

## Alzheimer's Disease: A Neurodegenerative Disorder

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### Abstract

Alzheimer's disease is the most common neurodegenerative disorder worldwide. It primarily affects the cerebral cortex and the hallmarks of the disease are accumulations of beta amyloid (A $\beta$ ) plaques and Tau tangles. Alzheimer's disease is a slowly progressing disease; it primarily causes long term memory loss and other symptoms like visual spatial dysfunction and Aphasia occurring at the end-stage of the disease. Common causes of death are infections like Pneumonia. Currently there is no way to cure Alzheimer's disease; current therapy revolves around the management of its primary and secondary symptoms. In Pakistan, the expected number of sufferers is estimated to be 0.2 million and expected to increase as life expectancy in the country improves.

**Keywords:** Alzheimer's disease; Cerebral cortex; Therapy; Secondary symptoms

### Introduction

Alzheimer's disease is an incurable neurodegenerative disorder, causing cognitive and behavioral impairment because of degeneration of cholinergic neurons. It primarily affects the elderly, with the age of onset being 65 years. It is the most frequent form of dementia around the world. According to the World Alzheimer report 2016, 47 million people currently live with dementia worldwide, with an expected increase to more than 131 million by 2050, as population age.

Alzheimer's disease is a major public health problem, due to the financial costs involved in the long-term care involved for managing the affected individuals [1].

The woman in her 50s suffered from short term memory loss and other puzzling symptoms. After her death 5 years later, sent her brain and her medical records to a lab in Munich, where he was working at. By studying sections of her brain, he discovered amyloid plaques and neurofibrillary tangles in the specimens [2].

The pathology and symptoms of the disease were presented for the first time and then termed as Presenile Dementia. The findings were formally published in 1907 [3].

### Literature Review

#### Pathogenesis and morphology

Alzheimer's disease primarily affects the cerebral cortex. At the Macroscopic level, autopsies reveal cortical atrophy, with narrow gyri, widened sulci and dilated ventricles. The hippocampus and amygdala are particularly affected [4].

The microscopic hallmarks of the disease are accumulations of beta amyloid (A $\beta$ ) plaques and Tau tangles [5,6].

Beta amyloid, a peptide, accumulates due to a mutation in its precursor, Amyloid Precursor Protein (APP), which increases the rate at which A $\beta$  is produced. In normal neurons APP undergoes alpha cleavage; beta cleavage leads to the production of beta amyloid. Since the gene encoding APP is present on chromosome 21, the risk factor for Alzheimer's disease is higher among individuals suffering from down syndrome. Accumulation of beta amyloid can cause an inflammatory response from the microglia and astrocytes. While this process is intended to clear the accumulated debris, it can lead to further neuronal damage, due to the secretion of mediators [7,8].

Healthy cells contain microtubules which stabilize the internal structure of the cells; in neurons, a special protein called Tau is an integral part of the micro tubular structure. In Alzheimer's disease, Tau accumulates as insoluble neurofibrillary tangles within the neurons. This is due to its hyper phosphorylation, which leads to an inability to bind to and stabilize microtubule. A $\beta$  accumulation is the key initiating event in the development of the disease, although both A $\beta$  plaques and Tau tangles contribute to the development of the disease.

**Clinical presentation:** Alzheimer's disease is a slowly progressing disease; its symptomatic course running for more than 10 years. At its onset, the individual presents with confusion and forgetfulness. This gradually progresses to long-term memory loss and other symptoms like visuospatial dysfunction and Aphasia [9]. In the end stages of the disease, the patients can become completely bed-ridden, along with an inability to speak. Secondary symptoms of the disease include depression, anxiety, hallucinations, weight loss and incontinence. They also suffer from undercurrent diseases, with the common cause of death being infections like Pneumonia [10].

**Workup and diagnosis:** To date, there is no specific diagnostic test; only a biopsy of the brain can lead to a definitive diagnosis. Current practice revolves around taking a thorough history of the

patient, from themselves and those who know them well, as well as performing a thorough neurological and physical examination of the patient to assess the stage of the disease [10].

