The Dichotomy of Gene-Environmental Factors on Alzheimer’s.

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Introduction

This paper will explore the dichotomous relationship between gene and environmental factors that influence risk factors for Alzheimer’s disease (AD). Alzheimer’s disease is a complex neurodegenerative disease that attacks nerve cells and slowly destroys memory and thinking skills. It is a common cause of dementia that propagates the loss of intellectual function, language skills, and behavioral changes. This is a major public health concern as the prevalence of AD will grow substantially and increase with the population’s increase of older adults. Currently, AD is most common in people aged 65 and older and consist of 6% to 10% dementia cases; this number is projected to quadruple by 2050 (Gatz, 2006). In order to decrease the prevalence of this disease, it is important to understand and investigate risk and protective factors that cause AD. The etiology of Alzheimer’s disease is multifactorial, consisting of a substantial proportion of genetic factors and environmental factors. Developing a perspective and investigating the relationship between the gene-environmental factors that are associated to play a significant role in the onset of AD will illuminate potential points of intervention (Reynolds, 2013). The ApoE4 gene provides an example of complex gene-environmental interactions that increase risks for Alzheimer’s disease.

Background

The ApoE gene is associated with many diseases such as cardiovascular disease, vascular dementia, mild cognitive impairment, but more specifically the late onset of Alzheimer’s disease. The ApoE gene is a fat bound protein that plays an integral role in cholesterol transport and consist of three alleles; E2, E3, and E4 (Hendrie, 2001). Research has found an association between the onset of late AD and the E4 allele, which is present in 15% of the US population and 5-41% in populations around the world (Gatz, 2006). The significant interaction between different cholesterol levels and the role ApoE4 plays in the process, suggests that cholesterol mediates the effects and increased risk factors that ApoE4 has on the late onset of AD. Therefore, increased cholesterol levels increase the risk of Alzheimer’s disease. Researchers have also found an association between the E4 allele and the increased number of protein clumps, called amyloid plaques. The increased buildup of amyloid plaques is associated with the risk of Alzheimer’s disease, as the toxic amyloid beta peptide can lead to the destruction of neurons and nerve cells, initiating the symptoms to late onset of the neurodegenerative disease (Schmechel et al, 1993). This refers to the process of oxidative stress which is essentially an imbalance in the production of reactive oxygen species and antioxidant defenses. The brain is specifically vulnerable to oxidative stress, as it can lead to the production of tissue and cell damage. The risk of the ApoE4 gene on increased cholesterol levels, oxidative stress, the toxic buildup of amyloid plaques shed importance on the environmental factors that significantly increase these risk factors. While the ApoE4 gene alone can increase the risk for Alzheimer’s by a factor of 2.83, the ApoE4-environment interaction can increase the risk factor by 11.42 (Stein et. al, 2008). Environmental factors can include education, poverty levels, head injury, and even use of nonsteroidal anti-inflammatory drugs (Reynolds, 2013). More importantly, western lifestyle is emerging as a key risk factor along with the ApoE4 gene in the onset of AD and other diseases. Environmental factors such as obesity, diabetes, smoking, physical inactivity, and engaging in a Western-type diet play a big role in cognitive deficiencies (Reynolds 2013). Researchers have concluded that lifestyle and diet interventions can greatly modify Alzheimer’s risk, as it can promote cognitively engaging activities. For instance, a high calorie diet with low levels of important antioxidants, such as vitamin C and E, produce greater evidence of oxidative stress and toxic end products. Diet can be seen as a mediating influence between the ApoE3 gene and AD (Hendrie 2001), as the gene-environment-diet interaction explains the inconsistent finding in some studies where only the ApoE4 gene is examined as a risk factor for the disease or condition.

