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A REVIEW OF ALZHEIMER'S DISEASE FORMATION, DIAGNOSIS AND TREATMENT

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Abstract

Alzheimer's disease is one prevalent form of dementia associated with ageing, which is affecting approximately 1.3% of the UK population. Although the exact cause of Alzheimer's disease remains unknown, it is widely accepted that the abnormal aggregation of proteins in the nervous system could be the primary cause resulting in this disease by damaging brain cells, and other risk factors also exist to increase the chances of having this disease such as ageing and a low education level. There are three possible distinct clinical phases in individuals with Alzheimer's disease pathology: asymptomatic, mild cognitive impairment and Alzheimer's disease. The symptoms of Alzheimer's disease progression worsen gradually over several years which generally involve memory loss, motor coordination problems and inability to perform routine daily tasks. Because Alzheimer's disease has a negative impact on not only the diagnosed patients but also their family members and the whole society, it is clear that treatment of this disease is required urgently. However, there is no current cure for Alzheimer's disease but the symptoms can be managed and even moderated by a cohort of drugs as well as some protective factors. For example, aiming at various pathological symptoms of Alzheimer's disease, different drugs have been investigated to resolve specific problems, thus help to control and alleviate the symptoms such as memory loss. There are also studies that discover numerous protective factors, which can reduce the risk of developing Alzheimer's disease like a high education level and regular physical activities. Despite all the research and findings, the progress on Alzheimer's disease is slow, and the prevention method is yet to be found, which means more attention and effort is needed to find an effective cure for this disease.

Keywords

Dementia, Alzheimer's Disease, Beta-Amyloid, Tau Proteins, Cognitive Functions, MCI

1. Introduction

Alzheimer's disease (AD) is a national mental health issue in the UK. According to National Health Service (NHS) in the UK, 850,000 people in the UK are living with AD, and this figure is predicted to ascend to 1 million by the year of 2025 and soar to 2 million by 2051 (Dementia UK report, 2014). AD poses a huge financial burden on the UK. It is estimated that the annual cost of AD is £26.3 billion, £4.3 billion of which is spent on healthcare, £10.3 billion is spent on social care and the rest is contributed by the work of unpaid caregivers and family members (Wittenberg, R., Knapp, M., Hu, B., Comas-Herrera, A., King, D., & Rehill, A., 2019).

People with AD can have difficulties in performing routine tasks. The symptoms begin with difficulties to recognise less familiar objects such as a friend's house or failing to use electronic devices. The symptoms progress to the point that the patients may not be able to recognise their family membersand even lose the identity of themselves. At later stages of AD, people can forget dressing, toileting and other simple tasks as the disease worsens progressively, which has a huge impact on both the patients and their families.

While the exact causation of the AD is unknow, it is directly linked to aggregations of proteins such as beta-amyloid and tau in the brain (Findeis, M., 2007). Investigations suggest that cardiovascular diseases, diabetes, a high fat diet, inflammation and viral infections can significantly increase the risk of AD formation and progression (Sauer, A., & Sauer, A., 2020). On the other hand, frequent cognitive exercise, physical training and active engagement in social events can delay the onset and control the symptoms of the condition (Nourhashémi, F., Gillette-Guyonnet, S., Andrieu, S., Ghisolfi, A., Ousset, P., & Grandjean, H. et al., 2020).

Despite having no definite cure, some medications are available to ameliorate the symptoms of AD, and these medications function by improving neurotransmitter release, motor function and memory (Alzheimer's disease - Diagnosis and treatment - Mayo Clinic., 2020).

This paper will provide a general view of dementia with a focus on AD diagnosis, symptoms and treatment.

2. Discussion

Dementia is an overall term that describes a group of symptoms associated with the loss of memory or the decline in the judgement and reasoning skills, which are severe enough to affect an

individual's ability to participate in daily activities (Shampo, M., Kyle, R., & Steensma, D., 2013). Initially described by Dr Alois Alzheimer in 1907, AD is the most common form of dementia (J, T., & C, L., 2018) (Figure 1).

