Literature review of Alzheimer's disease aetiology

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Abstract

Introduction: The most prevalent neurodegenerative illness and kind of dementia is Alzheimer's disease (AD). It shows up as a reduction in short-term memory and cognitive function that affects day-to-day functioning. The majority of Alzheimer's cases are idiopathic, but a tiny percentage of hereditary instances provide gene identification, which when combined with neuropathology provides crucial hints regarding the broader causes. The development and course of the illness are influenced by metabolic and environmental risk factors, such as vascular impairment and inflammation. We still don't fully grasp how neuronal shrinkage and synaptic loss occur across the cerebral cortex. The aim of this review paper is to give a concise overview of AD and its pathogenesis.

Methods: Relevant terms were applied to several databases (including CENTRAL; CINAHL; EMBASE; Medline Ovid; and PubMed NCBI) to search for studies exploring aetiology of AD.

Result and discussion: Eight etiological theories have been identified based our database search. These include: 1) The aging process; 2) The deterioration of cholinergic and cortical anatomic channels; 3) Environmental factors; 4) Genetic causes; 5) Metabolic malfunction resulting from defects in the mitochondria; 6) Blood/brain barrier impairments; 7) Immune and viral aetiology.

Key word: Alzheimer's disease, aetiology, Theory of Aging, Cholinergic hypothesis

Introduction

The clinical pathological features of Alzheimer's disease (AD) have been mainly examined in terms of three major outcomes in the years after Alois Alzheimer gave the first clinical description of dementia in 1907 (Small & Cappai, 2006). They are the formation of senile plaques (SP), the emergence of neurofibrillary tangles (NFT), and cognitive decline (Massano et al., 2012; Scheltens et al., 2021). Kraepelin first proposed the condition's medical term in 1910 following a review of clinical and pathological findings on dementia patients who had already been diagnosed. Two of these reports were made by Alzheimer, and both patients had numerous SPs. Only one, nevertheless, had appreciable NFT levels (Cipriani et al., 2011) (Gallardo & Holtzman, 2019). This revealed that AD might appear with pathological heterogeneity, which makes it extremely difficult for researchers to establish its likely origin (Seelaar et al., 2010). However, a number of experts have put up suggestions to explain why AD manifests in some people. This study will examine some of the more compelling ones, albeit it cannot cover them all. Eight pathologies have been identified based on these beliefs (Table 1):

TABLE 1: Theories to explain why AD develops

1. The acceleration of the aging process 2. The deterioration of cholinergic and cortical anatomic channels 3. Environmental factors, such as exposure to certain metals, brain injuries, and inadequate food. 4. Genetic causes (mutations in presenilin or amyloid precursor protein, variations in apolipoprotein allelic composition)	5. Metabolic malfunction resulting from defects in the mitochondria 6. Blood/brain barrier impairments as vascular triggers 7. Deficient Immune Reaction 8. Coming into contact with a virus

Each hypothesis is given a descriptive description in this review. It includes a summary of its importance to AD research and clinical investigations as well as an assessment of its individual advantages and disadvantages. It is intended to serve as a helpful resource for upcoming studies and others looking into the management of this illness.

Theories explaining the origins of AD

Theory of Aging

According to several experts, AD symptoms are essentially the same as those that come with aging naturally (Trevisan et al., 2019; Villemagne et al., 2011). Age certainly causes the weight and volume of the brain to decrease in a cognitively healthy individual. In important areas, the dendrites and synapses deteriorate while the ventricles enlarge (James et al., 2012). In addition to these symptoms, AD's hallmark clinical traits (NFT and SP) are also present (Dartigues & Féart, 2011; Démonet & Celsis, 2012; Sengoku, 2020). The issue is that the process is manifested more intensely and happens far more quickly than usual.

