

Risk Factors in Induction and Progression of Alzheimer's Disease: Impact on Protection and Disease-Modifying Factors

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that leads to memory loss and nerve cell death throughout the brain. It is the most common cause of dementia and represents the most important problem in elderly. Dementia characterized mainly by decline in memory, cognitive skills and ability to perform everyday activities as well as behavioral dysfunction. The decline occurs because neurons involved in cognitive function have been destroyed and affected other parts of the brain involved in different basic bodily functions.

Keywords: Alzheimer's disease; Progression; Risk factors; Protection

Introduction

The degeneration in the brain caused by AD is not usually the primary cause of death since it causes many other complications such as immobility, malnutrition and increased risk of pneumonia [1-3]. Death that occurred from AD have increased dramatically since 1991, the disease is ultimately fatal and represents growing public health problem with major socioeconomic burden. In the final stage of the disease patients require care around-the-clock. The prevalence of AD varies among different reasons and factors as age, genetics and education level [4]. There are two main forms of AD; familial one which affects people less than 65 years [5] while the other cases is classified as sporadic AD and occurs in older people [6].

Alzheimer's disease progresses gradually where symptoms of dementia increases over a number of years and can last for decades. The progression of the disease is time dependent; just starts it spread spontaneously. Typically, the disease progresses slowly in three main stages (mild, moderate, severe). In the early stage of the disease, memory loss is mild. However, in the late-stage of AD individuals completely lose their ability to respond to the environment and can't make any conversation [7,8]. Because AD affects people in different stages and by different ways, so each patient will experience symptoms as well as progress through its stages differently [9]. Consequently, rate of progression varies greatly; brain shrinks dramatically over time, plaques and tangles spread thus affecting nearly all brain functions.

There is lack of data in understanding AD progression. Researches revealed great deal but much is yet to be known about its progression as well as ways to its prevention. Scientists hope to model different stages of the AD as well as its progression. By identifying the stages of the disease, prediction will be possible, symptoms can be expected and the power to find real treatment will be enhanced.

Literature Review

Modeling stages of Alzheimer's disease in rats

The impact of Aluminum (Al) on neural tissues is well known [10]. It has been implicated in many aging related changes as well as in neurodegenerative diseases. Aluminum is a constituent of antacids, deodorants and food additives, thus allowed its easy access into the body. Excessive Al intake leads to accumulation of A β in the brain and over expression of β -amyloid precursor protein [11]. The neurotoxicity of A β is strongly related to oxidative stress which plays an effective role in the pathogenesis of AD [12]. The generation of reactive oxygen

species causes damage of neuronal membrane as well as lipids, proteins and nucleic acids [13]. It has been reported that Al toxicity is due to potentiating the activity of Fe²⁺ and Fe³⁺ ions to cause oxidative damage. Aluminum also interacts with calcium binding sites and disrupts calcium homeostasis and thereby induces neurodegeneration. The toxicity of Al was also found to be associated with reduced axonal length and dendritic branches in hippocampus [14,15].

In animal models, Al neurotoxicity has been clearly established and shown to be involved in etiology of neurodegenerative diseases such as AD [16]. It was found that, Al promotes the formation of amyloid- β protein plaques by aggregating tau proteins. Administration of AlCl₃ predominantly accumulates in the hippocampus which is known to be particularly susceptible in AD and play an important role in learning and memory as well as in many related behavioral functions [17].

Alzheimer's disease risk factors

Much attention has been paid to AD risk factors and disease-modifying factors. A number of factors may increase the chances of developing the disease. Some risk factors can be changed or controlled while others cannot. Risk factors mainly include age, genetics, environment and lifestyle. The majority of AD occurs as a result of complex interactions among genes and other risk factors. A connection has been found between a gene called Apolipoprotein E (ApoE) and the development of AD [18]. One form of this gene (ApoE4) has been shown to increase the chances of developing the disease, but the other form (ApoE2) can protect from AD [19]. Age is the greatest risk factor for developing AD; most cases of AD are seen in people ages above 65 years. Approximately, five percent of people have AD between the ages of 65 and 74. However, the risk of AD increases to 50 percent for peoples over 85 [20]. Family history represents strong risk factor; risk increases when more than one family member has the disease, those people are more likely to develop AD [21].

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Modifiable or controlled risk factors include stress, heavy smoking, excessive alcohol drinking, depression, cognitive inactivity or low education, malnutrition and physical inactivity. Connection between low educational level and the risk of developing AD had been established; people with low education seem to be at a higher risk. The exact cause for this relationship is unknown but it is postulated that formation of more synaptic connections is considered as a synaptic reserve in the brain and occurs in people with higher education level, thus enabling them to compensate the loss of neurons as the AD progresses [22]. Exposure to stress represents a risk factor in induction of AD especially in the developed countries, while protein malnutrition (PM) which increases the severity and progression of AD represents socioeconomic problem in the third world and developing countries [23,24]. On the other hand, researchers believe that depression is a risk factor, whereas others believe it may be an early symptom of the disease.

