

Alzheimer's Disease: A Major Health Problem of Elderly People

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ABSTRACT

Alzheimer's disease (AD) and other forms of dementia are a growing public health problem among the elderly people in developing countries. Alzheimer's disease (AD) is the most common cause of dementia in elderly people. It is an irreversible, progressive brain disease that slowly destroys and thinking skills and eventually even the ability to carry out the simplest tasks. In most people with AD, symptoms first appear after age 60. The purpose of this review article is to provide a brief introduction to Alzheimer's disease and the related concept of dementia and mild cognitive impairment (MCI). This article also demonstrates the other main aspects of AD including risk factors.

Keywords: Alzheimer's disease; dementia; mild cognitive impairment; biomarkers, risk Factors

INTRODUCTION

Alzheimer's disease (AD) and other forms of dementia are a growing public health problem among the elderly people in developing countries, whose aging population is increasing rapidly. [1] Alzheimer's disease (AD) is the most common form of dementia. With an aging population and no disease modifying treatments available, AD is quickly becoming a global pandemic. A substantial body of research indicates that lifestyle behaviors contribute to the development of AD, and that it may be worthwhile to approach AD like other chronic diseases such as cardiovascular disease, in which prevention is paramount. [2] AD most frequently presents with episodic memory impairment as the earliest and most prominent feature, with additional deficits in language, semantic memory, executive

functioning, visuospatial abilities, and functional impairment that emerge over the disease course. [3] A common misconception is that AD is a "normal" or expected occurrence of aging, and it is part of the typical trajectory of age-related cognitive decline. Rather, healthy aging has been found to be associated with relatively stable performance on measures of cognitive functioning when measured longitudinally. However, cross-sectional studies have indicated that some domains of cognitive functioning do in fact decline with age. [4]

The credit for first time describing a dementing condition, which later became known as Alzheimer's disease, goes to German psychiatrist and neuropathologist Dr. Alois Alzheimer. In his landmark 1906 conference lecture and a subsequent 1907 article, Alzheimer described the case of Auguste D, a 51-year-old woman with a 'peculiar disease of the cerebral cortex,' who had presented with progressive memory and language impairment, disorientation, behavioral symptoms (hallucinations, delusions, paranoia), and psychosocial impairment. [5-7] Alzheimer disease (AD) is an aggressive form of dementia, manifesting in memory, language and behavioral deficits. [8]

According to the Alzheimer's disease International (2014) there were about 46.8 million people living with AD in the world in 2015 which is estimated to double every 20 years. This will increase the population of the people with AD to 74.7 million in 2030 and 131.5 million in 2050. With this trend in the increase in proportion of persons with AD, it is estimated that the current proportion of 58% of the patients being from the middle and lower income

countries will increase to 63% by 2030 and 68% by 2050. These estimates show there are about 9.9 million new cases every year, with a new case occurring every 3.2 seconds. [9]

Alzheimer's disease (AD) and other forms of dementia are a growing public health problem among the elderly in developing countries, whose aging population is increasing rapidly. [1] In Nepal (age 60 years and above) is growing more than the general population. In 2001, there were 1.5 million older people in Nepal; this population has increased in 2011 to 2.7 million, accounting for 8.1% of Nepal's total population. The 2011 census has revealed that the rate of general population growth is 2.1% and 3.4% in the elderly. In the next ten years, over 1.3 million elderly populations will be added. [10] This would not only have great social implications but also on the health sector. This shift in the elderly cohort directly reflects to the increment in the number of dementia cases in the community as old age is an important risk factor for Dementia. The ADI has done a trend analysis of the disease in countries with similar social and economic structure and estimated that there were about 78,000 patients with AD in Nepal in 2015 and this number is bound to double every 20 years reaching 134,000 in 2030 and 285,000 in 2050. [11]

As individuals live to advanced ages (e.g., 80+), it can become more challenging to differentiate between the subtle cognitive declines that accompany aging and those that signify early dementia. The trajectory of AD is characterized along a continuum, ranging from healthy aging to preclinical AD, mild cognitive impairment (MCI), and dementia. Pathological changes that underlie AD begin to accumulate for years, or even decades, before emotional, physical, or cognitive symptoms emerge, eventually reaching a threshold at which the onset of a gradual and progressive decline in cognition occurs. [12]

As the elderly population continues to grow, these numbers are only expected to

increase. Alzheimer's disease (AD) has emerged as a serious public health concern, placing an immense burden on the individual, family, community, and health care resources. [13] This would not only have great social implications but also on the health sector. This shift in the elderly cohort directly reflects to the increment in the number of dementia cases in the community as old age is an important risk factor for Dementia. The purpose of this review article will provide a brief introduction to Alzheimer's disease and the related concept of dementia and mild cognitive impairment (MCI). This article also demonstrates the other main aspects of AD including risk factors.

