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Personalized Medicine Approach in the Treatment of Alzheimer›s Disease

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Abstract:
Alzheimer's disease (AD) is a neurodegenerative disease which leads to progressive and incurable cognitive and behavioral disorders. Personalized medicine, which is also called precision medicine, represents an approach to the treatment of the disease with the aim of improving the effectiveness of the treatment, which stops or slows the disease in an optimal and targeted manner at a certain time. It enables the physician to accurately and efficiently identify the most effective treatment. Personalized medicine is based on molecular knowledge. Genome sequencing by the Human Genome Project (HGP) represents one of the most powerful tools for personalized medicine, as along with transcriptomics, proteomics, and metabolomics development which can be used for both disease prognosis and better treatments. In this paper, we will review the strategies that personalized medicine offers for the treatment of AD for the future.

INTRODUCTION

Personalized medicine approach has been used for decades in the management of some rare diseases. Alzheimer's disease (AD) has been the sixth cause of death in recent years, and personalized medicine is a novel approach to preventing and treating the disease with a specific pattern of genetic diversity, environment, and lifestyle factors which contribute to chronic neurological disorders (1).

Dementia is the most common neurodegenerative disease with AD affecting one out of every 10 men and one out of every five women. AD is a devastating progressive neurological disease and is characterized by short-term memory loss, mood swings, and inability to perform daily tasks. Age is one of the main factors for the onset of Alzheimer's disease. AD usually causes plaque formation in the brain's hippocampus, which is responsible for encoding memories, as well as other parts of the brain's cortex that are critical for making sound judgments and decisions. In addition to cognitive impairments such as memory loss, behavioral disturbances can be seen through common neuropsychiatric symptoms such as depression, restlessness, delusions, and hallucinations (2).

Alzheimer's disease, causes and clinical manifestations

According to recent studies, the main cause of this disease is the accumulation of tau protein and the formation of beta amyloid plaques along with neurofibrillary tangles caused by oxidative stress, which is due to the imbalance between the production and accumulation of reactive oxygen species in cells as well as tissues and the detoxification ability of the biological system. Age is the main factor for Alzheimer's disease. Accumulation of beta amyloid plaques is associated with a gradual decline in memory and cognitive function due to the loss of brain tissue (atrophy) (3).

Recognized as the most common form of dementia in the elderly population, AD can manifest itself in two forms: rare early-onset dementia leading to AD (EOAD) before the age of 65 and common late-onset disease AD (LOAD) also known as senile dementia which occurs after the age of 65 due to aging (4, 5).

In 2018, the estimated number of patients of all ages with AD in the US was approximately 5.7 million, with LOAD accounting for more than half of the estimated cases. As the size of the US population over the age of 65 continues to grow, the number of Americans suffering from AD continues to rise, with an estimated number expected to reach 88 million by 2050 (6).

One of the main reasons for the complexity of this disease is the extensive genetic variations involved in AD mechanisms. Along with the progress in human genome sequencing project and bioinformatics tools, many genes mostly associated with the metabolic

pathways of proteins and enzymes of disease have been identified. A list of these genes is provided in Table 1 with some of their references (1, 7).

Despite the identification of these genes, many mechanisms of the AD are still unknown due to the existence of genetic variations, which has made it difficult to develop a definitive drug for the disease (1).

Conventional treatment and personalized medicine

AD is a neurological disorder caused by the accumulation of beta-amyloid plaques in the brain. Various drugs are available that aim to treat AD. For most common pharmaceutical forms, the characteristics of the blood-brain barrier (BBB) must be considered (27). Due to the lack of effective drug therapy for the treatment of AD, only symptomatic treatment is performed for AD patients. Currently, there is no definitive treatment for AD. The medicine available in the market has only the ability to slow down its progress. AD occurs due to excessive production of β-amyloid peptide (Aβ), which is deposited in the brain specifically around neurons which causes the loss of synaptic terminals and neurological disorders in the hippocampus as well as cerebral cortex. It also reduces the amount of certain neurotransmitters such as acetylcholine. Aβ is a peptide derived from the proteolytic cleavage of a membrane protein known as amyloid precursor protein (APP) by β- and γ-secretases (28). APP is an integral membrane protein mainly concentrated in the synapses of neurons and astrocytes. Specific inhibition of β- and γ-secretases can prevent Aβ production. However, this enzymes inhibition can have several side effects for the body (29-31).

In this regard, iAβ5 peptide has been discovered as an anti-amyloid therapeutic agent as a new treatment against AD. By binding to Aβ, iAβ5 peptide inhibits Aβ fibrillogenesis and prevents its further accumulation in amyloid fibrils. However, it was observed that the iAβ5 peptide is unstable and can be easily degraded by proteases. Hence, to construct an iAβ5 derivative with improved properties such as endurance, stability, and higher proteolytic solubility, polyethylene glycol (PEG) and charged sequences can be attached (32). However, this drug has a low level of BBB permeability, which limits its access to the brain.

