Dementia: Advances and Treatment

Chapter 5

Alzheimer's Diseases

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1. Introduction

In this chapter the description, Prevalence, Incidence,types and Symptoms of Dementia are discussed. Symptoms of AD, risk factors, different stages of AD and Diagnosis of AD are given in detail for the purpose of better understanding of Disease.

2. Dementia

According to Shaji K S et al., Dementia is a syndrome usually chronic, characterized by a progressive, global deterioration in intellect including memory, learning, orientation, language, comprehension and judgement due to disease of the brain [1]. Alzheimer's disease International (ADI) conducted a systematic review on global prevalence worldwide in 2009 and published the data in the World Alzheimer Report. In that it is estimated that there will be 36 million people with Dementia in 2010, nearly doubling every 20 years and it is anticipated the number to reach 66 million by 2030 and 115 million by 2050 [2].

2.1. Prevalence

The prevalence of Dementia refers to the proportion of people in a population who have Dementia at a given point of time. The number of people living with Dementia worldwide in 2015 was estimated at 47.47 million, reaching 75.63 million in 2030 and 135.46 million in 2050 [3].

As shown in **Figure 2.1**, the updated estimates are higher than the original estimates reported in the 2009 World Alzheimer Report, by 15% in 2030, and by 17% in 2050 [2].While 37% of the people living with Dementia live in high-income countries, 63% live in low and middle-income countries [2]. Hence the need of early Diagnosis is more for Low and Middle

Income Countries compared to high Income countries.

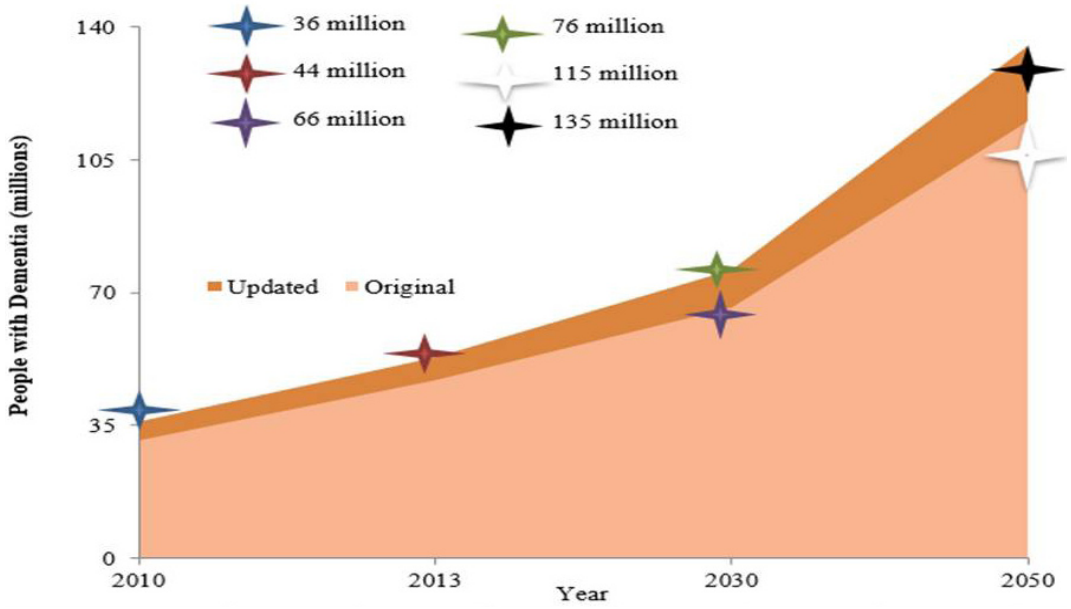

Figure 2.1: Increase in number of people with Dementia Worldwide (2010-2050), Comparing original and updated estimates

Figure 2.2: clearly indicates the number of people affected from Dementia is more in LMIC compared to HIC. The growth is almost constant in HIC whereas an exponential growth is observed in LMIC [2].

