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"a critique on *Alzheimer's disease* according to modern and *Ayurveda* perspective."

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Abstract- Alzheimer's disease (AD) is incredibly common. In all neurodegenerative diseases, Alzheimer's disease (AD) is the most important which comprises about 50-70% of dementias characterized by progressive impairment of cognitive functions with memory impairment and disturbances of the higher cortical functions. More than 90% of cases of AD are sporadic and occur in individuals older than 60 years. Alzheimer disease (AD) is a neurodegenerative disease characterized by a long preclinical phase with evolving and progressively irreversible pathology. Ayurveda correlates AD with *prana avrutta saman* vata as well as *smritibhrash*. Clinically, based on *Ayurvedic* interpretation, there are 3 subtypes observed. A critical review on this topic has been made in this article.

Keywords: Alzheimer's Disease, *Smritibhrash,* Ayurveda, neurodegenerative disorders.

Introduction:

The prevalence of AD continues to increase worldwide, becoming a great healthcare challenge of the twenty-first century. It is the most common form of dementia which occurs among the older people above the age of 60 years. The World Health Organization has declared Alzheimer's Disease as a global public health priority. Fastest evolution in life, weather changes, pollutants, extra use of artificial fertilizer and harmful chemicals during the production of eating stubs are seriously life threatening for people living on the earth and causing health hazards. These harmful chemicals produce neurotoxins that affect the transmission of

chemical signals between neurons resulting in neurodegenerative disorders. Among different kinds of neurodegenerative diseases[2].

This review broadly discusses Alzheimer's Diseases, its epidemiology, pathogenesis and Etiology in both Ayurveda and modern perspective.

Epidemiological Data:

- Current data indicate that AD is a major health problem, at least in developed countries. The prevalence of AD ranges from 1.9 to 5.8 per 100 population aged 65 years and older. Moreover, current demographic developments are likely to increase its prevalence over the next two decades. The prevalence of AD increases sharply with age and is higher in women. Incidence rates show a similar pattern, suggesting that AD should not be divided into presenile and senile on the basis of age of onset alone. An annual incidence of 2.4 cases per 100,000 population was reported between the ages of 40 and 60 years and 127 cases per 100,000 population after age 60 years.[3]
- With a rate of 50-75%, AD is the single most common cause of dementia, primarily in old age, prevalence approximately doubles every five years after age 65. The highest prevalence of dementia is expected among low- and middle-income earners. Countries with increasing patterns of cardiovascular disease and hypertension, Diabetes mellitus. Dementia – Acquired progressive cognitive impairment sufficient to cope Activities of daily living – a leading cause of dependence, disability and death. Worldwide there are currently 44 million people with dementia. That is expected to more than triple by 2050 as the population ages Dementia in the US alone could cost him over $600 billion[4].

Role of Genetics in Alzheimer's Disease:

Alzheimer’s disease (AD), the most common cause of dementia in aged populations, is believed to be caused by both environmental factors and genetic variations. Extensive linkage and association studies have revealed that a wide range of loci are associated with AD, including both causative and susceptibility (risk factor) genes. So far, at least three genes, APP, PS1, and PS2, have been identified as causative genes. Mutations in these genes have been found to primarily cause early-onset AD. On the other hand, APOE has been identified as the most common high genetic risk factor for late-onset AD. Polymorphisms in the coding regions, introns, and promoter regions of specific genes constitute another type of genetic variation associated with AD. Many other genes or loci have been reported to be associated with AD, but many show only weak associations or poorly replicated results. Currently, measurable genetic association accounts for approximately 50% of population risk for AD. It is expected that more new loci associated with AD will be discovered, either as causative genes or as

genetic risk factors, and ultimately understanding the genetic factors in the pathogenesis of AD will lead to the development of this disease. expected to be important in efforts to treat.[5]

Histopathological Features[6]: The first defined histopathologic features of AD were extracellular amyloid plaques and intracellular neurofibrillary tangles. Recently recognized histopathological features include synaptic degeneration, loss of hippocampal neurons, and aneuploidy. However, histopathological AD criteria currently only consider plaques and tangles. Several AD histopathologic criteria are commonly used.

Etiopathogenesis:

- Over the 110 years since the discovery of AD, many associated pathogenic mechanisms have been proposed, most notably the amyloid and tau hypotheses. However, almost all clinical studies targeting these mechanisms have failed to identify effective ways to treat AD. Scientists have gradually departed from the simple hypothesis proposed in the original amyloid hypothesis and have focused on gamma oscillations, prion transmission, cerebral vasoconstriction, growth hormone secretagogue receptor 1α (GHSR1α)-mediated mechanisms, and infection. are heading towards new theories of etiology, including Cholinesterase inhibitors (AChEIs) and NMDA receptor antagonists are currently the only treatments for AD.[7,8]
- A large body of data supports the view that the pathogenesis of AD to date is primarily composed of Aβ toxicity, tau protein, genetic mutations, synaptic damage, intermediate neurons and network abnormalities, altered mitochondrial function, chemokines, etc. Their pathogenesis may involve several theories and may involve several molecular signaling pathways, including Aβ, tau proteins and synaptic abnormalities. Mechanistic interrelationships work together to drive neurodegeneration[9].

