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Review

Comprehensive Review on Alzheimer's Disease: Causes and Treatment

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Academic Editors: Diego Muñoz-Torrero and Roman Dembinski

Received: 5 November 2020; Accepted: 6 December 2020; Published: 8 December 2020

Abstract: Alzheimer's disease (AD) is a disorder that causes degeneration of the cells in the brain and it is the main cause of dementia, which is characterized by a decline in thinking and independence in personal daily activities. AD is considered a multifactorial disease: two main hypotheses were proposed as a cause for AD, cholinergic and amyloid hypotheses. Additionally, several risk factors such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors play a role in the disease. Currently, there are only two classes of approved drugs to treat AD, including inhibitors to cholinesterase enzyme and antagonists to *N*-methyl D-aspartate (NMDA), which are effective only in treating the symptoms of AD, but do not cure or prevent the disease. Nowadays, the research is focusing on understanding AD pathology by targeting several mechanisms, such as abnormal tau protein metabolism, β-amyloid, inflammatory response, and cholinergic and free radical damage, aiming to develop successful treatments that are capable of stopping or modifying the course of AD. This review discusses currently available drugs and future theories for the development of new therapies for AD, such as disease-modifying therapeutics (DMT), chaperones, and natural compounds.

Keywords: Alzheimer's disease; neurodegeneration; β-amyloid peptide; tau protein; risk factors; disease-modifying therapy; chaperons; heat shock proteins

1. Introduction

Alzheimer's disease (AD) (named after the German psychiatric Alois Alzheimer) is the most common type of dementia and can be defined as a slowly progressive neurodegenerative disease characterized by neuritic plaques and neurofibrillary tangles (Figure 1) as a result of amyloid-beta peptide's (Aβ) accumulation in the most affected area of the brain, the medial temporal lobe and neocortical structures [1]. Alois Alzheimer noticed a presence of amyloid plaques and a massive loss of neurons while examining the brain of his first patient that suffered from memory loss and change of personality before dying and described the condition as a serious disease of the cerebral cortex. Emil Kraepelin named this medical condition Alzheimer's disease for the first time in his 8th edition psychiatry handbook [2,3]. Progressive loss of cognitive functions can be caused by cerebral disorder like Alzheimer's disease (AD) or other factors such as intoxications, infections, abnormality in the pulmonary and circulatory systems, which causes a reduction in the oxygen supply to the brain, nutritional deficiency, vitamin B12 deficiency, tumors, and others [4,5].

(SNPs) in ERβ and ERα genes may affect exogenous estrogen in older women and influence cognitive aging. PvuII (rs9340799) and Xbal (rs223493) are examples of SNPs found in ERα and are associated with AD and cognitive impairment. Also, several SNPs in ERβ have been proven to increase the risk of AD in women [69–72].

- Other Genes

Other genes' polymorphism associated with increasing the risk of AD include vitamin D receptor (VDR) gene polymorphism, which affects the affinity of vitamin D to its receptor and may cause neurodegenerative diseases and neuronal damage [73]. Moreover, epigenetic factors like DNA methylation, histone, and chromatin modifications were demonstrated to be involved in AD [33,74].

5.2.3. Environmental Factors

Aging and genetic risk factors cannot explain all cases of AD. Environmental risk factors including air pollution, diet, metals, infections, and many others may induce oxidative stress and inflammation and increase the risk for developing AD. Herein, we report the most important environmental factors and their relationships with AD [75,76].

- Air Pollution

The air pollution is characterized by modifying the nature of the atmosphere through the introduction of chemical, physical, or biological pollutants. It is associated with respiratory and cardiovascular diseases and recently, its association with AD was documented. Six air pollutants have been defined by National Ambient Air Quality Standards (NAAQSs) in the USA as a threat to human health, including ozone (O_3), nitrogen oxides (NO_x), carbon monoxide (CO), particulate matter (PM), sulfur dioxide (SO_2), and lead. Studies on animals and cellular models have shown that an exposure to high levels of air pollution can result in a damage to the olfactory mucosa and bulb, in addition to the frontal cortex region, similar to that observed in AD. In individuals exposed to air pollutants, there is a link between oxidative stress, neuroinflammation, and neurodegeneration, with the presence of hyper-phosphorylated tau and Aβ plaques in the frontal cortex. The air pollution can cause an increase in $A\beta_{42}$ formation, accumulation, and impaired cognitive function [77,78].

- Diet

In recent years, the number of studies on the role of nutrition in AD have been increased. Several dietary supplements such as antioxidants, vitamins, polyphenols, and fish were reported to decrease the risk of AD, whereas saturated fatty acids and high-calorie intake were associated with increasing the risk of AD [79]. The food processing causes degradation of heat-sensitive micronutrients (e.g., vitamin C and folates), loss of large amounts of water, and formation of toxic secondary products (advanced glycation end products, AGEs) from non-enzymatic glycation of free amino groups in proteins, lipids, and nucleic acids. The toxic effect of AGEs is referred to as their ability to induce oxidative stress and inflammation by modifying the structure and function of the cell surface receptors and body proteins. Different studies demonstrated that elevated AGEs serum level is associated with cognitive decline and progression of AD. The AGE receptor (RAGE) is located in different places within the body, including microglia and astrocytes, and was established to be overexpressed in the brain of AD patients and serve as a transporter and a cell surface receptor for Aβ [80]. Malnutrition is another risk factor for AD. Deficiency in nutrients such as folate, vitamin B12, and vitamin D may cause a decrease in cognitive function, in addition to the fact that patients with AD suffer from problems associated with eating and swallowing, which may increase the risk of malnutrition [81].