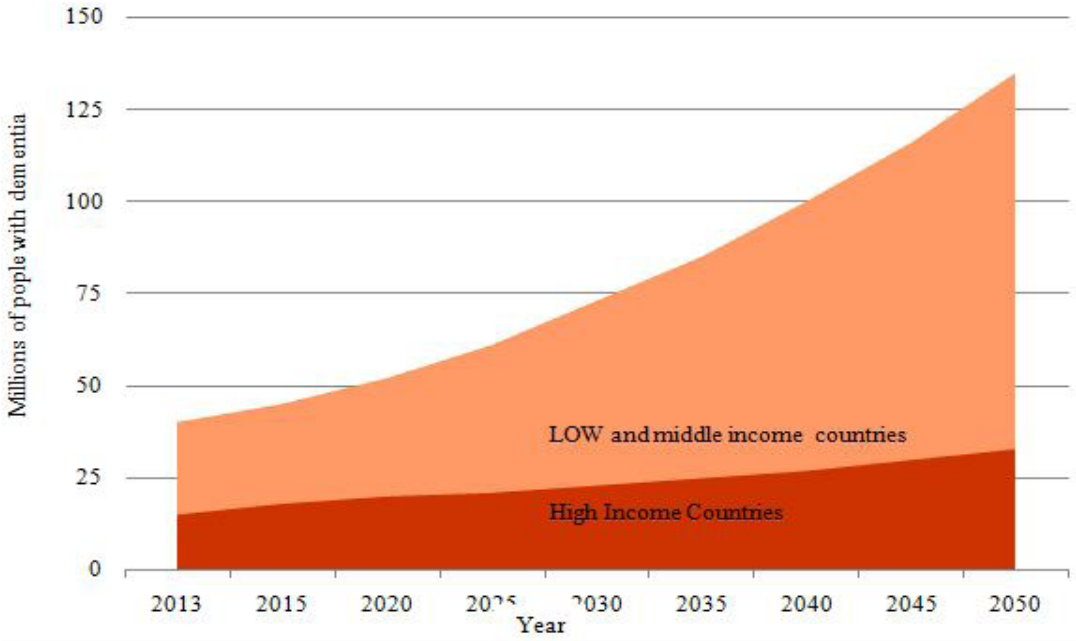

Figure 2.2: People with Dementia in LMIC andHIC

In USA, of those with Alzheimer's disease, an estimated, 4% are of age below 65, 15% are of age between 65 and 74, 43% are of group between 75 and 84, and 38 % are aged above 85 (**Figure 2.3**) [4].

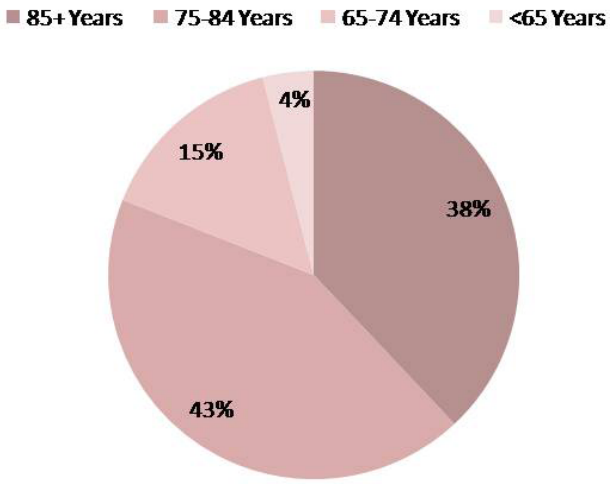

Figure 2.3: People affected byAlzheimer'sDisease, age-wise in the United States, 2015.

According to Thies W, Bleiler L, today, someone in America develops AD every 68 seconds. By 2050, one new case of AD is expected to develop every 33 seconds, or nearly a million new cases per year, and the total estimated prevalence is expected to be 13.8 million. AD is the sixth leading cause of death in the United States and the fifth leading cause of death in Americans of age 65 years and above[5].These facts and figures reveal us the need for early diagnosis of AD.

Shajiet.al.in their report on Dementia India report 2010 have mentioned that India was home to more than 75 million people older than sixty years in 2001.

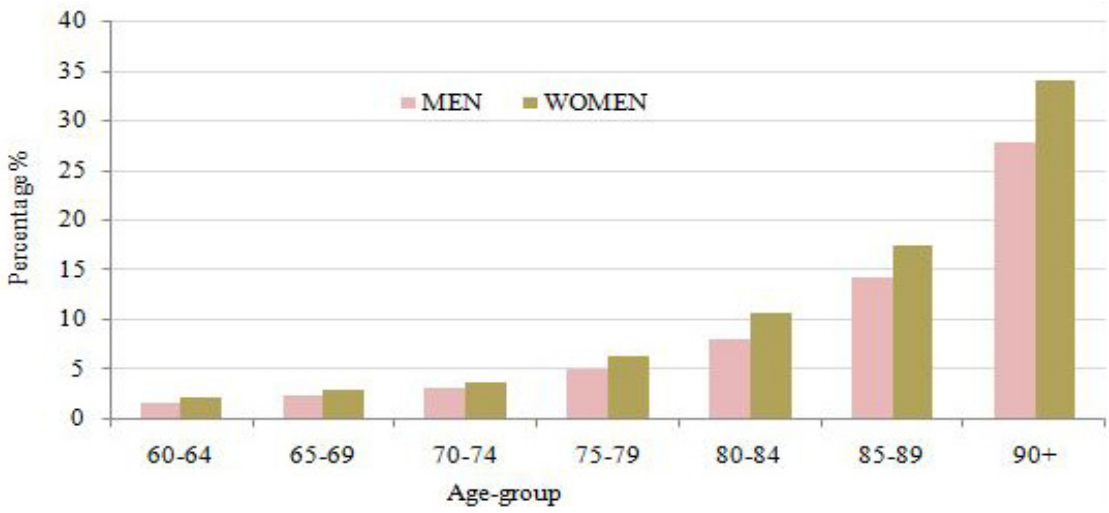

Figure 2.4: Prevalence of Dementia in India, 2010.

This age group, which was 7.5% of the population, is expected to grow rapidly in the coming decades [1]. For the year 2010, 3.6 million Indians are expected to have Dementia (2.1 million women & 1.5 million men). From **Figure 2.4**, it is understood, among demented, women are more in number compared to men.