Health Implications

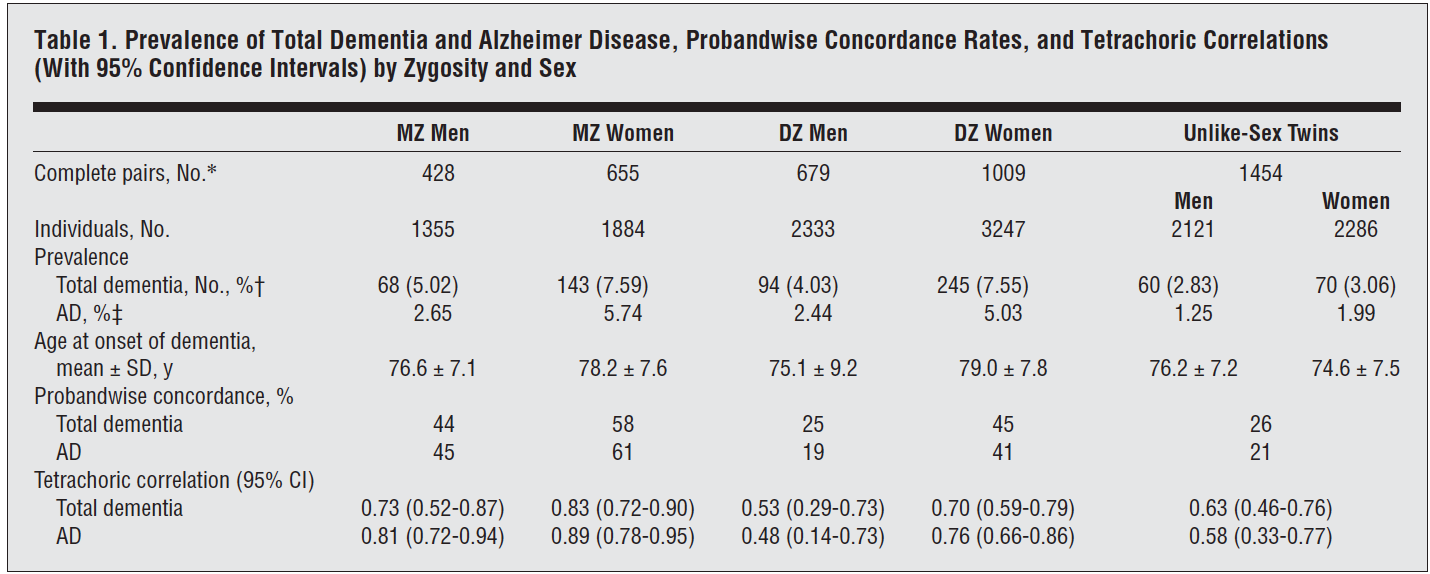
Alzheimer’s is a major public health concern as it has a profound impact on society, patients, and their families. The health implications of this disease refer to the severe intellectual impairment in the individual, loss of memory, and deterioration of personal relationships. Alzheimer’s has been commonly brushed aside as a condition caused by old age; it was only until two decades ago that there has been increased attention to this public health concern as to what factors can increase the risk of Alzheimer’s. As discussed previously, genetic and environmental factors play a significant role in the increased risk of Alzheimer’s. To better one’s understanding of this condition, it is highly important to understand the health implications of factors, as it may illuminate the multifactorial etiology of AD and possibly decrease the growing prevalence of this disease by future treatment interventions. In a study done recently, it was found that the toxic environmental and occupational exposures caused 21% or more of cognitive disorders in the thousand patients that were present in the clinic (Stein et al., 2008). The environmental chemicals have various health implications, including an increased risk of cognitive decline and lowered the age of onset of AD. For instance, lead is toxic in many organ systems, specifically the brain, and can lead to lead neurotoxicity in which lead crosses the blood-brain barrier and disrupt mechanisms. The increased exposure to lead from occupational and environmental factors can lead to adverse effects such as neuronal oxidative stress, aggregation of amyloid-beta, impairments in visual-spatial/visual-motor function, and memory; symptoms that increase the risk of the late onset of Alzheimer’s (Stein et al., 2008). Moreover, growing evidence is revealing a relationship between air pollution and neurodegenerative diseases. The pervasive complex mixture of gases, contained in air pollution, has shown to have profound health impacts on populations, including the increased risk of AD due to inflammation, accumulation of amyloid beta, and degeneration of brain tissue (Schmechel et al., 1993). Furthermore, it is important to note the comparison of frequency of risk factors between populations as life style differences and genetic variability can have various health implications. The ApoE3 gene-environment-western diet interaction discussed previously can tremendously increase the risk of Alzheimer’s. For instance, from a meta-analysis conducted, it was found that Caucasians whom carry one copy of the allele E3 increase their risk by threefold, and nearly 15-fold for those carrying two copies (Hendrie, 2001). In comparison, Africans carrying one or two copies of the allele, increase their risk by only 1.1 and 5.7 folds, respectively.

Methodology

For Alzheimer’s research, the twin study design is commonly used to explore the interaction between genetic and environmental influence. In this study, the researcher needs to first define whether both twins have the disorder, known as concordant, or if only one is affected, known as discordant. Evidence for environmental influence is found in discordant monozygotic (MZ) twins since they share 100% of their genes and difference between the twins can provide clues about the influence of environmental risk factors that may have led one twin to have AD and not the other (Gatz et al, 2006). For the study of dementia in Swedish twins, known as HARMONY, conducted in 1984, researchers create a 2-phase procedure that consisted of a screening phase and a clinical phase. Participants were gathered by questionnaires that were sent to all like-and unlike-sex twins. Individuals were classified as demented if they met the diagnostic criteria for dementia and or as nondemented if they did not meet the criteria. Next, all individuals were classified based on complete pairs (both were alive), incomplete pairs (one of the twin deceased), sex, and zygosity (MZ or DZ). The screening phase consisted of a telephone interview using a TELE questionnaire, in which the participants were given the Blessed Dementia Rating Scale. The clinical phase consisted of an in person diagnostic evaluation conducted by a physician and a nurse. The assessment consisted of a “neuropsychological testing, a semi structured interview with a knowledgeable informant, and a physical examination with blood panel” (Gatz et al. 2006). Moreover, the age of onset for the study was defined by the assessment team that conducted a detailed informant interview and defined it as the age in which “definite and enduring symptoms of dementia first appeared” (Gatz et al., 2006).