The treatments that are currently used in AD as a preventive or effective treatment mainly deal with cholinesterase inhibition as well as suppression of glutamatergic signals and ionotropic symptoms including donepezil (Aricept) (33), galantamine (Razadyne) (34) and rivastigmine (Exelon)(35) along with suppression of ionotropic glutamatergic signaling by memantine (Namenda) (36), all of which are prescribed only after the initiation of symptoms. Diarrhea, nausea, and sleep disturbances are common side effects of these drugs.

One of the benefits of pharmacogenomics in neurology includes the use of the drug Plavix, which is included in the category of blood platelet inhibitor drugs. Plavix inhibits the formation of blood clots and prevents strokes in Alzheimer's patients. People who have mutations in the CYP2C19 gene cannot properly metabolize Plavix (27).

The CYP2C19 gene is a member of the cytochrome P450 gene family. Enzymes produced from cytochrome P450 genes play a role in the metabolism of various molecules and chemicals inside cells. The CYP2C19 gene encodes an enzyme in endoplasmic reticulum of the liver, which is involved in processing and transport (37, 38).

Another effective treatment for AD is the use of vitamin E, which has direct effects on the nerves. Vitamin E is an essential micronutrient for the body, with 90% of people being unaware of its effects. Human body cannot synthesize this vitamin and must get it from the diet. Vitamin E is absorbed from the small intestine

Table 1. Main genes and related molecular pathway of AD (1,7)

Gene	Molecular pathway	Ref
APOE, SORL1, CLU, CR1, PICALM, BIN1, CASS4	Amyloid pathway	(8-10)
HLA-DRB5/DRB1, INPP5D, MEF2C	Immune response/ Inflammation	(11-13)
APOE, CLU, ABCA7, SORL1	Lipid transport and Endocytosis	(14-16)
BIN1, CASS4, FERMT2	Tau pathology	(17, 18)
PTK2B	Cell migration	(19-21)
MEF2C, PTK2B	Hippocampal synaptic function	(22)
CELF1, NME8, CASS4	Cytoskeletal function and axonal transport	(23, 24)
INPPD5	Microglial and myeloid cell function	(7, 25)
FBXL7	Phosphorylation- dependent ubiquitination	(26)

(39). According to a study on 3,000 elderly women, those who consumed less vitamin E-containing foods in their diet were mentally weaker (40). With oxidative stress being implicated in the onset of AD vitamin E acts as a major fat-soluble antioxidant. Individuals with intrinsically low alpha-tocopherol plasma levels may be more responsive to vitamin E treatment to combat oxidative stress. Alpha tocopherol is a member of the vitamin E family which is obtained from sunflower oil. Alpha tocopherol is the main type of vitamin E in human plasma. In evaluating the protective effect of alpha tocopherol against oxidative stress caused by bisphenol A in rats, laboratory alpha tocopherol can be used (41).

Over the past years, more attention has been paid to personalized medicine due to the unexpected failure of disease treatment and lack of response in patients or increased side effects in an individual. Also, the use of genetic markers for designing treatments is of great importance.

In a clinical test, the APOE-ε4 allele was selected as a biomarker for early diagnosis of AD using modern biomarker analysis tools (42, 43).

Also, bioinformatics with the wide availability of genome sequence has proved to be a low-cost and comprehensive method for genome analysis in personalized medicine. In personalized medicine, a genotype-to-phenotype relationship is established based on personal genomics information while pharmacogenomics connects the patient genomics information to the specific treatment for him/her. On the other hand, this new field in medicine requires novel analytical tools for analyzing huge amount of data. Thus, the application of artificial intelligence (AI) plays an important role in monitoring the disease-patient relationships, which is very important in early/optimal diagnosis, prevention, and treatment. Predictive algorithms and models are key factors of this innovative field (44).

In an effort to find therapeutic solutions consistent with personalized medicine, the Alzheimer's Prevention Initiative (45), the Dominantly Inherited Alzheimer's Network (DIAN) (46), AD Neuroimaging Initiative (ADNI) (47) and the A4 Trial (48) are presenting mechanisms of Alzheimer's pathogenesis based on clinical trials on patients who have been selected to investigate the performance of the proposed treatments.

CONCLUSION

Due to diverse genetic variations and differences in lifestyle and geographic environment, the causative of Alzheimer's as a neurological disease is still not fully understood. As a result, there is currently no definitive approach for prevention, diagnosis and early treatment of the disease.

The existing therapeutics are also symptomatic treatments that are prescribed from the appearance of the first signs of the disease.

While trying to find ways to prevent and diagnose AD, as well as investigating the genetic variations related to it, personalized medicine has also been implemented in order to provide new approaches for treatment of AD and other rare diseases based on the genetic characteristics, lifestyle, and environment of the patients. Although there is a long way ahead for personalized medicine to overcome this disease due to the existing complexities and the incompleteness of related techniques, in the future, the accomplishments of this field can address many complex problems related to the prevention and treatment of the disease.

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