2.2. The Incidence of Dementia Worldwide

Incidence is the number of new cases of a disease that develop in a given time period [6]. The incidence of Dementia increases exponentially with increasing age, based on the available

estimates for the global incidence of Dementia dating from 2010 [7].For all studies combined, the incidence of Dementia doubled with every 5.9 year increase in age, from 3.1/ 1000 person years at age 60-64, to 175.0/ 1000 person years at age 95+[6].While the incidence of Dementia appeared to be higher in countries with high-incomes than in low- or middle-income countries, this was largely an artifact, due to the specific diagnostic criteria used.

People of different age groups, expected to be affected from Dementia, worldwide, are shown in **Table 2.3** [3]. Word wide, every year 7.7 million new cases of Dementia are anticipated, with Asia as a major contributor, inferring one new case every 4.1 seconds.

Table 2.1: Estimated Annual Numbers of Incident Cases of Dementia, by Age Group.

Age Region	60-64	65-69	70-74	75-79	80-84	85-89	90+	Total
	People with Dementia in millions							
Asia	0.39	0.48	0.62	0.72	0.66	0.44	0.26	3.56
Europe	0.13	0.18	0.32	0.43	0.54	0.44	0.29	2.34
The America	0.10	0.13	0.17	0.21	0.25	0.23	0.17	1.25
Africa	0.07	0.09	0.10	0.11	0.09	0.04	0.02	0.53
World Total	0.69	0.88	1.22	1.46	1.54	1.15	0.74	7.68

Figure 2.5: indicates the incidence of people with Dementia in different age groups. The number of people in the age group of 65-74 years is expected to increase steadily over time till 2020 and after 2020 and a steep increment is predicted for people aged above 75 years [1].

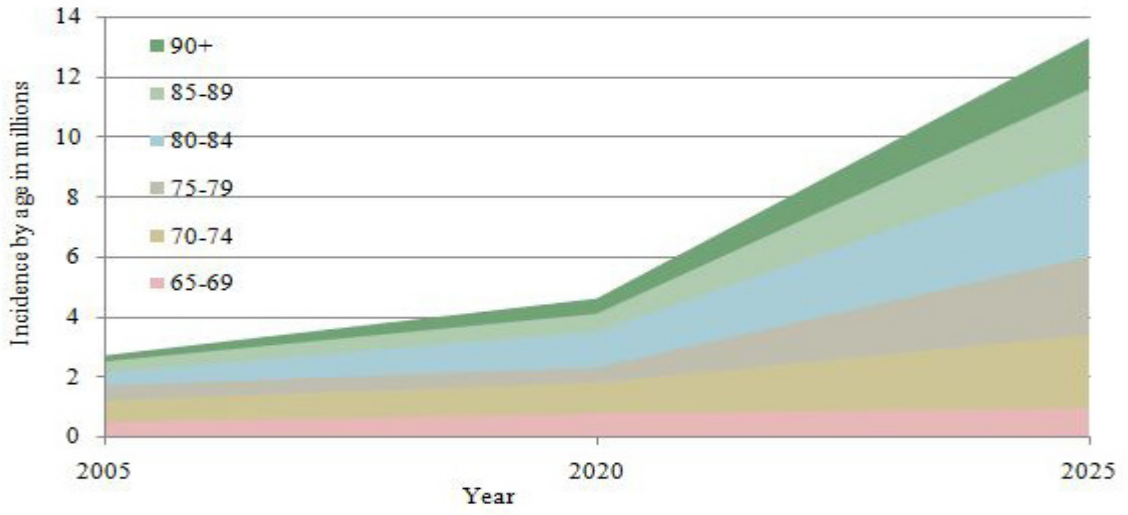

Figure 2.5: Trend in Dementia incidence by age over time (2005-2050).

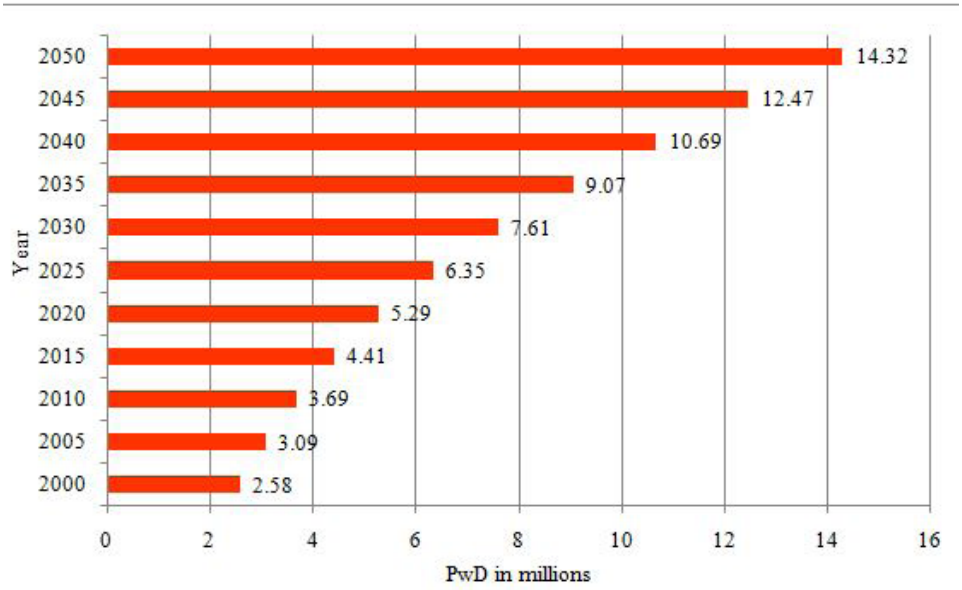

Figure 2.6: Estimation of number of PwD in India between 2000 and 2050.