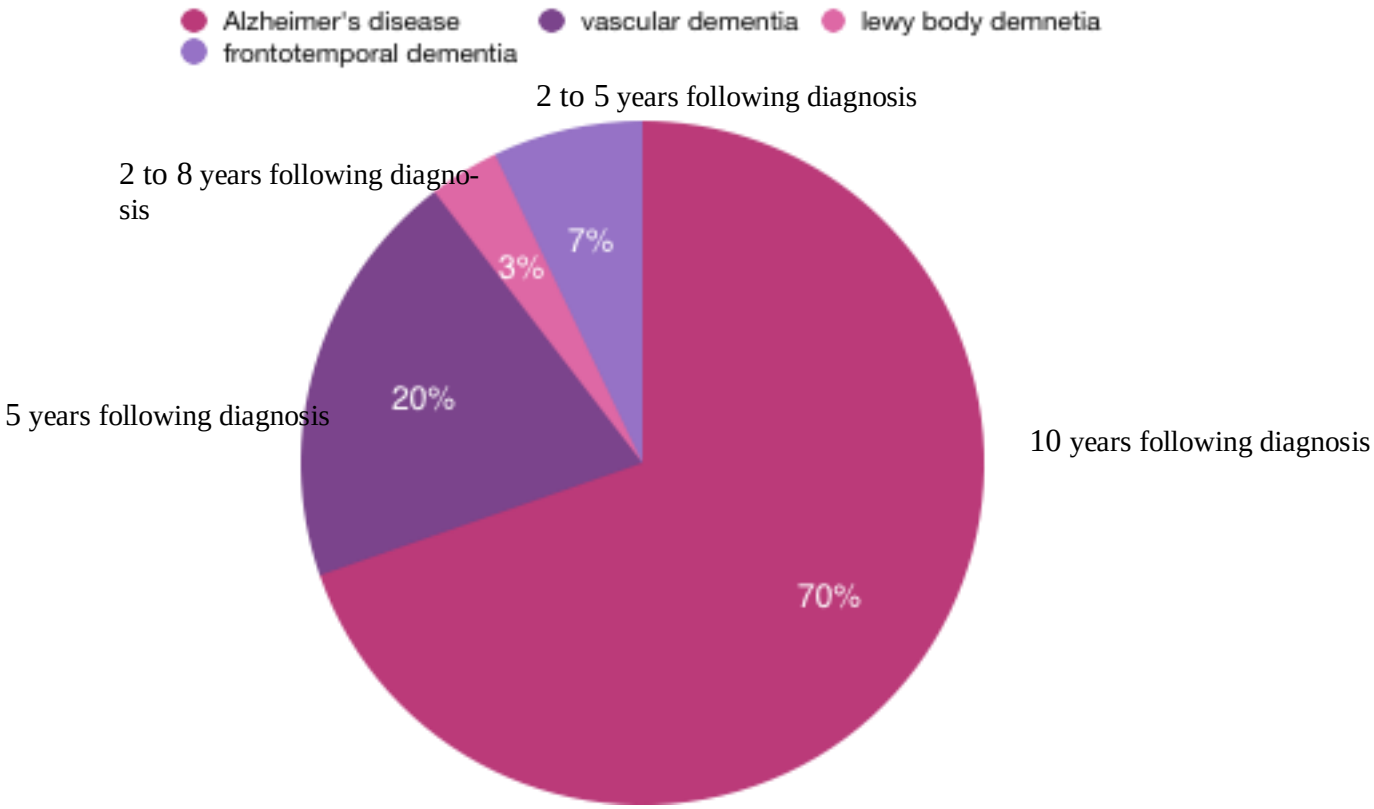

Figure 1: *An Approximation of the Percentage Prevalence and Average Lifespan after Diagnosis of Different Forms of Dementia in Male and Female Patients in the UK in 2019*
The figure is adopted from: Dementia Statistics Hub, 2019.

Dementia has some other forms such as vascular dementia, which usually occurs after one or more strokes. Vascular dementia is the second most common type of dementia, and it can also show a 'step-wise' deterioration occasionally(Symptoms of vascular dementia, 2019). Lewy Body dementia shows similar symptoms to AD, except that it involves more day-to-day symptomatic fluctuations, more hallucinations and Parkinson-type symptoms(Bradshaw, J, 2004). Lastly, Fronto-Temporal dementia happens when nerve cells in the frontal and the temporal lobes of the brain die, and the pathways connecting the lobes alter, the patients with this type of dementia may also suffer from the neglect of hygiene, the lack of social awareness and the loss of memory as a common symptom of dementia (The Different Types of Dementia | Join Dementia Research News., 2017). Although four types of dementia disorders are irreversible due to permanent damages to nerve cells, many other conditions can lead to reversible dementia such as depression, thyroid problems and vitamin deficiencies (About dementia, 2017).

