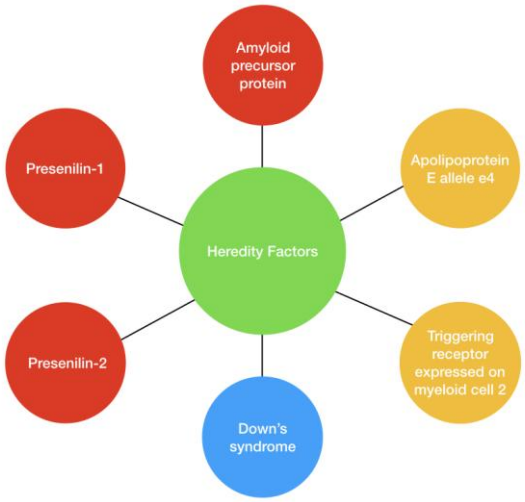


Figure 5. Heredity risk factors associated with AD. Red circles represent deterministic genes, yellow circles represent risk genes, and the blue circle represents an alteration in chromosomal number. The graph is generated based on data obtained from [16].

D. Lifestyles

Unhealthy lifestyles such as excess junk food consumption, obesity, and lack of physical activity can also increase the risk of AD development. Exercise, including physical and mental exercise, can both help to prevent AD or control AD development. Psychological factors, especially depression, are also highly related to AD patients as depression and AD often occur simultaneously [11]. Even environmental factors such as air pollution can be a risk factor for AD [15]. Trans–fatty acids increase the risk of dementia, while vitamins may decrease it [18]. On the other hand, vitamin D deficiency can increase the risk of developing AD [19]. Some other diets, such as seafood may also decrease the risk of AD [20].

TEST Engineering & Management

May – June 2020
ISSN: 0193-4120 Page No. 8361 - 8367

III. DIAGNOSIS

A. Interview

Currently, the most common diagnosis for AD is directly asking patients as well as their relatives or friends about the health condition, medical history, capacity of conducting routine activities, and behaviour or personality changes of the patient [21]. Although this is an efficient and quick diagnostic approach because it only takes up the limited time of the doctor and can provide much information, it is not the only test. Following the interview, the physician may conduct mental tests such as those showing memory and language capacities for the patient [21]. These can help to identify whether the patient has dementia, with low failure possibilities.

B. Stages and mortality

AD spectrum is usually classified into pre-dementia and dementia stages; dementia stage is further divided into three phases with different durations from mild to moderate and severe (Table 1).

Table 1. An overview of different stages of AD and their associated symptoms.

Stages/ Phase		Symptoms
Pre-dementia/Early stage		A slight decrease in cognitive ability Daily living is unaffected
Dementia stage	Mild dementia	Performing routines without significant difficulties Recent memory loss Emotional apathy Troubles tackling with complicated puzzles
	Moderate dementia	Increased memory loss Processed decline of cognitive ability Personality changes, becomes irritable Insufficient activities of daily living Cannot conduct outdoor activities Remain sanitation
	Severe dementia	Fragmented Few responses to the external environment Deprived activities of daily living Lethal complications

Patients with mild dementia can still perform their daily routine activities without significant difficulties (Table 1); however, they show difficulties in learning new things as well as having impairments in their communication, focus and orientation [16].

Moderate dementia patients show severe damages of long-term and short-term memories; and have severe difficulties in spatial and temporal orientation, motor tasks, mental calculations, languages, and performing daily activities (Table 1) [16].

Severe dementia patients rely completely on others and can retain only fragmented memories (Table 1) [22]. They may finally become unconscious and die from complications such as multiple organ failure, thrombus, and asphyxia or aspiration pneumonia. Mortality may be easily underestimated; as death caused by AD may be regarded as a regular ageing process. This fallacy is also more common in developing countries [10].

C. Biomarkers

The presence of AD can usually be tested with the presence of biomarkers found in the brain or CSF. Amyloid β-protein and tau, two candidates for the defining biomarker of AD, are most frequently tested among the biomarkers [21].