The future projections are estimated on the assumption that prevalence of Dementia is stable over time, which may not be true. The prevalence increases with increase in the incidence and with increasing life expectancy. In India, for the next 35 years, an exponential growth in Incidence is anticipated (**Figure 2.6**).

From (**Figure 2.7**), it is clear that, by the year 2025, UK is projected to have 1 million PwD and till 2050, is expected to be almost constant. According to current estimates, India has more than 3 million PwD (People with Dementia) and is expected to overtake USA in the coming years and by 2050 India is expected to have maximum PwD.

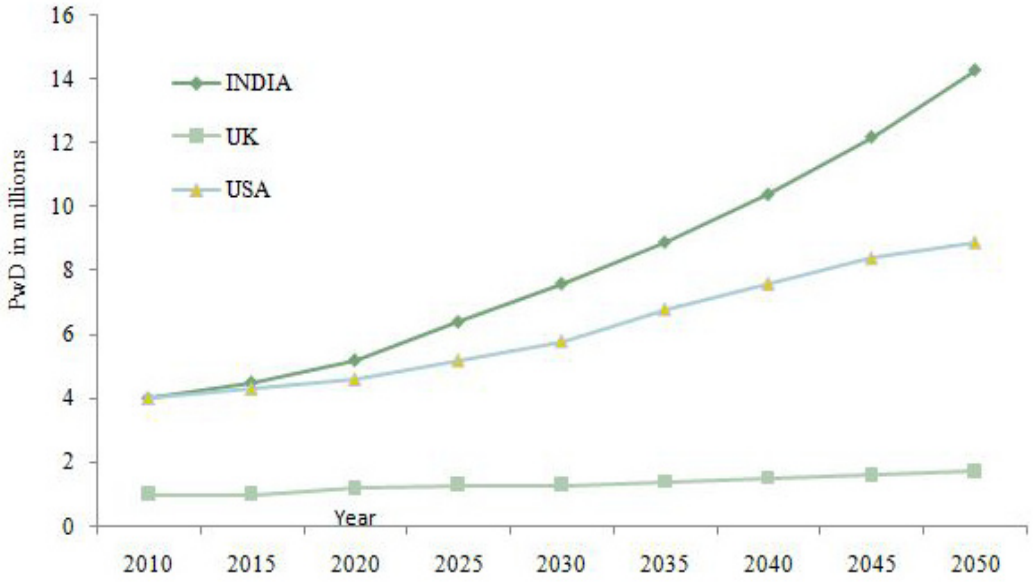

Figure 2.7: Estimated number of PwD aged above 60 years in India, UK and USA.

A key finding from the Global Burden of Disease report is that chronic non-communicable diseases are rapidly becoming the dominant causes of ill-health in all developing regions except Sub-Saharan Africa.

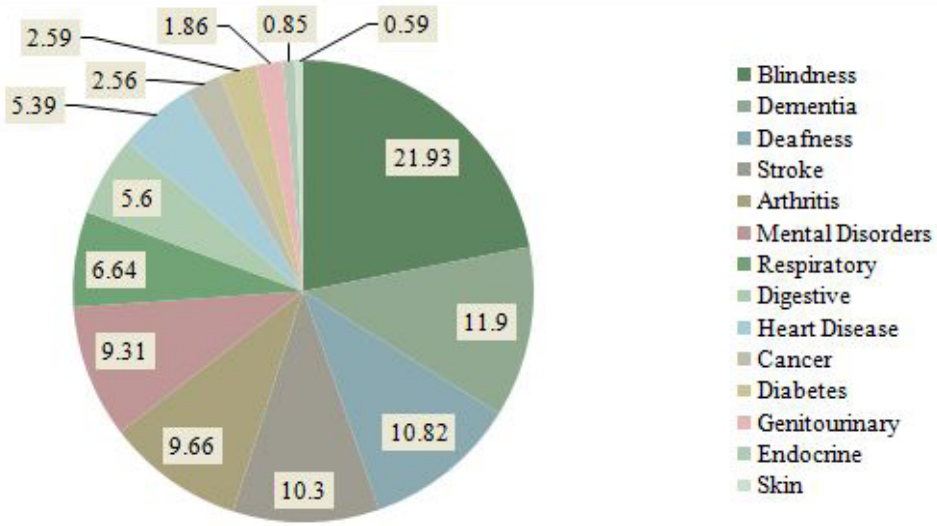

Figure 2.8: Contribution of chronic diseases.

Contribution of Dementia is 11.9% to total chronic diseases **(Figure 2.8)**. After Blindness Dementia stands second inferring the need for early diagnosis [1].