3. Pathological symptoms of AD

AD can be diagnosed by the formation of beta-amyloid plaques which can accumulate in the brain and cause the formation of insoluble fibrils and oligomers in the brain. Tau is another protein which appears as tangles in dementia. Normally, Tau is involved in the microtubule formation, and it is necessary for the growth of axons and the development of neurons(C, P., 2018) (Figure 2).

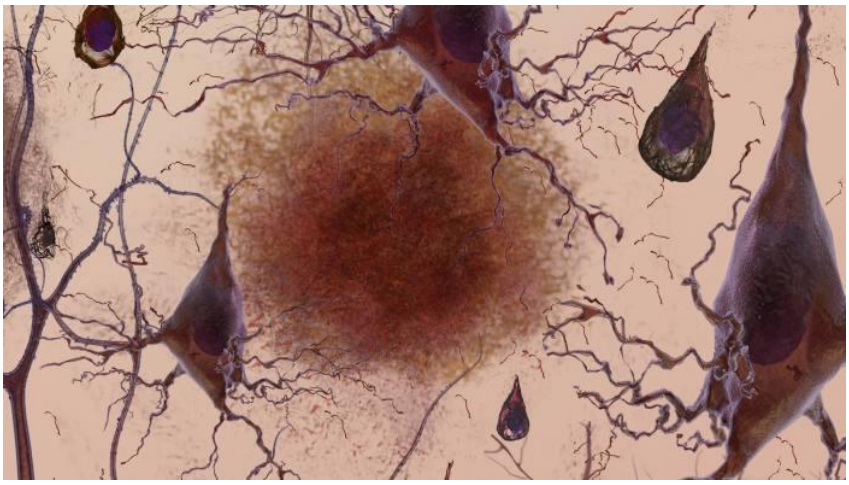

Figure 2: *The Graph Demonstrating Formation of Amyloid Plaques and Neurofibrillary Tangles in the Brain of a Patient with AD. The Figure is adopted from (D, C., 2016)*

Beta-amyloid is a glycoprotein formed by proteolytic cleavage of amyloid precursor protein in the nerve cell, which is catalysed by the enzyme secretaries and pre-senilins. Hyper-phosphorylated Tau proteins can accumulate into helical and filamentous that is deposited within neurons of the cerebral cortex. However, the exact causation of tangle and plaque formation is unknown (Kametani, F., & Hasegawa, M., 2018).

AD is generally categorised into two types: sporadic Alzheimer's Disease (SAD) and familial autosomal dominant Alzheimer's Disease (FAD). Accounting for 90%-95% of the cases, sporadic AD often shows a late onset resulting from an overproduction of dysregulated beta-amyloid precursor. While patients with SAD may or may not have a family history, the next generations of these patients will have higher risks of developing SAD (Bali, J., Gheinani, A., Zurbriggen, S., & Rajendran, L., 2012). With a dominant inheritance pattern, FAD has an early symptomatic onset and is caused by a single gene mutation that results in the accumulation of beta-amyloid (Morgan, J., 2016).

4. Risk Factors and Protective Factors Associated with AD

There is still a lack of comprehensive understanding of the underlying causes and molecular mechanisms leading to AD. The fact that the majority of AD happen sporadically indicates that the

disease could arise by combinations of various environmental and genetic risk factors. Since a high proportion of AD is seen among the elderly, ageing is widely considered to be the most prevalent risk factor. The possibility of developing ADdramatically increases after the age of 65 and the percentage of people who suffer rises to 32.5% among the 95-year-old (Table 1). Other behavioural risk factors include obesity, smoking and high blood pressure (Risk factors and prevention, 2019).

Table 1: *An Estimated Percentage of People with Late-Onset Dementia by Age Groups and Genders in the UK*
This figure is adopted from: alzheimers.org.uk., 2014

Age (years)	Females percentage	Males percentage	Total percentage
65-69	1.0	1.5	1.3
70-74	2.4	3.1	2.9
75-79	6.5	5.1	5.9
80-84	13.3	10.2	12.2
85-89	22.2	16.7	20.3
90-94	29.6	27.5	28.6
95+	34.4	30.0	32.5

On the other hand, factors such as frequent physical exercise and a high education level can function as protective factors for AD (Nourhashémi, F., Gillette-Guyonnet, S., Andrieu, S., Ghisolfi, A., Ousset, P., & Grandjean, H. et al., 2000). For example, a study performing lumbar punctures of participants and measuring the level of beta-amyloid and Tau proteins in the spinal fluid found that cerebrospinal fluid markers displayed fewer age-related problems with those who have higher education. One plausible theory about the protective effects of a high education level on AD is related to cognitive reserve theory, which means people with more educated background have an increased ability to compensate for the decline in the brain structure by shifting the mental processing to other areas of the brain (How is education linked to Alzheimer's progress?, 2019).