Concept of Dementia

Dementia is a syndrome characterized by disturbance of multiple brain functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation. [14, 15] Dementia is a clinical syndrome that involves progressive deterioration of intellectual function. [16]

Alzheimer disease is the most common form of dementia and possibly contributes to 60 to 70% of cases. Other types of dementias include vascular dementia, dementia with Lewy bodies, and a group of diseases that contribute to fronto temporal dementia. The boundaries between subtypes are indistinct and mixed forms often co-exist. [17] Importantly, the cognitive and behavioral changes that occur with dementia interfere with work, social activities, and relationships and impair a person's ability to perform routine daily activities.

When an individual has symptoms of dementia, a physician will conduct tests to identify the cause. Different causes of dementia are associated with distinct symptom patterns and brain abnormalities.

Studies show that many people with dementia symptoms have brain abnormalities associated with more than one cause of dementia.^[18] For example, studies report that about half of people who had the brain changes of Alzheimer's dementia on autopsy also had the brain changes of a second cause of dementia, most commonly vascular dementia.^[19] This is called mixed dementia. In some cases, individuals have dementia-like symptoms without the progressive brain changes of Alzheimer's or other degenerative brain diseases. Common causes of dementia-like symptoms are depression, delirium, side effects from medications, thyroid problems, certain vitamin deficiencies and excessive use of alcohol. Unlike Alzheimer's and other brain diseases, these conditions often may be reversed with treatment.

Epidemiology of AD

AD is a multifactorial disease, with no single cause known, and several modifiable and non-modifiable risk factors are associated with its development and progression. Age is the greatest risk factor for the development of AD. The likelihood of developing AD increases exponentially with age, approximately doubling every 5 years after age 65.^[20, 21] The vast majority of individuals suffering from AD are aged 65 or older and have 'late-onset' or 'sporadic' AD (95% of all cases). Rare genetic mutations are associated with the development of AD before age 65, which is known as 'early onset' or 'familial' AD (5% of all cases).^[22]

People with familial forms of AD have an autosomal dominant mutation in either one of the presenilin genes located on chromosomes 1 and 14 or in the amyloid precursor protein (APP) gene located on chromosome 21. In addition, individuals with Down's syndrome (trisomy 21) have an increased risk of developing early-onset AD. The genetics of sporadic AD are more complex and less well understood. It is known that the epsilon four allele of the apolipoprotein E (APOE) gene located on chromosome 19 is a risk factor for the

development of sporadic AD.^[23] The prevalence of AD is higher among females, reflecting the longer life expectancy of women.^[24]

Lower educational attainment has been associated with increased risk of AD dementia^[20] consistent with the idea that education serves to increase a person's cognitive reserve and resilience to AD pathology.^[25]

A large body of evidence suggests that cerebrovascular risk factors play a significant role in both the development and progression of AD; people with a history of diabetes, hypertension, obesity, and smoking have a substantially elevated risk of AD.^[26] Family history of AD in first degree relatives and a history of head injury with loss of consciousness are also risk factors for the development of AD.^[16] Most scientists seem to agree that there are two proteins in the brain that are heavily involved. One is beta-amyloid, usually just called amyloid, which reaches abnormal levels in the brain of someone with Alzheimer's and forms plaques that collect between neurons and disrupt cell function. The other is called tau. This also reaches abnormal levels, and forms neurofibrillary tangles inside neurons which block the neuron's transport system. What scientists don't know is exactly how these proteins relate to each other, or what causes them to build to such damaging levels.^[27]