Clinical Features: Alzheimer's disease is a progressive neurodegenerative brain disease that begins slowly but leads to dementia, abnormal behavior, personality changes, and ultimately death. The preclinical stages of Alzheimer's disease are subtle and, by definition, there are almost no reliable and effective symptoms or signs that can be diagnosed very early before irreversible damage develops[10]. These symptoms reflect the degree of damage to nerve cells in different parts of the brain.

1. **Mild Alzheimer's Dementia[9,10]-** In the mild stage of Alzheimer's dementia, most people are able to function independently in many areas but are likely to require assistance with some activities to maximize independence and remain safe.
2. **Moderate Alzheimer's Dementia[9,10]-** The moderate stage of Alzheimer's dementia is often the longest stage and can make it

difficult to communicate and perform everyday tasks, including activities of daily living (such as bathing and dressing). Intermittent incontinence; begins with personality and behavioral changes, such as distrust and restlessness.

3. **Severe Alzheimer's Dementia[9,10]-** In the severe stages of Alzheimer's dementia, people need help with activities of daily living and may need around-the-clock care. At this stage, the effects of Alzheimer's disease on physical health are particularly pronounced. People become bedridden due to damage to areas of the brain involved in movement. Being bedridden makes you more susceptible to conditions such as blood clots, skin infections, and sepsis, which can cause inflammation throughout the body and lead to organ failure.If the areas of the brain that control swallowing are damaged, eating and drinking becomes difficult. increase. This may cause food to be swallowed through the windpipe (trachea) instead of the esophagus (esophagus). Because of this, food particles can lodge in the lungs and cause pulmonary infections.This type of infection is called aspiration pneumonia and contributes to the deaths of many AD patients.

Diagnosis of Alzheimer's Disease:

- AD is now associated with increasing numbers of clinical, biochemical, and histologic markers[12]. Along with the bedside examination and lab investigations, predictors and biomarkers play vital roles in identifying patients early in the course of the disease, when disease-modifying interventions may have the greatest chance of success. Existing AD biomarkers provide limited sensitivity and specificity for clinical and preclinical diagnosis and have been adopted in research but not in clinical practice[13]. It is generally accepted that the development of reliable predictive blood biomarkers is an important step in the quest for disease-modifying interventions for Alzheimer's disease and its widespread implementation.[14]
- Establishing biomarkers as reliable for the pathology of Alzheimer's disease will allow us to use biomarkers as diagnostic tools rather than relying on brain biopsy or autopsy to arrive at a definitive diagnosis. Furthermore, up to 50% of patients clinically diagnosed with mild cognitive impairment and 25% of mild Alzheimer's disease cases have no evidence of amyloid deposits, which has been "misleading" in studies examining anti-amyloid therapy. shown. It likely explains the failure of amyloid therapy in these attempts. Therefore, biomarkers used in clinical trials will improve the diagnostic accuracy of 'purely biological AD' in enrolled

subjects and facilitate drug development in this population.[15]

- Amyloid β42 and tau protein are well-established major cerebrospinal biomarkers. New biomarker candidates include amyloid-β oligomers and synaptic markers. MRI and fluorodeoxyglucose PET are established imaging modalities for diagnosing Alzheimer's disease. Amyloid PET has gained clinical traction, but its efficacy and cost-effectiveness are yet to be proven. Tau-PET provides new insights and may be of great help in differential diagnosis and selection of patients for study. Amyloid β42 and tau protein are well-established major cerebrospinal biomarkers. New biomarker candidates include amyloid-β oligomers and synaptic markers. MRI and fluorodeoxyglucose PET are established imaging modalities for diagnosing Alzheimer's disease. Amyloid PET has gained clinical traction, but efficacy and cost-effectiveness are yet to be proven[16].

Ayurvedic perspective of Alzheimer's Disease:

Ayurveda is an Indian system of traditional medicine. No direct references of this disease in Ayurvedic text have been observed. In Ayurveda, *Pranavrutta saman vata* fromVatavyadhi (neurodegenerative diseases) can be linked to AD[17,18]. Based on an Ayurvedic interpretation, there are 3 basic phenotypes of AD, named Vata, Pitta, and Krimi. The classification of AD into these three Ayurvedic subtypes may be very useful for the treatment management.[18]