Amyloid deposition (Figure 3) shows a clear correlation with AD diagnosis. Clear amyloid β-42 plaques between neurons present when patients have AD (Figure 3) [4]. Intriguingly, it is known that a lower concentration of amyloid β-42 in CSF can be a strong predictor of AD as early as 20 years before symptoms of AD are observed [5], [23].

Meanwhile, tau is another important indicator of AD (Figure 3) [1]. It is tested as neurofibrillary tangles, usually along with testing of amyloid β-protein [5].

D. Brain imaging

Neuroimaging is another diagnostic approach. This is a study, which was initiated from radiology, for in vivo detection of the central nervous system's anatomical structure and function [24]. Up to now,

May – June 2020
ISSN: 0193-4120 Page No. 8361 - 8367

common strategies of neuroimaging include computed tomography, magnetic resonance imaging, and emission computed tomography which includes positron emission tomography (PET) and single photon emission computed tomography [24]. As a booming field, new techniques develop constantly. For clinical application in AD, neuroimaging is usually helpful with early detection; the PET Scans are used to image mild radioactive markers specifically bound with amyloid plaques [21].

IV. Treatments

A. Overview

Currently, a definitive cure for AD is still unavailable; drugs prescribed by doctors can only alleviate the symptoms instead of curing AD [21]. The extent of AD treatment depends on the diagnosis. Current treatments can be categorized into drug treatment, psychological treatment and surgery [12].

Type of treatment	Treatment methods
Drug treatments	Cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) NMDA receptor antagonist (memantine) Antianxiety Antidepressant Antipsychotics Antioxidant (vitamin E) Anti-inflammatory drugs Brain derived neurotrophic factor Anti-amyloid treatment Anti-tau treatment
Psychological treatments	Social contact Reading and mental exercises
Surgery	Deep brain stimulation Neural stem cell implantation Neural circuitry treatment

B. Medical Treatments

Several medical treatments are available. Cholinesterase inhibitors, including donepezil, rivastigmine, and galantamine are recommended medicines for AD patients in all stages of dementia (Table 2) [25].

Table 2. An overview of current treatment methods available for AD. The table is generated based on data obtained from [16], [21], [26].

They activate acetylcholine receptors by preventing degradation of acetylcholine, which is important in divergent aspects including modulation of cardiovascular diseases, ingestion, drinking, sleep and arousal, sensory, and movement [16].

Apart from cholinesterase inhibitors, NMDA receptor antagonist such as memantine is often used for patients with moderate or severe AD (Table 2). It serves as a non-competitive antagonist of N-methyl-D-aspartate receptor, which controls memory and plasticity of synapses, and as dopamine agonist [26].

Antianxiety, antidepressant, and antipsychotic drugs are also used to treat behavioural and psychological symptoms of dementia which are concurrent with AD (Table 2) [16].

C. Non-medical Treatments

Psychological treatments are frequently used in addition to medicines. These are accessible to most people and hardly cause side effects. Although widely regarded as the final attempt; surgeries can also alleviate the symptoms of AD; thus, they are usually used when medicines show poor effects. Deep Brain Stimulation (DBS) is one of those therapies which is used for treating many different cerebral diseases, such as movement disorder (Table 2) [27]. Some patients with a mild stage of AD report an improvement of memory twelve months after DBS therapy [28]. Researches show that DBS is effective in preventing cognitive decline by enhancing glucose metabolism of the brain, and preserving volumes of the hippocampus and cortical grey matter [29].

Neural stem cell therapy is also a potential means of treatment. Rat models with dementia showed an improved learning and memories after injecting neural stem cells into the frontal association cortex; suggesting hippocampus lost cells may be replaced to partially restore brain functions (Table 2) [16].

D. Novel treatments

Several novel treatments are expected to treat AD effectively with reduced side effects. Some people

May – June 2020
ISSN: 0193-4120 Page No. 8361 - 8367

believe vitamin E is a substantial medicine as it functions as an antioxidant via neutralizing free radicals (Table 2) [30]. Researches show that some pathologic neurodegeneration and subsequent brain ageing are caused by oxidation of certain chemicals and accumulation of free radicals; thus, vitamin E may be useful to prevent AD [30].