Researchers have made great strides in the areas of AD, with respect to etiology, prevention, diagnosis, and treatment. However, while the exact etiology still remains a mystery, definitive diagnosis can only be made postmortem, and current treatments can only slow disease progression temporarily. Late-onset AD, the most common form of the disease, occurs in individuals over the age of 65. While researchers have not found any causal determinants for this particular type, they have identified several associated risk factors, including age, female gender, low educational and occupational attainment, prior head injury, sleep disorders, estrogen

replacement therapy, and vascular risk factors, such as diabetes, hypercholesterolemia, and hypertension occurs. [12]

Diagnosis of AD

No one knows exactly what starts the AD process or why some of the normal changes associated with aging become so much more extreme and destructive in people with the disease. The clinical diagnosis of Alzheimer's disease is based on the observation of the compatible clinical picture and the exclusion of other causes of dementia due to both laboratory and neuroimaging tests. Computed tomography and magnetic resonance imaging reveal atrophy of the cerebral cortex and hippocampus, resulting in a probable diagnosis of the disease. As a possibility, monitoring of the evolution of the patient's clinical condition is also feasible, however, for definitive diagnosis, anatomopathological examinations. Therefore, the efficacy in the confirmation of the diagnosis becomes high when imaging tests are used together with the clinical findings of the disease. [28]

Analysis of cerebrospinal fluid may reveal the detection of elevated levels of abnormal components in the cerebrospinal fluid, such as β -amyloid substance, Tau protein, and phosphorylated Tau protein. Again, this type of laboratory analysis added to the neurological imaging tests gives a greater accuracy to the diagnosis. [29]

The clinical diagnosis of Alzheimer's disease follows a logical sequence: the history should include information from an informant; a mental state assessment should include a validated cognitive function test; and the physical examination should focus on vascular and neurological signs supplemented by investigations. Assessment of dementia involves a two-step process. Firstly, it is important to distinguish dementia syndromes from other conditions that can mimic them, such as depression, delirium, and mild cognitive impairment. Secondly, once dementia

syndrome is recognized, the diagnosis of a subtype is important because it may determine the kind of treatment possible. The progression of Alzheimer disease can be divided into a series of stages: pre-dementia, mild, moderate and severe. The pre-dementia stage is often unreliably distinguished from normal aging or stress-related issues. [30, 31] One of the first signs is the deterioration of episodic memory. No decline in sensory or motor performance occurs at this stage, and other aspects such as executive, verbal and visuospatial functions are slightly impaired at most. An individual remains independent and is not diagnosed as suffering from Alzheimer disease. [31]

The much rarer, early-onset form of AD, occurring in fewer than five percent of individuals with the disease, typically affects individuals between the ages of approximately thirty and sixty. This form of the disease is caused by one of three identified genetic mutations that are passed down in an autosomal dominant fashion among families: the amyloid precursor protein (APP), presenilin-1, and presenilin-2 genes. [4]

Biomarkers of Alzheimer's Disease

A Biomarker is a biological signature that can be used as an indicator of a pathological situation. According to the 1998 Consensus Report of the Working Group on Molecular and Biochemical Markers of Alzheimer Disease, ideal biomarkers for AD should be: 1) reflective or indicative of AD pathology; 2) reliable; 3) easy to perform/analyze; and 4) relatively inexpensive. [15]

A biomarker is a characteristic that can be measured and evaluated as an indicator of normal or pathological process, or to monitor the effect of therapeutical interventions on specific biological cascades. [32] The ideal diagnostic marker for AD should meet at least three basic requirements: (i) reflect core neurobiological changes subsequent to the disease process; (ii) be validated by post-mortem studies, assuming that the

neuropathological findings as gold standards; and (iii) be measurable as early as possible in the disease continuum ideally at pre-symptomatic stages. [33] Additional requirements include being non-invasive and simple to perform, precise and reliable, and adequate for large-scale screenings. Among many candidate markers of amyloidogenesis, those with the most promising results and potential to clinical application are the amyloid- β 1-42 (A β 42) peptide in the cerebrospinal fluid (CSF) and the in vivo, molecular imaging of A β 42 deposits in the brain with positron emission tomography (PET). [34] The identification and characterization of amyloid- β (A β) and tau as the main pathological components of Alzheimer disease (AD) has driven many efforts in search for suitable biomarkers for AD. While these two proteins represent the two key pathological mediators of disease, other aspects of this multifaceted disease such as oxidative stress, calcium mediated toxicity, and neuro inflammation are being unravelled, giving rise to possible new biomarkers for diagnostic or disease progression. [35]