Research indicates that around 60% of healthy aging individuals do exhibit signs of SPs. In fact, in most cases, it is impossible to distinguish between early phase AD and healthy physical aging in in deceased patients (Mann et al., 1987; Trejo-Lopez et al., 2023). It should be noted that healthy persons have lower amounts of SPs (Sperling et al., 2012). Arriagada et al. (1992) states that practically all healthy adults over the age of fifty-five have SPs. This suggests that early phase AD, elderly healthy brains, and the most advanced phases of the illness might all have a logical pathological transition (Armstrong, 2012; Breijyeh & Karaman, 2020).

Some researchers report that tau-immunoreactive NFT is present in tiny levels in the majority of cognitively normal persons (Crary et al., 2014; Vinters, 2015). In comparison to AD patients, they also exhibit lower levels of astrocytosis and microglial responses (Fakhoury, 2018) . However, NFT is seen in the entorhinal cortex's Lamina II and the hippocampal regions in people without dementia. This makes the debate over whether healthy aging causes NFT to occur heated. There is no unifying clinical opinion at this time.

There are two more age-related shifts that are frequently connected to the onset of AD. The first is the myelin deterioration process, which is accelerated by aging naturally (Papuć & Rejdak, 2018). It should be mentioned, nevertheless, that some scientists think myelin damage only manifests in late phase AD and is essentially supplementary to the destruction of the neurons (Bartzokis, 2004). The decrease in cells inside the locus caeruleus is the second. It provides noradrenaline to the brain and inhibits the microglia's production of Aβ (Giorgi et al., 2017; Heneka et al., 2010; Heppner et al., 2015) .

Degeneration of anatomical pathways

Cholinergic hypothesis

AD is frequently described as Parkinson's disease's "cholinergic" counterpart. It is thought that the substantia nigra is where the degradation of dopamine neurons and their cortical connections begins in Parkinson's disease patients (Hampel et al., 2019). Likewise, an initial investigation into the genesis of AD identified a specific form of deterioration in the vicinity of the cholinergic neurotransmitter (Hampel et al., 2018; Martorana et al., 2010). Previous research has found significant decreases in acetylcholine in AD brains before this (Ni et al., 2013). More recent studies corroborate this, showing a significant decline in acetylcholinesterase (ACHE) and choline acetyltransferase (CAT), especially in more advanced instances (Bagwe & Sathaye, 2022). Furthermore, compared to healthy people, the cerebral cortex responses are 30–50% lower (Bagwe & Sathaye, 2022; Kumar & Singh, 2015).

Cortico-cortical pathways

A sophisticated neuronal network of "modules" and "columns" defines the anatomical structure of the cerebral cortex. Indeed, several findings unequivocally imply that AD is associated with the degradation of these cortical circuits (Braak & Del Tredici, 2018). The idea that AD causes the structural pathways connecting various parts of the cerebral cortex to break down has gained more traction over time (Salat et al., 2010).

Pathogenic protein transfer from cell to cell

One of the first studies to suggest that AD-related impairment could be connected to neurons and their capacity to transport various chemicals was Saper et al. (1987), It specifically makes the case that the mechanism may be shared by synaptic projections in good health. Several recent studies seem to support this theory, stating that cells create pathogenic proteins including tau, α-synuclein, Aβ, and degenerative prion protein (PrPsc) (Braak & Del Tredici, 2011; Gadad et al., 2011; Steiner et al., 2011). They could produce small intracellular accumulations within infected cells.

Environmental factors theory

Numerous environmental factors have been linked to the development of AD. But the majority of research concentrate on one of the three potential causes (table 3). These are exposure to harmful levels of aluminum, the effects of a poor diet, and the aftermath of a brain injury.