Although risk factors such as age and family history cannot be changed, other risk factors can be changed or modified to reduce the risk of cognitive decline and dementia. Recent report on the influence of modifiable risk factors on dementia and cognitive decline stated strong evidence between regular physical activity and management of different cardiovascular risk factors thus, reduce the risk of cognitive decline as well as the risk of dementia. There is also strong evidence that healthy diet and continuous learning and cognitive training can reduce the risk of dementia and cognitive decline. Chronic stress also considered as risk factors for cognitive decline; it has been strongly implicated in AD progression [25].

Strong evidences established the closely linked relation between the brain health and the overall health of blood vessels and the heart. The risk of developing AD or vascular dementia appears to be increased by conditions that damage the heart or blood vessels. Brain is nourished by networks of blood vessels, so healthy heart can ensure that enough blood is pumped through these blood vessels to the brain with oxygen and nutrient to allow its normal functions. Many risk factors for cardiovascular disease are also considered as high risk factors for AD and dementia. These factors include heavy smoking [26,27] obesity especially in midlife [28-30] as well as diabetes [31-34]. Studies demonstrated that impaired glucose processing also results in increased the risk of developing dementia [35,36]. Moreover, hypertension especially in midlife [37-39] as well as high cholesterol [40,41] are also considered as risk factors for dementia. Conversely, factors that protect the heart can also protect the brain and reduce the risk of developing AD and; physical activity is considered as the central of these factors [42-44]. In addition, it is well known that consuming a healthy heart diet is associated with reduction of AD and dementia [45-48].

Some other medical conditions can increase the chances of developing AD and dementia including Parkinson's disease, Down syndrome and some other learning disabilities. Strong link has been also shown between serious head injuries especially when involve loss of consciousness as well as trauma especially when occurred repeatedly and the future risk of AD development [49]. Accordingly, scientists hope to prevent or delay AD especially in the high-risk individuals.

Discussion

Protection and disease-modifying factors

Until now there is no real or effective treatment for preventing neuronal death associated AD and leads to cognitive decline and memory impairment [50,51]. Indeed, the risk of development and progression of AD can be lowered by enhancing physical and mental

activity and by maintaining strong social connections during aging. However, the underlying mechanisms of the relationship between better cognitive function and frequent social interaction are still unclear [51-53]. Additional studies revealed that remaining social and cognitive engagement throughout life may affect biological processes and support brain health and reduce the risk of AD [54-60] but the exact mechanism by which this may occur is unknown [61].

Conclusion

In general, healthy aging and lifestyle can help reduce the risk of AD and other dementias. Cognitive engagement, physical activities [62], reduce stress [23], quitting or reducing smoking, avoid excessive alcohol consumption have been associated with decreased risk of AD. Healthy food as well as dietary supplementation of antioxidants, B vitamins, polyphenols, polyunsaturated fatty acids, Zinc and moderate coffee drinking can reduce AD incidence and provide protection. Although the mechanisms of these nutrients on AD are not clear, but reducing oxidative stress, inflammatory mediators and both A β and tau pathologies can attenuate cognitive deterioration [63-65].

Consequently, multi-target directed strategies showed higher effects for reducing the prevalence of the disease as well as for providing marked symptomatic and disease modifying benefits. These strategies include the use of the combined treatments or the protective agents together with socialization as well as programs of both physical and mental activities. In animal experimental models, multi-target directed strategies showed promising results and provided protection especially in the presence of different risk factors as stress, isolation and protein malnutrition [23,24,61]. For example, EGCG is effective in minimizing the hazards of aluminum-induced AD in rats; however the combined therapy of Epigallocatechin-3-gallate (EGCG) and coenzyme Q10 (CoQ10) or EGCG and vitamin E and selenium has more pronounced protective effects than EGCG alone [4,24,63]. Moreover, co-administration of moderate doses of both caffeine and nicotine can reduce the risk of neuronal degeneration and attenuate the impairment of memory than each of them alone [64]. In addition, the deleterious effect of stress on the brain can be also counteracted by using EGCG together with Diazepam [23].

On the other hand, the impact of cocoa, wheat grass and different nutraceuticals as well as vinpocetine either alone or in combination was also studied [66-69]. They showed variable protective effects which greatly increased by using different combination of them. Their combined treatments can greatly enhance the power of physical and mental activity against the development of AD as well as against the deleterious effects of different stressful conditions and risk factors as social isolation and protein malnutrition [70-73]. However, further researches are needed to improve the quality of evidence associated with the reduction of AD prevalence and incidence.

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