Case Study 1

HARMONY, the study of dementia based on a twin study design discussed in methodology was launched in 1984 in order to gain information about the environmental risk factors of Alzheimer’s disease. There was a 71.5% participation rate for screening process and 69.7% participation rate of the clinical phase (Gatz et al., 2006). Out of 13,519 individuals who participated in the telephone interview, 1565 were reported positive for dementia. As seen in Table 1 below, prevalence rates tend to be higher in women than in men and in those who were older as opposed to younger. In this study, they have found that heritability of this disease is high and does not differ by sex as the same genetic effects are operating on both men and women. Moreover, environmental factors and lifestyle have also been taken in account as risk to developing Alzheimer’s disease. While risk factors can include poor nutrition, socioeconomic status, sickness; protective factors can consist of physical activity, nutritious diet, and complexity of work. The variable of discordant MZ pairs or concordant pairs whom had different ages of onset was an important observation as it allows one to explore the multifactorial etiology of AD, in which life style and environment play a role in the development of this disease.



Case Study 2

A case study conducted in 2016 also used the twin study design in order to examine the genetic and environmental influences on cortical mean diffusivity (MD) through the use of magnetic resonance imaging (MRI) (Elman et. al, 2017). Changes in mean diffusivity of cortical gray matter has been detected by MRI scans to provide early detection of Alzheimer’s disease. This study was done in middle aged men from wave 2 of the Vietnam Era Twin Study of Aging (VETSA). The study sample of 420 subjects consisted of 96 monozygotic (MZ) pairs, 67 dizygotic (DZ) pairs and 94 unpaired individuals (Elman et. al, 2017). The mean diffusivity was found to be heritable in a majority of cortical regions and had distinct genetic influences on individual variability. Altered mean diffusivity of cortical gray matter is seen as an indication of early degeneration and onset of AD; since there is a positive genetic correlation between the cortical MD, future studies can investigate neurodegenerative diseases and gene association (Elman et. al, 2017). Moreover, environmental factors, such as exposure to head injuries, can explain the covariance and lower genetic correlations that were found in older ages.

Analysis

The twin study design conducted in 1984 was different than past twin studies as the size of the study was greater in the number of participants, it was representative of the sample, there was inclusion of unlike-sex pairs to test for sex limitation, and it incorporated age correlation to the disease threshold (Gatz et al., 2006). However, it consisted of many limitations as well, as it was unable to distinguish whether discordant pairs differ in disease onset or in age onset. Influence of genetic and environmental factors was relative; if there was low genetic variability, it indicated a high estimation for environmental factor; therefore, the results do not include specific genetic or environmental factors that were involved. Moreover, not all twins agreed to participate; nonparticipation was tested using information available in Inpatient Discharge Registry and Cause of Death Registry. The implication of the HARMONY study suggest that AD risk is strongly influenced by genetic and non-genetic influences; environmental factors increase risk of dementia in early and midlife exposures. Risk factors in early exposures consist of inflammation, poor nutrition, and sickness; while risk factors in midlife exposures include overweight, high cholesterol, and diabetes (Gatz & Steuer, 2011). Alzheimer’s disease can be best studied from prospective observational studies as the disease develops slowly and over time, and can consider the genetic, environmental, and behavioral influences over time.

Solutions

There are many protective environmental and lifestyle factors that can safeguard one’s brain against Alzheimer’s disease. Education is one of the factors, and is recognized as one of the most studied and reliable protective factors since it is associated with lower risk of dementia as it permits better compensation for brain pathology (Gatz & Steuer, 2011). Cognitive engagement, such as reading and taking part in cultural and social activities, is a protective factor particularly for women, as it provides a means to reduce dementia risk through cognitive enrichment. Occupation is also considered a protective factor as career choices that involve complex interaction with people, problem solving skills, require synthesis, and analysis relate to a lower risk of AD as it postpones the clinical diagnosis of dementia. Physical activity has consistently been seen as a strong protective factor for both sexes as not only does it have cardiovascular benefits, but it plays an important role in brain plasticity and cognitive performance (Stein et. al, 2008). Lastly, nutrition, diet, and supplements are protective factors for Alzheimer’s as vitamins A, E, C, and β-carotene protect the brain with their antioxidants.

Conclusion

This paper examined the role of genetic and environmental factors on Alzheimer’s disease, through the exploration of health implications of risk and protective factors. By observing the interaction between the gene-environmental factors, one is able to gain insight into the multifactorial etiology of AD and understand the severity and importance of this public health issue, which was once recognized as a condition simply brought by old age. Higher level of engagement and attention needs to be given to Alzheimer’s disease and its relationship with gene-environmental factors as it’s prevalence is projected to quadruple by 2050.

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