TABLE 3: Environmental triggers that linked to AD development

Aluminium • The majority of the evidence supporting this notion is disputed and coincidental; there is no concrete evidence that coming into touch with particular metals acts as a primary trigger rather than a complicating element(Campbell, 2002; Kawahara & Kato-Negishi, 2011). • Epidemiological studies have found a weak (and often unconvincing) correlation between aluminum exposure and AD(Colomina & Peris-Sampedro, 2017). • It's unclear how increased aluminum affects the brain in its entirety. There may be an innate tendency for brains with pre-existing deficits to aggregate aluminum (Armstrong, 2013). Nonetheless, NFT and SP development may be linked to metal interaction.
Head injury • Primary dysfunction is generally the result of head trauma. It can spread harmful cytokines to parts of the brain that were not previously injured. Consequently, due to increased activity in the nervous system's microglia and immune cells, head traumas may exacerbate pre-existing diseases (Johnson et al., 2010; Kempuraj et al., 2020; Sivanandam & Thakur, 2012). • A link between head injuries and the development of AD has been suggested by several research. Amyloid precursor protein (APP) is frequently found in the DN around Aβ accumulations and the neuronal perikarya in survivors of severe head injuries (Takahashi et al., 2017). This is consistent with observations made in patients with late-stage AD (Van Den Heuvel et al., 2007).
Diet and malnutrition • Nutrition and undernourishment • Abalan (1984) was among the first to connect AD with a bad diet. • Giving the specimens excessively high quantities of cholesterol during a rabbit research caused a reduction in Aβ (Sparks et al., 1994). • People with an AD diagnosis who had the family APP gene mutation (APP717, Val-Glycine) were more likely to experience vitamin deficiencies (Armstrong, 2013; Zhuo & Praticò, 2010).

Genetics theory

Numerous studies conducted in the 1990s found strong evidence to support the hypothesis that there is a connection between specific genetic markers and familial AD (Armstrong, 2013; Selkoe & Schenk, 2003) . This led to additional diagnoses being looked at in connection to APP mutations (Jonsson et al., 2012; Levy-Lahad et al., 1995; Muratore et al., 2014) and a considerably wider spectrum of PSEN1/2 mutations, even though some genes are still unknown. Allelic variation within the Apo e locus of chromosome 19 has also been identified as a significant risk factor for patients with late-onset AD (Pericak-Vance et al., 2000; Roses, 1996).

Aβ38 is much lower in the brain's vessel walls. Mutations in the APP are probably the source of this (Armstrong, 2011; Moro et al., 2012). The Amyloid Cascade hypothesis, which has emerged as the most significant paradigm for the molecular pathophysiology of AD during the past 25 years, defines the process (Hardy, 2006; Kirabali et al., 2019).

Nevertheless, PSEN gene mutations are linked to the most common kind of familial AD. Although the influence is probably more of a complicating element

than a direct cause, it is thought that these alterations contribute to the decline in Aβ levels (Kabir et al., 2020; Kumar-Singh et al., 2006). Additionally, compared to cognitively sound individuals, AD patients have 2-3 times more allele. Allelic variations within Apo E have been shown to be a significant risk factor for patients with late-onset AD (Bertram et al., 2010; Serrano et al., 2021)

Mitochondrial dysfunction theory

The hypothesis that AD may be associated with defective mitochondria has been the subject of several significant investigations and dates back to the early era (Castellani et al., 2002; Maruszak & Żekanowski, 2011). It should be mentioned that the enlargement and malfunction of mitochondria are among the initial effects of AD development (Cadonic et al., 2016; Castellani et al., 2002). It causes their brain metabolic rate to drop significantly. Furthermore, an excess of maternal inheritance may contribute to a certain amount of the familial accumulation of AD, and this is common to mitochondria. Lastly, it's thought that consuming carbohydrates causes a loss of several important enzymes, like phosphofructokinase and pyruvate dehydrogenase, which are mitochondrial indicators (Castellani et al., 2002; Yan et al., 2020).

Blood brain barrier dysfunction theory

Importantly, there is disagreement among studies about the contribution of cerebral blood vessels to the development of AD (Bell & Zlokovic, 2009; Korte et al., 2020). Some claim that the quantity and frequency of Aβ deposits, as well as the common spatial patterns of the blood vessels, are indicators of deterioration. It's probable that some materials transported between the vessels aid in the formation of these deposits (Bell & Zlokovic, 2009; Yamazaki & Kanekiyo, 2017). However, some studies contend that these geographical tendencies are coincidental and that the presence of substantial amounts of Aβ and capillary profiles is the only reason for them to arise (Kawai et al., 1990; Thal et al., 2010).