The use of biomarkers in all stages of Alzheimer's disease will facilitate the development of treatments that target the underlying brain changes at each stage. Depending on the stage, such treatments might prevent or delay the onset or progression of clinical symptoms. Biomarker may have different roles, which have different standards. One is a surrogate for the disease, which demands nearly perfect sensitivity and specificity. The other is a supporting measure in the diagnosis, which again, requires a fairly high sensitivity and specificity. Another is as risk factor for future event, cardiovascular disease has many examples, such as the ratio of LDL to HDL, while not deterministic of a MI, predictive and used to intervene, at least to lower one marker (LDL), while there are essentially no effective pharmacological therapies that substantially raise HDL. [15]

Neuroimaging Biomarkers

A number of studies comparing imaging data with autopsy findings have demonstrated that beta-amyloid positron emission tomography (PET) imaging accurately reflects levels of amyloid deposits in the brain. While elevated levels of beta-amyloid detected via PET cannot be used in clinical practice to conclusively diagnose the disease, they give clinicians reason to conduct additional Alzheimer's testing. In addition, in a person with persistent MCI with an unknown cause, the presence of beta-amyloid detected by PET greatly increases the likelihood of that person having MCI due to AD and thus being in the early stages of Alzheimer's. Likewise, non-elevated levels of beta-amyloid indicate a reduced likelihood that cognitive impairment is due to Alzheimer's and may be reason for clinicians to explore other diagnoses. [36]

Three other Alzheimer's neuroimaging biomarkers are currently used for research and in some cases are used to aid in clinical diagnosis. Elevated cortical tau shown with PET imaging [37] is a biomarker for neurofibrillary tangles; decreased glucose metabolism shown by fluorodeoxyglucose (FDG)-PET imaging and atrophy shown by structural MRI are biomarkers for neurodegeneration or neuronal injury. [38]

CerebroSpinal fluid (CSF) and Blood Biomarkers

Additional types of biomarkers currently being studied in Alzheimer's disease and used mainly for research purposes are found in CSF and blood. CSF biomarkers reflect the rates of both protein production and clearance at one point in time rather than the cumulative damage assessed by neuroimaging biomarkers, but nevertheless may provide insight into the pathological changes of Alzheimer's. [39] A lower CSF level of a specific form of the amyloid protein, known as Ab42, is a biomarker for beta-amyloid deposition in the brain. [40] Elevated CSF levels of phosphorylated tau and total tau are biomarkers of neurofibrillary tangles and

neurodegeneration, respectively. Candidate blood biomarkers, currently in the early stages of development, include neurofilament light protein as a proxy for neurodegeneration [41] and specific forms of the amyloid protein as a screening tool for the accumulation of beta-amyloid in the brain. [42] It is important to note that while much research has been conducted on biomarker levels in white populations, less is known about these markers in diverse populations. [43]

Imaging and Radiological Markers

Magnetic resonance imaging (MRI) and computer aided tomography (CAT) scans can be used to visualize brain structure and help in AD diagnostic. In AD patients, a considerable reduction of hippocampus region, involved in memory processes, is observed. This anatomical measurement is useful in predicting the transition from normal to MCI and from MCI to AD. [44] However, there are concerns that this approach may lack the specificity needed to clearly diagnose AD. While some individuals have hippocampal atrophy without substantial AD pathology, one of the challenges to volumetric measures, particularly sub-regions, is the accuracy, i.e. variability around the measure. [15]

Metabolism is another important neurological parameter measured in AD diagnostic. As a result of brain atrophy and neuronal loss, patients in early stages of AD demonstrate reduced levels of brain metabolism. [45] Functional magnetic resonance imaging (fMRI) and PET scans with flurodeoxy glucose (FDG) PET as secondary measures of metabolic activity in various parts of the brain are key markers of brain metabolism. [46] fMRI measures changes in oxygen concentrations related to regional cortical blood flow, while FDGPET measures glucose metabolism in neuronal populations.