2.3. Symptoms

The symptoms of Dementia are as follows,

- **Problems with memory, thinking and language:** Forgetting words for things or people, or not understanding what's being said are the common symptoms of Dementia. Problems with memory lead to confusion.

- **Problems with doing day-to-day things:** Problems with getting dressed, eating and going to the toilet are the expected symptoms of demented. People with Dementia find following instructions as a difficult task.

- **Different behavior:** People with Dementia can become agitated, irritable, and restless. They may start pacing the room or wandering. They may shout at their family or lash out. They might also feel anxious or depressed. Or they may laugh out loud or start crying at the inappropriate times. Some people get delusions (imagining that something is happening when it isn't). For example, they think somebody is trying to steal their things. Some get hallucinations (seeing or hearing things that aren't there) [4].

2.4. Common Types of Dementia and their Typical Characteristics

Dementia is classified into Alzheimer's disease, Dementia with lewy bodies, Parkinson's disease, Normal Pressure Hydrocephalus, Vascular Dementia, Front temporal labor degeneration Dementia. The different types of Dementia, their symptoms, neuropathology and their proportion are listed in Table 2.5. Alzheimer'sDisease is the major stakeholder [7].

Figure 2.2: Characteristics of Dementia Subtypes

Dementia Subtype	Symptoms	Neuropathology	Proportion of Dementia
Alzheimer'sdisease	Impaired memory, apathy and depression, gradual onset	Cortical amyloid and neurofibrillary tangles.	60-80%
Vascular Dementia	Impaired ability to make decisions, Inability to plan or organize	Blood vessel blockage or damage leading to strokes or bleeding in the brain.	20-30%
Dementia with Lewy bodies	Marked fluctuation in cognitive ability, visual hallucination, parkinsonism	Cortical lewy bodies.	<5 %
Front temporal lobar degeneration	Personality changes, mood changes, language difficulties.	No single pathology, damage limited to frontal and temporal lobes.	15-10%
Parkinson`s disease	Problems with movement, slowness, rigidity, vibration and changes in pace.	Alpha-Synuclein aggregates appear in the area deep in the brain called the substantia nigra. The aggregates cause degeneration of the nerve cells that produce dopamine.	6-8%
Normal pressure hydrocephalus	Difficulty walking, memory loss and inability to control urination	Impaired reabsorption of cerebrospinal fluid and consequent increaseof fluid in the brain increases pressure in the brain. People with brain hemorrhage and meningitis are at increased risk.	<5%

3. Alzheimer's Disease

Alzheimer's disease was discovered in 1906 by Alois Alzheimer, a German neurologist and psychiatrist. The disease was initially observed in a 51-year-old woman named Auguste D. Her family brought her to Dr. Alzheimer in 1901 after noticing changes in her personality and behavior. The family reported problems with memory, difficulty in speaking, and impaired comprehension. Dr. Alzheimer later described Auguste as having an aggressive form of Dementia, manifesting in memory, language and behavioral deficits. Doctor noted many abnormal symptoms including agitation, difficulty with speech and confusion. He followed her care for five years, until her death in 1906. Following her death, Dr. Alzheimer performed an autopsy, during which he found dramatic shrinkage of the cerebral cortex, fatty deposits in blood vessels, and atrophied brain cells. He discovered neurofibrillary tangles and senile plaques, which has become indicative of AD. The condition was first discussed in medical literature in 1907 and named after Alzheimer in 1910 [8].

Though AD was first identified in the beginning of 19th century and as most common type of Dementia in the first quarter of the century, research reveals that the precise biologic changes that cause the disease is not yet identified [3]. Researchers believe that early detection will be key to peventing slowing and stopping Alzheimer's diseases.

Alzheimer's disease was first identified more than 100 years ago but 70 years passed

before it was recognized as the most comman cause of dimentia and a “major killer”. Although research has revealed a great deal about Alzheimer’s, much is yet to be discovered about the precise biologic changes that causes Alzheimer’s.

3.1. Symptoms of Alzheimer’s Disease

Alzheimer’s symptoms vary among individuals. The most common initial symptom is a gradually worsening ability to remember new information. This memory decline occurs because of the death of the neurons in brain regions which are involved in the formation of new memories. The following are common symptoms of Alzheimer’sdisease.

- Memory loss that disrupts daily life.
- Challenges in planning or solving problems.
- Difficulty completing familiar task at home, at work or at leisure.
- Confusion with time or place.
- Trouble in understanding virtual images and spatial.
- New problems with words in speaking or writing.
- Misplacing things and losing the ability to retrace.
- Decreased or poor judgment.
- Withdrawal from work or social activities.
- Changes in mood and personality including apathy and depression.

The pace at which symptoms advance from mild to moderate to serve varies from person to person. As the disease progresses,cognitive and functional abilities decline. People need the assistance with basic activities such as bathing, dressing,eating and using the bathroom; loose their ability to communicate; fail to recognize loved ones; and become bed-bound and reliant and need round the clock care. When individuals have difficulty in movingthey are more vulnerable to infections,including pneumonia (infection of the lungs). Alzheimer’s related pneumonia is often a contributing factor to the death of people with Alzheimer’sdisease.