Some researchers divide plausible future treatments into anti-amyloid, anti-tau, and neural circuitry treatments (Table 2) (Figure 6), which is based on the attempt that AD is related to the dysfunction of the whole neuronal network in some extent [26].

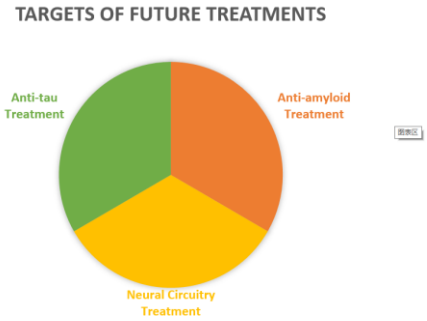


Figure 6. Possible targets of future AD treatments. Based on the hypotheses that amyloid plaques or hyperphosphorylated tau may be direct causes of AD; or AD is related to the dysfunction of the whole neuronal network [26].

CONCLUSION

Although it has been studied for decades, the underlying cause and development of AD are still not completely understood. Because of the high prevalence of AD in elderly people worldwide, its significance has increased along with an increase in global population and life expectancy; while infectious diseases are becoming decreasingly severe. Clinical diagnosis and treatment methods are still insufficient. Patients can hardly be diagnosed before obvious symptoms of dementia are seen; hence their quality of life is usually decreased after the diagnosis. Treatment methods are often limited to improve life quality and to slow down development of AD. Curing AD is still inaccessible. AD may remain as a severe health problem for years; hence additional researches are necessary in order to understand the molecular mechanism of AD, therefore, developing preventive and therapeutic measures.

REFERENCES

[1] James, B. D., & Bennett, D. A. (2019). Causes and Patterns of Dementia: An Update in the Era of Redefining Alzheimer's Disease. [Online] Available at: https://www.annualreviews.org/doi/10.1146/annurev-publhealth-040218-043758 [Accessed on 25th Dec, 2019]

[2] Alzheimer's Disease International. (2019). World Alzheimer Report 2019. [Online] Available at: https://www.alz.co.uk/research/world-report-2019 [Accessed on 5th Feb, 2020]

[3] Barker, W. W., Luis, C. A., Kashuba, A., Luis, M., Harwood, D. G., & Loewenstein, D. et al. (2002). Relative frequencies of Alzheimer disease, lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the state of florida brain bank. Alzheimer Disease & Associated Disorders, 16(4), 203-212.

[4] Anil, Kumar, Arti, Singh, & Ekavali. (2015). A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacological Reports.

[5] DeTure, M. A., & Dickson, D. W. (2019). The neuropathological diagnosis of Alzheimer's disease. [Online] Available at: https://doi.org/10.1186/s13024-019-0333-5 [Accessed on 25th Dec, 2019]

[6] Alzheimer's Disease International. (2015). World Alzheimer Report 2015. [Online] Available at: https://www.alz.co.uk/research/world-report-2015 [Accessed on 25th Dec, 2019]

[7] Schultz, C., Tredici, K. D., & Braak, H. (2004). Neuropathology of Alzheimer's Disease. Humana Press.

[8] Nelson, P. T. et al. (2011). Alzheimer's disease is not "brain aging": neuropathological, genetic, and epidemiological human studies. Acta Neuropathologica, 121(5), 571-587.

[9] Norins, L. C. (2019). Predicted economic damage from a quick, simple Alzheimer's disease cure. [Online] Available at: https://doi.org/10.1016/j.mehy.2019.109398 [Accessed on 31th Dec, 2019]

[10] Galende, V. et al. (2019). Report by the Spanish Foundation of the Brain on the social impact of

May – June 2020
ISSN: 0193-4120 Page No. 8361 - 8367

Alzheimer disease and other types of dementia. [Online]
Available at:
https://doi.org/10.1016/j.nrleng.2017.10.004
[Accessed on 26th Dec, 2019]

[11] Neugroschl, J., & Wang, S. (2011). Alzheimer's Disease: Diagnosis and Treatment Across the Spectrum of Disease Severity. Mount Sinai Journal of Medicine A Journal of Translational & Personalized Medicine, 78(4), 596-612.