Signs and Symptoms of AD

Much research is being done to identify these early changes, which may be useful in predicting dementia or AD. An

important part of this research effort is the development of increasingly sophisticated neuro-imaging techniques and the use of biomarkers. Biomarkers are indicators, such as changes in sensory abilities, or substances that appear in body fluids, such as blood, cerebrospinal fluid, or urine. Biomarkers can indicate exposure to a substance, the presence of a disease, or the progression over time of a disease. For example, high blood cholesterol is a biomarker for risk of heart disease. [47] Such tools are critical to helping scientists detect and understand the very early signs and symptoms of AD.

Concept of Mild Cognitive Impairment (MCI)

As some people grow older, they develop memory problems greater than those expected for their age. But they do not experience the personality changes or other problems that are characteristic of AD. These people may have a condition called mild cognitive impairment. [47] 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 the individual is still able to carry out everyday activities. Approximately 15 percent to 20 percent of people age 65 or older have MCI. [48] People with MCI, especially MCI involving memory problems, are more likely to develop Alzheimer's or other dementias than people without MCI. [49] In other words, the MCI is a syndrome characterized by memory and or other cognitive impairments that exceed the decline in cognition associated with the normal aging process. MCI is often regarded as a precursor to dementia or a transitional state between healthy cognitive aging and dementia. [50]

Mild AD

As AD spreads through the brain, the number of plaques and tangles grows, shrinkage progresses, and more and more of the cerebral cortex is affected. Memory loss continues and changes in other cognitive abilities begin to emerge. The clinical

diagnosis of AD is usually made during this stage. [47] There are different signs of mild AD such as: memory loss, confusion about the location of familiar places, taking longer than before to accomplish normal daily tasks, trouble handling money and paying bills, poor judgment leading to bad decisions, loss of spontaneity and sense of initiative, mood and personality changes, increased anxiety and or aggression.

Moderate AD

By this stage, AD damage has spread to the areas of the cerebral cortex that control language, reasoning, sensory processing, and conscious thought. Affected regions continue to shrink, ventricles enlarge, and signs and symptoms of the disease become more pronounced and widespread. Behavioral problems, such as wandering and agitation, can occur. [47] The symptoms of this stage can include: increasing memory loss and confusion, shortened attention span, inappropriate outbursts of anger, problems recognizing friends and family members, difficulty with language and problems with reading, writing, and working with numbers, difficulty organizing thoughts and thinking logically, inability to learn new things or to cope with new or unexpected situations, restlessness, agitation, anxiety, tearfulness, wandering-especially in the late afternoon or at night, repetitive statements or movement, occasional muscle twitches, hallucinations, delusions, suspiciousness or paranoia, irritability, loss of impulse control, an inability to carry out activities and so on.

Severe AD

In the last stage of AD, plaques and tangles are widespread throughout the brain, most areas of the brain have shrunk further, and ventricles have enlarged even more. People with AD cannot recognize family and loved ones or communicate in any way. They are completely dependent on others for care. [47] Other symptoms can include: weight loss, seizures, skin infections, difficulty swallowing, groaning, moaning, or grunting, increased sleeping, lack of bladder and bowel control, pneumonia etc.

Risk Factors for Alzheimer's Disease

Age

The single greatest risk factor for developing Alzheimer's disease is age, one of the non-modifiable risk factors. Most cases of Alzheimer's disease are seen in older adults, ages 65 years or above. Between the ages of 65 and 74, approximately 5 percent of people have Alzheimer's disease. For those over 85, the risk increases to 50 percent. Various studies show that aging can impair the body's self-repair mechanisms, including in the brain. And, many of the cardiovascular risk factors increase with age, such as high blood pressure, heart disease, and high cholesterol. [6] The age-specific incidence rates for Alzheimer disease demonstrate a doubling of incidence for about every six years of added life, which indicates an exponential increasing risk with increasing age. Most patients develop AD after the age of 65 years old. The risk of developing AD reaches 50% for individuals beyond age 85. Because more and more people live longer lives this disease is becoming a serious concern. [15]

Sex

The overall incidence of Alzheimer's disease was similar in men and women. Over the age of 90 years the incidence of Alzheimer's disease was higher for women than men. The risk of vascular dementia was higher for men than women across all age groups. Both studies found that the incidence of dementia and Alzheimer's disease continued to increase with age up to 85 - 90 years, after which rates increased in women but not in men. [48]

Family History

Another risk factor is family history. Research has shown that those who have a parent, brother or a sister with Alzheimer's are more likely to develop the disease than individuals who do not. The risk increases if more than one family member has the illness. [51]

A family history of Alzheimer's is not necessary for an individual to develop the disease. However, 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. [52] Those who have more than one first-degree relative with Alzheimer's are at even higher risk. [53] When diseases run in families, heredity (genetics) and shared environmental and lifestyle factors may play a role.