3.2. Risk Factors

There are various risk factors which contribute to the development of the disease namely age, genetics, smoking, consuming alcohol, cholesterol, Down syndrome [4].

A. Age

The greatest risk factor for Alzheimer's disease is advancing age, but Alzheimer'sis not a typical part of aging. Most people with Alzheimer's disease are diagnosed at age 65 or older. However, people younger than 65 can also develop the disease rarely. Advancing age is not the only risk factor for Alzheimer's disease.

B. Family History

Individuals who have a parent, brother or sister with Alzheimer's are more likely to develop the disease than those who do not have a first-degree relative with Alzheimer's [9].

C. Mild Cognitive Impairment (MCI)

MCI is a condition in which an individual has mild but measurable changes in thinking abilities that are noticeable to the person affected and to family members and friends, but that do not affect the individual's ability to carry out everyday activities. People with MCI are more likely to develop Alzheimer's and other Dementia related diseases than people without MCI, as MCI involves memory problems. Nearly half of all people who have visited a doctor about MCI symptoms will develop Dementia in 3 or 4 years [10].

D. Cardiovascular Disease Risk Factors

Growing evidence suggests that the health of the brain is closely linked to the overall health of the heart and blood vessels. The brain is nourished by one of the body's richest networks of blood vessels. A healthy heart ensures that enough blood is pumped through these blood vessels to the brain, and healthy blood vessels ensures that the brain is supplied with the oxygen- and nutrient-rich blood it needs to function normally.

Many factors that increase the risk of cardiovascular disease are also associated with a higher risk of developing Alzheimer's and other Dementia related diseases. These factors include smoking obesity diabetes, high cholesterol in midlife and hypertension in midlife [3].

E. Education

People with fewer years of education are at higher risk for Alzheimer'sand other Dementia and related diseases than those with more years of formal education. Some researchers believe that having more years of education builds a "cognitive reserve" that enables individuals to better compensate for changes in the brain that could result in symptoms of Alzheimer'sor another Dementia [11-14]. According to the cognitive reserve hypothesis, having more years of education increases the connections between neurons in the brain and enables the brain to compensate for the early brain changes of Alzheimer'sby using alternate routes of neuron-to-neuron communication to complete a cognitive task. However, some scientists believe that the

increased risk of Dementia among those with lower educational attainment may be explained by other factors common to people in lower socioeconomic groups, such as increased risk for disease in general and less access to medical care [15].

F. Social and Cognitive Engagement

Additional studies suggest that other modifiable factors, such as remaining mentally and socially active, may support brain health and possibly reduce the risk of Alzheimer'sand other Dementia and other related diseases [16-19].

G.Traumatic Brain Injury (TBI)

Moderate and severe TBI increase the risk of developing Alzheimer'sdisease and other Dementia and other related diseases. TBI is the disruption of normal brain function caused by a blow or jolt to the head or penetration of the skull by a foreign object [4].

3.3. Changes in the Brain-Associated With Alzheimer's Disease

Brain has three main parts namely cerebrum, cerebellum and brain stem. Cerebrum is the largest part of the human brain. The functions of this include thinking, reasoning, interpretation, judgment, will, emotions, speech, intelligence, memory and personality traits. Cerebellum lies at the back of the head under cerebrum. It co-ordinates the contraction of voluntary muscles and maintains body balance. Brain stem connects the brain to the spinal cord and controls automatic functions such as breathing, heart rate and blood pressure. Cerebrum has wrinkled outer surface known as cortex. Scientists have mapped the cortex by identifying areas strongly linked to certain functions, some of them are Generation of thoughts, solving problems and making plans, Interpretation of sensations from the body and sights, sound and smell from outside world and forming and storing information in memories.

A healthy adult brain has 100 billion neurons, each with long, branching extensions. Signals that form memories and thoughts move through an individual nerve cell as a tiny electrical charge. Nerve cells connect to one another at synapses. When a charge reaches a synapse, it triggers the release of tiny bursts of chemicals called neurotransmitters. The neurotransmitters travel across the synapse, carrying signals to other cells. Scientists have identified trillions of synapses and dozens of neurotransmitters. Alzheimer's disease disrupts both the electrical charges travel within cells and the activity of neurotransmitters.

The accumulation of protein beta-amyloid (called beta amyloid plaques) outside neuron and accumulation of an abnormal form of the protein tau (called tau tangles) inside neurons are two of several brain changes believed to contribute to the development of Alzheimer's. In Alzheimer's disease, information transfer at synapses begins to fail, the number of synapses declines, and the neurons eventually die. The accumulation of beta-amyloid is believed to in-

terfere with the neuron-to-neuron communication at synapses and to contribute to cell death [6].

Alzheimer's disease leads to nerve cell death and tissue loss throughout the brain. Over time, the brain shrinks dramatically, affecting nearly all its functions. In addition to the brain shrinkage, the cortex shrivels up, damaging areas involved in thinking, planning and remembering. Hippocampus, an area of the cortex that plays a key role in formation of new memories is shirked severely and is shown in (**Figure 2.9**).