5. Signs and Symptoms of AD

Despite the variation in AD progression in different people, the general signs and symptoms are usually shared between different individuals (Table 2).

Table 2: *Typical Symptoms of Alzheimer's Disease in Pathological and Behavioural Aspects*

Pathological Symptoms	Behavioural Symptoms
Abnormal aggregation of beta-amyloid into plaques Abnormal accumulation of hyper-phosphorylated Tau proteins into neurofibrillary tangles irreversible damages to neurons	Agnosia (loss of memory) Aphasia (impairment of language skills) Apraxia (motor disorder) spatial disorientation depression

Due to its progressive, degenerative and irreversible nature, some of the typical signs and symptoms of AD include the continuing decline of memory by starting with a gradual onset. Aphasia, the impairment of language, also occurs during AD which can considerably affect a person's daily communications by impoverishing the ability of both understanding the languages (receptive aphasia) and expressing the ideas (expressive aphasia) (Kirshner, H., 2012). Apraxia, the inability to perform practiced motor tasks such as cooking, and agnosia, the incapacity to recognize familiar objects, are also seen as characteristic symptoms in people with AD (Green, R., Goldstein, F., Mirra, S., Alazraki, N., Baxt, J., & Bakay, R., 1995). In addition, spatial disorientation, which means the difficulty of navigating, also occurs in people with AD (Henderson, V., Mack, W., & Williams, B., 1989). AD patients at early stages of the disease may display symptoms like sleep disturbances, apathy which is a lack of emotional response as well as depression, then they progress to show hallucinations, physical and verbal aggression and inappropriate sexual advances later in life. In the final phases of the AD, patients show increasingly more severe physical conditions like incontinence, gait disturbances and seizures and eventually, a vegetative state will be seen in the final stage of AD which shows no visible brain activities (Table 3).

Table 3: *The Changes of Behavioral Problems in the Progress of Alzheimer's Disease*

Mild stage	Moderate stage	Severe stage
Depression Apathy Disturbed sleep Repetitive actions	Psychotic symptoms Psychomotor agitation Inappropriate sexual behaviours Arguing and anger	Tremor Myoclonus Gait disturbances Urinary incontinence Seizures A vegetative state

6. Diagnosis

Due to a lack of visible symptoms, AD can remain undiagnosed for several years before patients present themselves to the clinicians. Mild cognitive impairment (MCI) is a normal part of ageing which may occur after the asymptomatic stage and before AD. It includes abnormal cognitive performances, but does not negatively impact an individual's life and everyday activities. MCI can last for several years, and the progression of these symptoms depends on different people; thus, the various distribution of amyloid plaques and tangles (Gu, J., Fischer, C., Saposnik, G., & Schweizer, T., 2013). Therefore, it is essential to use some neuropsychological tests to distinguish between the normal ageing process and other symptoms such as delirium and depression and the abnormal decrease in cognitive abilities (Contributor, N., & Contributor, N., 2014). Therefore, it is essential that AD is diagnosed early to halt the progression of the disease.

People who are suspected to have the AD can carry out a mental status test such as mini mental status exam which includes questions aiming to test the participant's memory, orientation, concentration, aspects of language and the construction ability (Khachiyants, N., & Y. Kim, K., 2012). People who perform poorly on the test will take more reliable and accurate laboratory tests such as a blood test and an imaging test. Blood tests are usually done to test reversible dementia conditions like thyroid or vitamin problems and an early onset of Alzheimer's disease (C, P., 2019) and imaging tests, including structural imaging and functional imaging, are carried out to examine

the presence of pathological symptoms of AD (Desmyter, S., van Heeringen, C., & Audenaert, K., 2011).

7. Treatment

Although there are no confirmed medications to cure Alzheimer's disease, the cognitive decline can be slowed down by certain drugs proved by the NHS (Table 4).