Genetics of AD

The vast majority of Alzheimer disease is not genetically inherited although some genes may act as risk factors. Genetically identified forms of Alzheimer disease, which usually have an onset before the age of 65, have been identified and account for 0.1% of disease cases. [54] The current thinking is that there are sporadic/late onset and familial/early onset cases of Alzheimer disease. [15] In sporadic Alzheimer's disease, there is no appearance of a genetic pattern of inheritance. A connection has been found between a gene called Apolipoprotein E (ApoE) and the development of Alzheimer's disease. This gene is supposed to be responsible for the protein that carries cholesterol in the blood vessels. One form of the gene, ApoE4, has been shown to increase the chances of developing the disease to a greater extent. However, the ApoE2 form protects from the disease. [55] The APOE gene provides the blueprint for a protein that transports cholesterol in the bloodstream. Everyone inherits one of three forms of the APOE gene-e2, e3 or e4-from each parent. The e3 form is the most common. The e4 form is the next most common, and the e2 form is the least common. [56] In the cases occurring before age 65, a mutation of chromosomes can be responsible. This rare form of the disease is called Familial Alzheimer's disease and it affects less than 10 percent of Alzheimer's disease patients. Other cases, that do not exhibit autosomal-dominant inheritance are termed sporadic AD. Genetic risk factors have been identified such as the inheritance of the allele of the alipoprotein (APOE). [57] Risk genes increase the likelihood of developing a disease, but do

not guarantee it will happen. Alzheimer disease is a complex multi-factorial and multi-mechanism disease merging genetics and epistasis that can unravel novel pathways. [15]

When Alzheimer disease is caused by these deterministic variations, it is called "autosomal dominant Alzheimer disease (ADAD)" or "familial Alzheimer disease". Many family members in multiple generations are affected. Symptoms develop before age 60, and may appear among persons between 30 and 40 years old. Most of autosomal dominant familial AD can be attributed to mutations in the amyloid precursor protein (APP) and/or presenilins 1 and 2 gene. Mutations in the APP and presenilin genes lead to the production of protein A β 42 (beta amyloid 1-42) that accumulates into amyloid plaques and cause death of neurones by increasing the production of protein A β 42. [58, 15] Autosomal dominant forms of Alzheimer's disease represented only 5 % of all Alzheimer's disease cases. Most AD patients have the sporadic form of the disease but for these Alzheimer's disease cases, genetic susceptibility factors could also increase or decrease the risk of developing the disease. [59]

Education and Occupational Status

It is observed that there is a connection between educational level and the risk of developing Alzheimer's disease. People with fewer years of education seem to be at a higher risk as they are unaware of the prevalent causes. The exact cause for this relationship is unknown, but it is theorized that a higher education level leads to the formation of more synaptic connections in the brain. This creates a "synaptic reserve" in the brain, enabling patients to compensate for the loss of neurons as the disease progresses. [60] Some researchers believe that having more years of education builds "cognitive reserve." Cognitive reserve refers to the brain's ability to make flexible and efficient use of cognitive networks (networks of neuron-to-neuron connections) to enable a person to continue

to carry out cognitive tasks despite damaging brain changes, [61] such as beta-amyloid and tau accumulation. The number of years of formal education is not the only determinant of cognitive reserve. Having a mentally stimulating job and engaging in other mentally stimulating activities may also help build cognitive reserve. In addition, having fewer years of formal education is associated with lower socioeconomic status [62] which in turn may increase one's likelihood of experiencing poor nutrition and decrease one's ability to afford health care or medical treatments, such as treatments for cardiovascular risk factors.