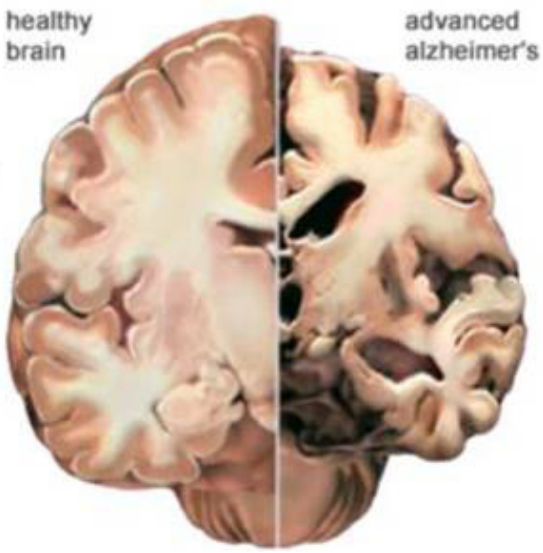

Figure 2.9: Image of hippocampus.

Alzheimer's tissue has many fewer nerve cells and synapses than a healthy brain. Plaques, abnormal clusters of protein fragments, build up between nerve cells. (Figure 2.10) shows the formation of dead and dying nerve cells containing tangles, which are made up of twisted strands of another protein.

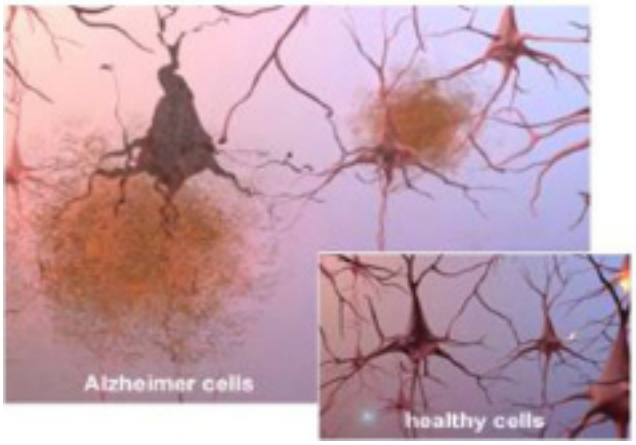

Figure 2.10: Dead and dying nerve cells.

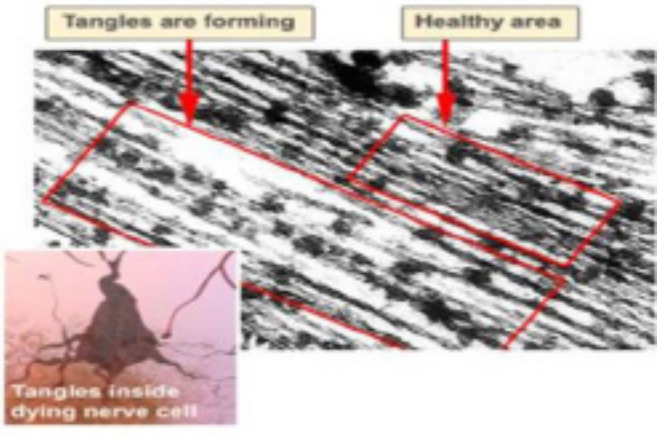

Figure 2.11: Formation of Tangles.

(**Figure 2.11**) shows the formation of tangles that happen in the brain of the diseased. Tangles destroy a vital cell transport system made of proteins. This electron microscope picture shows a cell with some healthy areas and other areas where tangles are forming. In healthy areas, the transport system is organized in orderly parallel strands somewhat like railroad tracks. Food molecules, cell parts and other key materials travel along the "tracks." A protein called

tau helps the tracks stay straight. In areas where tangles are forming Tau collapses into twisted strands called tangles. The tracks can no longer stay straight. They fall apart and disintegrate. Nutrients and other essential supplies can no longer move through the cells, which eventually die. Tau tangles block the transport of nutrients and other essential molecules inside neurons and are also believed to contribute to cell death.

(**Figure 2.12**) shows the formation of plaques in the brain of AD patient. Plaques are formed when protein pieces called beta-amyloid clump together. Beta-amyloid comes from a larger protein found in the fatty membrane surrounding nerve cells. Beta-amyloid is chemically "sticky" and gradually builds up into plaques.

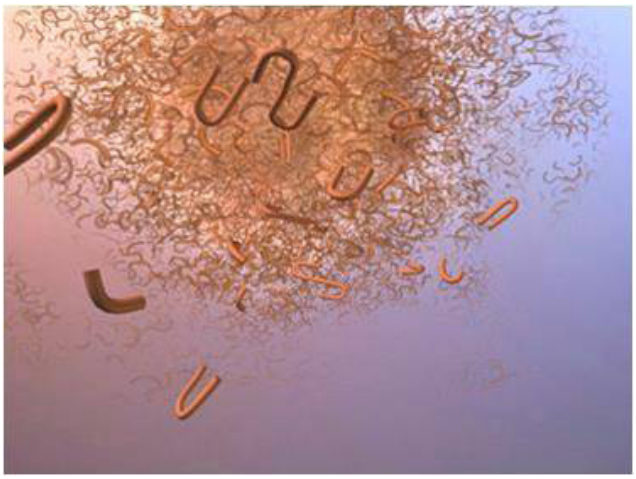

Figure 2.12: Formation of Plaques.