1. **Vata Type AD**

- **Etiology Factors *(Nidana)*** - Because AD is an age-related neurodegenerative disease that occurs in the *vata* life stage, *vata* AD is compatible with the metabolic profile of type 2 AD, which is characterized by deprivation of nutritional support and decreased hormonal support.[18,20] It is caused due to Vata aggravating food and lifestyle in addition with predisposing conditions toward developing the AD Vata aggravating lifestyle includes unstable routines; overwhelming stress; and eating a dry, cold, light diet. This may be related with all types of *vata* named *Prana Vayu* (inward moving air-absorption of impressions), *Samana Vayu (*afferent impulses—movement of thoughts), *Vyana Vayu* (efferent impulses—processing of thoughts), *Udana Vayu* (memory and recall) and *Apana Vayu* (digestion and dispersion of thoughts) suggesting a failure to absorb healthy impressions from all 5 senses. This may ultimately affect cognition and the thought process characterized by personality and behavioral abnormalities[18,24,25,26].
- **Clinical Features (*Rupa*)**- In addition to memory decline, patients exhibit mood swings, confusion,

emotional lability and sleeplessness. They fail to absorb new information and have difficulty finding words. Constipation may be a major issue among these patients as well. Other Vata-type disorders associated with this condition include insulin resistance (Madhumeha-subtype of Vataja Prameha),[27] and early hormonal loss in women (Artava Kshaya)[28]. Atrophy or degeneration, especially of the temporoparietal region mainly associated with decreased glucose utilization, as indicated by fluorodeoxyglucose-positron emission tomography (FDG-PET)[29].

2. **Pitta Type AD**

- **Etiological Factors (*Nidana*):** Pitta-type AD is compatible with the metabolic profile in type 1 AD (inflammatory AD)[29]. Although AD is primarily a Vata disorder, the condition can precipitate in people of Pitta nature exhibiting excess heat from a Pitta aggravating food and lifestyle that fastens the degeneration process of the hippocampal/cortical cells.[18,30,31]
- **Clinical Features (*Rupa*):** The key symptom indicating the role of Pitta is inflammation that is an underlying phenomenon in AD, pathogenesis characterized by the presence of proinflammatory cytokines, inflammatory microglia and activated astroglia, chemokines, acute-phase reactants, and other mediators. Pitta-aggravating factors include the regular intake of hot, sour, salty, strongly acidic and fermented foods. Alcohol, anger, rage and chronic exposure to sun may also be remarkable causes [33,18,34,35].

3. **Krimi-TYPE AD-**

- Although we did not encounter any patients who had symptoms suggestive of Kapha-type AD, some of the Kapha-associated symptoms may occur concurrently with Vata AD or Pitta AD. At this time, no studies are there to suggest a Kapha-specific AD pathology[18].
- **Etiological Factors (*Nidana*)-** The concept of germs that includes various pathogens was known in Ayurveda and is referred to by the term Krimi,indicating parasitic infection and toxin poisoning.[37,38] Based on the clinical evidence presented by several AD subjects who did not fall into either the Vata or Pitta categories, we chose to classify these people in the Krimi-type AD based on 2 external factors that were common to most of these patients, namely (1) exposure to mycotoxins, aqua toxins, and other pathogens; and/or (2) exposure to toxic chemicals and metals[18].
- **Clinical Features *(Rupa):*** The profile of patients falling in the Krimi-AD category is somewhat different than the first 2 subtypes; the onset is typically younger and ApoE genotype is usually 3/3. The onset usually follows a period of high stress, insomnia, and depression.

These patients retain new memories but fail to recall old memories. Imaging studies reveal widespread cerebral atrophy and frontal-temporal-parietal abnormalities on FDG-PET. The symptoms presented by these patients are characteristic of patients exposed to biotoxins/mycotoxins that include molds present in water-damaged buildings, tick-borne pathogens, or aqua toxins that trigger Lyme disease and/or exposure to high levels of mercury, lead, or arsenic. Most of these patients also have low serum zinc, and zinc deficiency is known to affect many functions similar to cognitive performance and AD.[36,18, 38]

Pathogenesis *(Samprapti)* of AD from Ayurved perspective[39]:

It is said that *smritibhrash* can be caused due to food aggravating Tamas *and Rajas)* and activities which Vitiates of body Constituents affects the mind and body and leads to *Smritibhrash*. *Vata Dosha* gets vitiated due to *Dhatu kshaya* and *Margavarodha* (obstruction). Protein accumulation can be understood as the accumulation of *Aama* at the cellular level. *Margavaroda* can be caused by the formation of *ama* caused by *Vishamagni* formed by *Vatadushti*. *Kayagni* (digestive fire) is the final process of metabolism that occurs at the tissue level and involves biological enzymes that determine the proper formation of *sara* (food) and *kitta* (waste) at that level. The proper functioning of *vata* at the cellular level uses nutrients to build tissues and remove waste products from the system. *Kayagni* and *Vata vikruti* at the neuronal level are responsible for the generation of *ama* leading to Alzheimer's disease. is. This accumulation of waste products can be correlated with protein aggregation, which can lead to imbalance and degenerative changes. This degeneration further undermines vata and creates a vicious cycle.

Conclusion:

Alzheimer's disease is a very common neuropathological condition. It is a commonly occuring form of dementia which occurs among the older people above the age of 60 years. In Ayurveda AD can be correlated with *Smritibhrash* and pranavrutta *saman Vata*. 3 subtypes of AD from the Ayurved perspective can be formed. Still this remains a very less explored topic. Future research over this topic is needed.

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