Higher occupational attainment has also been highlighted as a potentially protective factor against risk of developing dementia. [63] This could either be a result of lifelong opportunity to build Cognitive Reserve; a result of the "use it or lose it" principle whereby continued mental exercise helps forestall cognitive decline, or as a result of higher socioeconomic status being associated with superior health care and health behaviours. Education and occupational status are likely to be closely related, and adjusting for educational level in studies on occupational status may help clarify to what extent effects operate independently of one another. [9]

Oxidative Stress and β -Amyloid

Oxidative stress plays a substantial role in the pathogenesis of AD, a damaging disease of the elderly. The brain is more vulnerable than other organs to oxidative stress, and most of the components of neurons can be oxidized in AD due to mitochondrial dysfunction, increased metal levels, inflammation and β -amyloid peptides. [64] The amyloid precursor protein observed in Alzheimer's disease pathology, suggests a time-course of plaque development beginning with neuronal amyloid precursor protein accumulation. [65] The brain's unique characteristics, including its high rate of metabolism and its long-lived cells, may make it especially vulnerable to oxidative damage over the

lifespan. The discovery that beta-amyloid generates free radicals in some AD plaques is a potentially significant finding in the quest for better understanding of AD as well as for other neurodegenerative disorders and unhealthy brain aging. [47]

Environment and Lifestyle Factors for AD

Several studies indicate a role for environmental effects on AD development. In a recent review Richard Mayeux and Yaakov Stern summarized the role of diet, activities, or diseases that potentially play a role in the onset of Alzheimer disease. Diabetes, hypertension, smoking, obesity, and dyslipidemia have all been found to increase risk as well a history of brain trauma, cerebrovascular disease and vasculopathies. [15]

A healthy diet and exercise can reduce obesity, lower blood cholesterol and high blood pressure, and improve insulin action. A growing body of evidence now suggests that these lifestyle factors may be related to cognitive decline and AD. Epidemiologic studies show that higher levels of physical activity or exercise in older people are associated with reduced risk of cognitive decline and reduced risk of dementia. Researchers also have explored whether diet may help preserve cognitive function or reduce AD risk, with some intriguing findings. For example, studies have examined specific foods that are rich in antioxidants and anti-inflammatory properties to find out whether those foods affect age-related changes in brain tissue. [47]

CONCLUSION AND DISCUSSIONS

In this review article, Alzheimer Disease (AD) and its main aspects like epidemiology, diagnosis with specific biomarkers, sign and symptoms etc have been briefly discussed. Various risks factors such as age, genetics, education, family history, lifestyle etc. are associated with Alzheimer disease. In addition, environmental factors, vascular factors and

psychosocial factors also contribute to Alzheimer disease.

Alzheimer's disease and related dementias are a major cause of disability and dependency among older adults worldwide, having a significant impact not only on individuals but also on their families, communities, and societies. It is widely acknowledged that immediate policy action is necessary to curb the growing burden of AD in tandem with the ongoing efforts to develop more efficacious treatments or prevention. Success will require all stakeholders, including policymakers, healthcare industry leaders, advocacy groups, societies and associations, academia, biopharma, payers, clinicians, and researchers, to work shoulder to shoulder to address roadblocks that are hindering our understanding of the scope, scale and nature of the costs of AD so that we can develop, assess, and prioritize effective, evidence-based policies, strategies, and interventions to meet this growing global health crisis.

In 2012, dementia was declared a public health priority by the World Health Organization. Due to the ageing of the world population the number of patients with Alzheimer disease will rise significantly. If no treatment is available, this will be a major health issue with enormous financial burdens to health care systems. Thus, there is an urgent need for both early diagnosis with specific markers as well as effective therapies that could be taken at the different stage of the disease. [15]

There is no single stakeholder can solve all the scientific, health system, and public health challenges related to AD. Such a complex problem requires solutions that involve collective commitment, collaboration, investment, and effort. There is an urgent need for integrated and innovative approaches to measure, manage and mitigate the burden of AD by developing and implementing better tools, measures, policy and programs. Investing and preparing for the advent of biomarker-

based tests that can help accurately identify the hallmarks of AD and the contributions of multiple pathologies to clinical symptoms and to improve provision of a timely diagnosis and to better inform prognosis and effects of early intervention and care.

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