The most damaging form of beta-amyloid may be groups of a few pieces rather than the plaques themselves. The small clumps may block cell-to-cell signaling at synapses. They may also activate immune system cells that trigger inflammation and devour disabled cells.

The brains of people with advanced Alzheimer's show dramatic shrinkage from cell lose and widespread debris from dead and dying neurons. The time between the initial brain changes of Alzheimer's and the symptoms of advanced Alzheimer's is considered by scientists to represent "continuum" of Alzheimer's. At the start of the continuum, individuals are able to function normally despite these brain changes. Further along the continuum, the brain no longer can compensate from the neural damage that has occurred, and individuals show subtle decline in cognitive function. Later, neural damage is so significant that individuals show obvious cognitive decline, including such as memory loss or confusion as time or place. Later, performing basic functions become difficult.

3.4. Stages of Alzheimer's Disease

Alzheimer's disease continuum can be viewed in three different stages. They are

1. Early-stage
2. Moderate stage

3. Severe stage

A. Early-Stage Alzheimer's Disease

This is the initial stage, is often when the disease is first diagnosed, which usually lasts 2 to 4 years. In this stage, family and friends may begin to realize that there has been a decline in the patient's cognitive ability.

Common symptoms include: Difficulty in; retaining new information, problem solving, decision making, managing finances, expressing thoughts, daily living. The person may begin to withdraw socially or show lack of motivation. Misplacing belongings and getting lost are also common symptoms. The patient may have difficulty in navigating in familiar surroundings.

B. Moderate Alzheimer's Disease

Patients often experience increased difficulty with memory and may need help with day to-day activities. This lasts for 2 to 10 years, the longest stage of the disease. Symptoms include: increasingly poor judgment, confusion in identifying family members, lose orientation to time and place, may begin wandering, making it unsafe for them to be left alone. With greater memory loss, patients may begin to forget their own personal details.

C. Severe Alzheimer's Disease

In this final stage of the disease, cognitive capacity continues to decline and physical ability is severely impacted. This stage can last between 1 and 3 years. Due to the family's decreasing ability to care for the patient, this stage often requires nursing home or other long term care facility placement. Common symptoms include: Loss of ability to communicate, the patients may still speak short phrases, but are unable to carry on a coherent conversation, depending on others for personal care such as eating, bathing, dressing, and toileting. The person may be unable to walk or sit independently. Muscles may become rigid and swallowing can eventually be impaired.

3.5. Diagnosis

The diagnosis can be done by using medical testing or Psychological evaluation. The medical tests include,

1. Blood or urine tests that are carried out to exclude other causes of Dementia symptoms, by testing for infections, vitamin and nutrient levels, as well as kidney, liver and thyroid function.

2. Brain scans can be used to detect brain tumors, strokes or brain hemorrhages, brain

shrinkage and increased pressure of fluid in the brain. Routine brain scans include computerized tomography (CT) scans and magnetic resonance imaging (MRI). These procedures produce an image of the brain, allowing the identification of abnormal changes. Other types of brain scans are used primarily in research studies. SPECT (Single Proton Emission Computed Tomography) is a brain scanning technique used primarily in research studies that can show functional changes in brain activity. FMRI (Functional Magnetic Resonance Imaging) also provides information about brain function as well as structure and is typically used in research studies. PET (Positron Emission Tomography) is another type of functional brain imaging, typically used in a research setting [20]. In the current study there was an option to use brain scan or neuropsychological tests for diagnosis. Brain scans do not always show abnormalities in people diagnosed with Dementia, as sometimes there are no visible changes in the brain. For example, a person with vascular Dementia might show evidence of strokes or other vascular changes in the brain, whereas a person with Alzheimer's disease might show either brain shrinkage or no changes at all [21]. The Prevalence and the growing incidence indicate the demand for early diagnosis of Dementia.

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Author(s) Biography

1. Bhagyashree S R : Dr. Bhagyashree S R has done her Bachelor of Engineering in Electronics & Communication Engineering, M. Tech in VLSI and embedded systems. She has obtained the Doctorate from University of Mysore on the topic "A novel approach in the diagnosis of Alzheimer disease and designing an embedded system for patients suffering from AD". She is the **First Indian** to apply machine learning for 10/66 for LMIC setting. She has worked at various capacities. She has put in around 25 years of service in both Teaching and Industry. At present she is working as Professor, Department of Electronics & Communication Engineering, ATME College of Engineering, Mysore, Karnataka, India. She has presented her papers both in India and abroad. She has published her work in many International peer reviewed journals; Scopus & H indexed journals with H index 97. She has chaired many of national and International Conferences. She is Academic & Editorial Board member of many International journals. She has guided many Undergraduate & Post graduate students. She has organized good number of workshops, Faculty Development programs and Conferences. She is a reviewer of many international journals that include Elsevier, BMC neurology. She has reviewed the papers of Conferences of IEEE and Springer. In connection with professional body membership, she holds the positions of **Senior member IEEE, Fellow IETE,** Life member of ARDSI, ISTE, IEI.

RESEARCH INTEREST

Machine learning, Embedded systems, Neuropsychology

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