The relationship between Aβ deposits in AD patients and blood arteries can be explained in a number of ways. For example, alterations in the smooth muscles of the blood vessel walls or the basement membranes may result in the deposits (Villemagne et al., 2018; Watts et al., 2014; Zlokovic, 2005). According to Tian et al. (2006) research , blood vessels in AD patients undergo detrimental changes. The smooth muscle cells are damaged and the quantity of Aβ decreases. Another possibility is that axon terminals or glial cells that are sensitive to the vessel wall release Aβ (Zlokovic, 2011). Alternatively, transmission may be initiated by deteriorated clusters of capillaries or arterioles near the larger blood arteries. This

is a convincing argument since reduced blood vessel function or malfunctioning endothelia are normal outcomes of Aβ loss. As a matter of fact, 90% of AD patients have them %) (Grammas, 2011). There's also a possibility that the strength of the brain's microvasculature is related to the degeneration of neurons and, in particular, the age-stimulated loss of cells(Bonda et al., 2011). It should be mentioned that the severity and stage of the illness likely influence endothelial cell impairment. Studies on AD-stricken mice have shown that endothelial cell activation and death have a direct impact on the decline in Aβ (Wang et al., 2011).

Infectious agent's theory

Wisniewski et al. (1981)'s research offers some evidence in favor of the theory that infection and AD development are related. It's conceivable that a virus causes the microglia and pericytes to become activated, which lowers amyloid. Renvoize et al. (1987) also contend that the herpes simplex virus may be the cause. It may cause abnormal protein secretion, which would result in the existence of PHF and NFT. The spinal fluid of AD patients has been found to contain antibodies against the virus.

Discussion and conclusion

Many theories have been proposed over time to explain why AD develops in some people. This paper's goal is to list the most significant and talk about their importance for AD research and the development of new therapies. Most importantly, any proposed pathology must take into consideration a number of significant elements. The diversity of AD as a clinical illness is the first (a). The fact that it doesn't always progress in the same manner makes it challenging to identify a common cause. Additionally, it needs to address the following: (b) the connection between the illness and aging in general; (c) the similarities between FAD and SAD; (d) the potential for tau and Aβ to be responsive proteins; (e) the function of the cerebral blood vessels; (f) the impact of immune responses; and (g) the observation that some AD patients do not exhibit high densities of NFT or SP.

The ACH and cholinergic explanation-based hypotheses are the ones that have had the most impact and longevity (Kepp, 2016). Nevertheless, even though they are both connected to the disease's aetiology, they may not provide a complete or foolproof solution. The most challenging aspect of evaluating an AD hypothesis is that it is not always possible for a researcher to distinguish between a primary and secondary result. However, there is strong evidence that cholinergic dysfunction

plays a role in AD patients, even if it is just related to the degeneration of few areas or modules. Likewise, there are flaws with ACH theories as well. The NFT and SP, for example, could be responsive rather than causative. In actuality, there is no widely accepted explanation explaining how Aβ causes NFT. Consequently, it seems unlikely that cholinergic variables are the primary cause of AD, and further research is needed before ACH ideas can be taken seriously as a potential explanation for the development of AD.

Regarding a few of the less popular ideas, our research has excluded exposure to aluminum or other dangerous metals as a plausible explanation. Nonetheless, some scientists contend that the brain does react immunologically to particular metals. A limited quantity of data indicates that the substance may accumulate in the brain and cause modifications that result in the release of tau and a decrease in Aβ. It is believed that theories about poor diet and brain trauma are markers or risk factors rather than the actual causes of AD development. Likewise, immunological transition and mitochondrial dysfunction are likely reactions to earlier pathogenic processes such as the synthesis of toxic proteins. However, there is a substantial correlation between the illness and a healthy aging process. Importantly, every sign of AD may be partially or fully identified in a brain that is normal and healthy. A decrease in LC neurons during normal aging may have an adverse effect on the blood-brain barrier and raise the chance of acquiring certain degenerative diseases. Lastly, there is strong evidence to support the idea that important anatomical channel degeneration is a major driver for AD transmission across cells.

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