Table 4: *Five Typical Drugs to Treat Alzheimer's Disease and their Common Curative and Side Effects*

Generic names (Brand names)	Curative effects	Side effects
Donepezil (Aricept)	Enzyme blockers working by restoring the balance of neurotransmitters in the brain. They can treat confusion related to Alzheimer's disease by improving memory, awareness and the ability to function.	Tiredness Nausea Vomiting Diarrhoea Muscle cramps Sleep disturbances
Galantamine (Reminyl)		
Rivastigmine (Exelon)		
Memantine (Namenda)	This medication works by blocking the glutamate in the brain. It can improve Alzheimer's disease related confusion including memory loss and the inability to perform everyday tasks	Tiredness Vomiting Diarrhoea Constipation Fast heart rate Aggression Headache

The death of neurons in the nucleus basils can lead to the deficiency in acetylcholine, which acts as a neurotransmitter involved in memory storage, targeting at this deficiency byDonepezil has been investigated. It can function as a specific and reversible inhibitor of cholinesterase to increase levels of available acetylcholine; thereby, the Donepezil may compensate for the loss of functioning cholinergic brain cells (Core Journal., 2006). Similarly, Reminyl and Exelon also act as cholinesterase inhibitor and have similar benefits as Donepezil which are effective agents recommended for the treatment of cognitive decline in patients with mild to moderate AD. Besides, side effects are also seen in these cholinesterase inhibitor drugs. For instance, 30% of people taking these drugs get

upset stomach, vomiting, diarrhoea and other symptoms (Alzheimer's disease: How effective are cholinesterase inhibitors? 2020).

A high level of glutamate is another typical feature of AD. Functioning as a neurotransmitter, glutamate can bind to the receptors on neurons when a high level of glutamate are present and can result in too much calcium ions to flow through to cause overstimulation thus lead to the damage of brain cells. It is found that Memantine, as a group of medicines called N-methyl-D-aspartate receptor antagonists, can bind to the same receptors and block glutamate, prevent the overstimulation of glutamate and moderate the damages to the neurons (How do drugs for Alzheimer's disease work? 2019). A medication named Gingko Biloba, is also shown to have certain slight benefits towards Alzheimer's disease such as reducing the memory loss (Janßen, I., Sturtz, S., Skipka, G., Zentner, A., Garrido, M., & Busse, R, 2010).

Hormones can also play a positive effect on AD. It is known that both males and females can produce oestrogen and females produce more of it. However, as women go throughmenopause, the levels of produced oestrogen decline. On the other hand, men continue to produce testosterone throughout their lives which can also be converted into oestrogen in men's brain cells, which means females in their menopause have lower levels of oestrogen than males of the same age. Accordingly, a higher prevalence of AD in women after the menopause can be due to the lower levels of oestrogen, so it is possible that oestrogen has protective effects on the neurons in the brain by blocking the harmful effects from beta-amyloid and women taking oestrogen are less likely to develop Alzheimer's Disease (Grimm, A., Lim, Y., Mensah-Nyagan, A., Götz, J., & Eckert, A, 2012). Indeed, the optimal methods towards AD are prevention rather than treatment and the best approach for prevention is the development of vaccines against b-amyloid formation.

In addition to the medical treatment, emotional and pastoral support by family and caregivers can play a significant role in the recovery of AD patients. For example, family members can help the patients by making memory aids such as memory tips to remind the patients about their activities, therefore practice patients' memory skills and strengthen their memories. Also, caregivers are instrumental in providing care to the patients by performing self-care and mobility tasks, such as helping patients with walking, bathing, dressing, feeding, toileting and keeping track of medications.

8. Conclusion and Outlook

AD is the most common of many causes of dementia, and its prevalence is increasing worldwide. Disease pathology begins many years before obvious symptoms. Neuropsychological imaging, and spinal fluid tests can establish the diagnosis with high accuracy. Despite the fact that

there are currently no treatments that slow the disease process, management of the cognitive and behavioural symptoms of AD can dramatically improve the lives of patients and their family members (Cleveland Clinic Center for Continuing Education).

In conclusion, although the human and social cost of AD as a disease of ageing is staggering, there is still hope that with increased knowledge of this disease, earlier diagnosis and intervention can be achieved to delay the progress of AD symptoms. Also, with more focus from the NHS on AD and the fast-paced research of neurology, more effective symptomatic drugs and vaccines can be investigated to lead to a better future for ageing populations.

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