Alzheimer's disease is usually not noticeable at its pre-clinical stage; diagnosis is usually made at its mild stage when the symptoms of memory loss and confusion first appear. As it reaches its moderate stage, the individual starts suffering from symptoms of Aphasia, with a difficulty in reading and writing, particularly with numbers. In its last stages, memory loss becomes severe, to the point that the patient is unable to recognize close family members and friends, as well as lose their ability to communicate with others. When making a diagnosis for Alzheimer's disease, it is important to exclude other probable causes of dementia and memory loss, e.g. subdural hematomas, normal-pressure hydrocephalus, thyroid disorders, vitamin deficiencies, carcinomas, etc. The American Academy of Neurology recommends the measurement of cobalamin (vitamin B) levels, as well as thyroid function tests. Radio imaging studies like MRI and PET scans, can help in ruling out strokes, carcinomas, etc. as a cause of dementia. Lumbar puncture has also proven to be useful in select cases where the cause of dementia was normal-pressure hydrocephalus or a central nervous system infection [11].

**Treatment and management:** Currently there is no way to cure Alzheimer's disease; current therapy revolves around the management of its primary and secondary symptoms. Standard therapy involves slowing the decline in cognitive ability using Acetyl cholinesterase inhibitors and NMDA receptor antagonists. Numerous studies have proven that the memory loss associated with the disease is due to the progressive degeneration of cholinergic neurons within the brain. Therefore, the use of acetyl cholinesterase inhibitors improves the function of the remaining intact neurons and has proven to be efficacious during the mild to moderate stages of the disease. Overstimulation of the glutamate receptors within the brain has been suggested to have a toxic effect on neurons, leading to apoptosis. Hence, the inhibition of its receptors using NMDA antagonists slows the degeneration of neurons and improving symptoms in the moderate to severe forms of the disease. Psychotropic agents like Antidepressants, for depression, Anxiolytics and beta-blockers for anxiety and Neuroleptics for hallucinations, are used for the management of secondary symptoms associated with the disease. Pharmacologic research for a cure is focusing on halting mechanisms involved in production of Beta-amyloid plaques and Tau tangles. To date, no drug has managed to pass phase 3 trial show ever, a phase 2 study has shown promising results for an anti-amyloid agent among patients with early stage Alzheimer's disease. The agent has shown to reduce amyloid plaques if administered at high doses, along with a significant decrease in the decline of cognitive abilities and memory loss [12].

**Reflection from Pakistan:** While difficult to get an exact number of people suffering from Alzheimer's disease in Pakistan, it is estimated to be 0.2 million and expected to increase as life expectancy in the country improves. The diagnosis rate for Alzheimer's disease in Pakistan is low, with many cases being unreported. Social stigma surrounding any mental health disorder is strong within the region, with a fear of being marginalized, which leads to an extremely late diagnosis when the disease has reached its end stage. It is also often ignored as a symptom of old age; hence professional opinion is not sought after. In extreme cases, the dementia is considered to be due to black magic, leading to harsh treatment of the patient. The loss of sense of time of the day leading to forgetfulness about the number and

the time that prayers need to be performed, conflicts with the religiosity of the people in Pakistan; the resulting strong feelings of guilt and shame are a strong factor for not seeking professional help, as highlighted by the interim findings of a report published by Alzheimer's Pakistan. Lack of neurologists who specialize in treating Alzheimer's disease is another problem for the citizens of this country. In cases where professional help is sought, inadequate training of healthcare professionals often leads to a misdiagnosis and an incorrect documentation of the disease [13].

To improve healthcare facilities for Alzheimer's patients in Pakistan, the Punjab health department is planning on starting geriatric services in public hospitals which provide a range of services like hospital-based memory clinics, improvement of resources to increase early diagnosis rates, counselling services for affected individuals and their families, in accordance with the WHO's global plan on dementia, to which Pakistan is a signatory [14].

At the community level, Alzheimer's Pakistan, for the past two years, has been playing an active part in spreading awareness in the form of interactive sessions and conferences, to reduce the social stigma surrounding the disease [15].

## Conclusion

Alzheimer's disease, while not being treatable yet, if diagnosed at an early stage, can be effectively managed, leading to an improvement in the quality of life of individuals suffering from the disease.

To achieve this, training programs for medical students, residents and specialists need to be improved. Full time care-givers also need to be trained to better manage the symptoms of the disease on a daily basis. At the community level, awareness programs need to be conducted to end the social stigma surrounding dementia and its dismissal as being a symptom of old age. This will enable early detection of Alzheimer's disease and allow its sufferers to receive improved palliative care.

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