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Why Test for Risks of Alzheimer's Disease?

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Dementia is a general term for different disease processes that adversely impact the ability to think, remember, reason, and control feelings and emotional responses. The largest risk factor for the development of dementia is advanced age. Roughly one third of dementia patients have only Alzheimer's Disease (AD), one third have a mixture of AD and vascular disease dementia, and one third have only vascular disease dementia, with a small percentage of dementia patients suffering from Lewy body dementia and frontotemporal dementia.[1] The Mayo Clinic estimates that about 6.5 million people in the US have AD, with more than 70 percent aged 75 or older.[2] It is difficult to disentangle the exact contribution of vascular disease to the causation of AD. However, given the high percentage of dementia that has some contribution from vascular disease, control of blood pressure, cholesterol levels, and blood sugar levels can play an important role in the prevention of dementia.

The second largest risk factor for AD comes from an unexpected source—a protein called Apolipoprotein E (APOE), which plays a central role in fat metabolism.[3] An allele is an alternative form of a gene. A child receives one copy of an allele from each parent. There are three common alleles of the APOE gene: APOE ε2, APOE ε3, and APOE ε4. In the predominately European-derived US population, the ε4 allele prevalence is approximately 25.5 percent, constituted by a small portion of ε4 homozygous individuals (2 percent of the US population) with a larger proportion being ε3/ε4 (22 percent) and ε2/ε4 heterozygous (1.5 percent).[4]

Prehistoric Origins

Until 300,000 years ago, ancestors of modern humans were ubiquitously ε4/ε4, and then the ε3 allele mutated from the ancestral ε4 allele.[5] The ε3 allele displayed a competitive survival advantage sufficiently robust to result in the current predominance of the APOE ε3 gene, with a prevalence of approximately 82 percent in the US population with 60 percent or slightly more being homozygous ε3/ε3.[6] The ε3 is thought to have been successful because of its protection against atherosclerotic heart disease, memory loss, and dementia in progressively older age ranges.

Similarly, the ε2 allele mutated from the ε3 allele about 200,000 years ago, but this protective allele has remained relatively rare, with the homozygous ε2/ε2 variant less than 1 percent, and ε2/ε3 heterozygosity occurring in about 11 percent of the population.[7] The failure of the ε2 allele to compete successfully against the ε3 allele is not surprising, given that its benefit on cognition and protection from AD pathology does not contribute to survivability until an advanced age well after the average life expectancy of our ancestral hunter-gatherer populations.[8] In addition, possession of the ε2 allele is associated with elevated triglyceride levels, which can increase heart disease risk in middle-aged individuals, and predispose individuals to certain infections that can occur in younger age groups.[9]

In non-Hispanic whites, possession of one ε4 allele increases the risk of developing AD by 3- to 4-fold, and possession of two ε4 alleles increases risk by 15-fold, as compared with the ε3/ε3 genotype, with a large part of the variation being related to substantially earlier age of onset. Over 60 percent of patients with non-familial AD carry the ε4 allele.[10] In April 2017, the US Food and Drug Administration (FDA) approved 23andMe's personal genetic test for Alzheimer's disease. This test determines whether someone is carrying one or two copies of the ε4 allele.

Strategies for Prevention

Other than dying peacefully in one's sleep at an advanced age, the prospect of dying from any disease process is unappealing. A diagnosis of AD is particularly dreaded because of the anticipated loss of independence, personality changes, and extended period of decline. If nothing could be done to prevent the onset of AD, knowledge of an increased risk could be a source of anticipatory anxiety without significant benefit. However, if knowledge of increased risk can inform an individual to take preventative measures that might either prevent or delay the onset of AD, then testing for the ε4 allele presents a favorable risk-to-benefit ratio.

The prospect of delaying presentation of AD is very important. In elderly patients, the risk of developing AD rises significantly with each passing year. If preventative measures only delayed onset of AD, a significant percentage of elderly patients would die from other common causes of mortality like cardiovascular disease and cancer. The steepness of the increase in AD risk with age can be seen in the greater number of females affected by AD as compared with males, whose lifespans are 5.8 years shorter on average in the US.[11]

Although the suggestive data on prevention of AD are not as definitive as the data for blood pressure, cholesterol, and blood sugar control reducing the risk of vascular dementia, several factors are thought to be relevant. First, there is general agreement among AD researchers that exercise could be helpful. Activities that stress the skeleton, walking for example, release osteocalcin. This protein hormone improves memory.[12] After discovering osteocalcin, Nobel laureate Eric Kandel started walking to his office at Columbia University. Exercise also stimulates the secretion of the protein brain derived neurotrophic factor (BDNF), which plays an important role in memory and cognition.[13] While listening to lectures on osteocalcin and BDNF, I sent a text message to my primary care physician, saying that exercise was thought to be preventive for