Letters to the Editor

More Evidence Needed Regarding the Utility of Genetic Testing for Alzheimer Dementia

Original Article: Evaluation of Suspected Dementia

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See additional reader comments at: https://www.aafp.org/afp/2018/0315/p398.html

To the Editor: I would like to thank Drs. Falk, Cole, and Meredith for their review. Their article concludes with recommendations for genetic testing for family members of persons with Alzheimer dementia (AD). It is important to differentiate between early- and late-onset AD in assessing the predictive value of the apolipoprotein E4 allele.

Early-onset AD typically presents in an autosomal dominant pattern with symptoms starting between 30 and 60 years of age. It is better understood and better studied than late-onset AD. Mutations in three genes (amyloid precursor protein, presenilin 1, and presenilin 2) are responsible for 60% to 70% of early-onset AD cases. There are more than 30 mutations in the amyloid precursor protein gene that can cause early-onset AD.[1] The presenilin 1 gene is associated with earlier presentation of symptoms with more than 150 different mutations linked to early-onset AD.[2] Presenilin 2 is the least common of the three genes with less than 20 known mutations.[3] There is little conclusive evidence on how to use this information to prevent, treat, or predict the development of early-onset AD.

A variety of genetic factors contribute to late-onset AD. Although not the only genetic factor involved, the apolipoprotein E4 allele is the best studied since its role was recognized in 1993. It is the only allele loci that has been confirmed to increase susceptibility for late-onset AD, although apolipoprotein itself has three different alleles (E4, E3, and E2), all located on chromosome 19. Other genetic factors include mutations at other alleles, such as clusterin and complement receptor 1 on chromosomes 8 and 1, respectively,[4] which have not been as well studied.

Apolipoprotein E4 has been strongly associated with developing later-onset AD but is also affected by the patient's race and sex, environmental triggers, and vascular risk factors. Although it improves the specificity of diagnosing late-onset AD, it has limited value in predicting the development of late-onset AD. Because of its low positive predictive value, apolipoprotein E4 genotyping should not be routinely performed despite its wide availability.

Patients and family members of those diagnosed with AD, especially early-onset AD, will often ask about genetic testing. As primary care clinicians for patients navigating this evolving and complex field of genetic testing, we need more evidence to counsel our patients on the utility of formal genetic testing.

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In Reply: Thank you kindly for your commentary and additions to our article's brief discussion of genetic considerations regarding dementia. We agree that early-onset dementia (symptoms starting before 60 years of age) should prompt consideration for genetic testing because it often appears in an autosomal dominant pattern. Late-onset dementia is more difficult with regards to genetic counseling recommendations. We agree that more evidence is needed in these areas as we aim to guide our patients and their families through these often complex and heart-wrenching diagnoses.

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