[12] Raúl. et al. (2019). Alterations in cholesterol metabolism as a risk factor for developing Alzheimer's disease: Potential novel targets for treatment. The Journal of steroid biochemistry and molecular biology.

[13] Bondi, M. W., Edmonds, E. C., & Salmon, D. P. (2017). Alzheimer's Disease: Past, Present, and Future. Journal of the International Neuropsychological Society, 23(9-10), 818-831.

[14] Shepherd, C. E. et al. (2019). Intracellular and secreted forms of clusterin are elevated early in Alzheimer's disease and associate with both Aβ and tau pathology. [Online]
Available at:
https://doi.org/10.1016/j.neurobiolaging.2019.10.025
[Accessed on 25th Dec, 2019]

[15] Oudin, A. (2019). Short review: Air pollution, noise and lack of greenness as risk factors for Alzheimer's disease- epidemiologic and experimental evidence. [Online]
Available at:
https://doi.org/10.1016/j.neuint.2019.104646
[Accessed on 30th Dec, 2019]

[16] Ding, F. et al. (2016). Neurobiology. 3rd Ed. Peking: Science Press

[17] Liu, C. C. et al. (2013). Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nature Reviews Neurology, 9(2), 106-118.

[18] Barnard, N. D., Bush, A. I., Ceccarelli, A., Cooper, J., De Jager, C. A., & Erickson, K. I. et al. (2014). Dietary and lifestyle guidelines for the prevention of Alzheimer's disease. Neurobiology of Aging, 35, S74-S78.

[19] Littlejohns, T. J. et al. (2014). Vitamin D and the risk of dementia and Alzheimer disease. Neurology, 83(10), 920-928.

[20] Morris, M. C. et al. (2016). Association of seafood consumption, brain mercury level, and APOE ε4 status with brain neuropathology in older adults. JAMA, 315(5), 489.

[21] Society for Neuroscience. (2018). Brain Facts. 8th Ed. Washington, DC: Society for Neuroscience

[22] Marinda. et al. (2019). Predictors of care dependency in nursing home residents with moderate to severe dementia: A cross-sectional study. International journal of nursing studies.

[23] Siemers, E. et al. (2016). Function and clinical meaningfulness of treatments for mild Alzheimer's disease. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 2, 105-112.

[24] Fulham, M. J. (2004). Neuroimaging. [Online]
Available at:
https://doi.org/10.1016/B978-008045046-9.00309-0
[Accessed on 6th Feb, 2020]

[25] Howard, R., Knapp, M., Brown, R., Banerjee, S., Adams, J., & Ballard, C. et al. (2012). Donepezil and memantine for moderate-to-severe Alzheimer's disease. N Engl J Med, 366(10), 893-903.

[26] Jason, W., & Andrew, B. (2018). Current understanding of Alzheimer's disease diagnosis and treatment. F1000Research, 7, 1161-.

[27] Yu, D. et al. (2019). A circuit view of deep brain stimulation in Alzheimer's disease and the possible mechanisms. Molecular Neurodegeneration, 14(1), 33.

[28] Laxton, A. W. et al. (2010). A Phase I Trial of Deep Brain Stimulation of Memory Circuits in Alzheimer's Disease. Annals of Neurology, 68(4), 521-534.

[29] Jacobs, M., Lee, D. J., & Lozano, A. M. (2019). Modifying the progression of Alzheimer's and Parkinson's disease with deep brain stimulation. [Online]
Available at:
https://doi.org/10.1016/j.neuropharm.2019.107860
[Accessed on 17th Jan, 2020]

[30] Boccardi, V., Baroni, M., Mangialasche, F., & Mecocci, P. (2016). Vitamin e family: role in the pathogenesis and treatment of Alzheimer's disease. Alzheimers & Dementia Translational Research & Clinical Interventions, 2(3), 182-191.