

Cardiovascular genetic assessment and treatment in middle age to reduce the risk of heart disease and dementia in old age

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Abstract

Assessment and treatment of cardiovascular disease (CVD) risk factors as a preventable cause of cognitive decline, morbidity and mortality is an important clinical goal. The apolipoprotein E (Apo E) gene provides a genetic link between CVD and the development of Alzheimer's disease (AD). The E4 allele increases the risk of coronary heart disease by more than 40% and contributes to the development of late-onset AD in more than 50% of affected patients. Disease expression in the presence of this allele is triggered by interaction with modifiable risk factors such as smoking, alcohol intake and high-calorie diets. It also displays differential therapeutic responses with use of cholesterol-lowering statins and acetylcholinesterase inhibitors. Apo E genotyping as part of a comprehensive evaluation of multiple CVD risk factors, performed in conjunction with nutrition and cognitive assessments, provides the opportunity to optimise treatment to the needs of the individual.

Introduction

The rapidly aging population drives an increase in the incidence and prevalence of cardiovascular disease (CVD), which affects 1 in 3 men and 1 in 4 women in South Africa before the age of 60 years. As a consequence of the rising prevalence of CVD and increased longevity, an explosion of Alzheimer's disease (AD) is seen. It has been proposed that most patients with vascular dementia are actually AD patients with prominent vascular risk factors and associated strokes. The overlap between AD and cerebrovascular disease produces a disorder that might be amenable to therapeutic approaches based on either mechanism.

Studies performed in approximately 10 000 Californians followed for an average of 27 years have shown that the same risk factors that lead to the development of CVD in middle

age may significantly increase the risk of dementia in old age.^{1,2} Identification of high total cholesterol levels, hypertension, diabetes and smoking in mid-life (age 40-44) was associated with a 20-40% increased risk of dementia in later life. Obese individuals furthermore had a 74% increased risk of dementia, and overweight people a 35% greater risk compared with those of normal weight. Folate deficiency leading to homocysteine accumulation may also contribute significantly to rapid progression of AD.³ Treatment of certain CVD risk factors could reduce the risk of dementia by more than 50%.

Apolipoprotein E and Alzheimer's disease

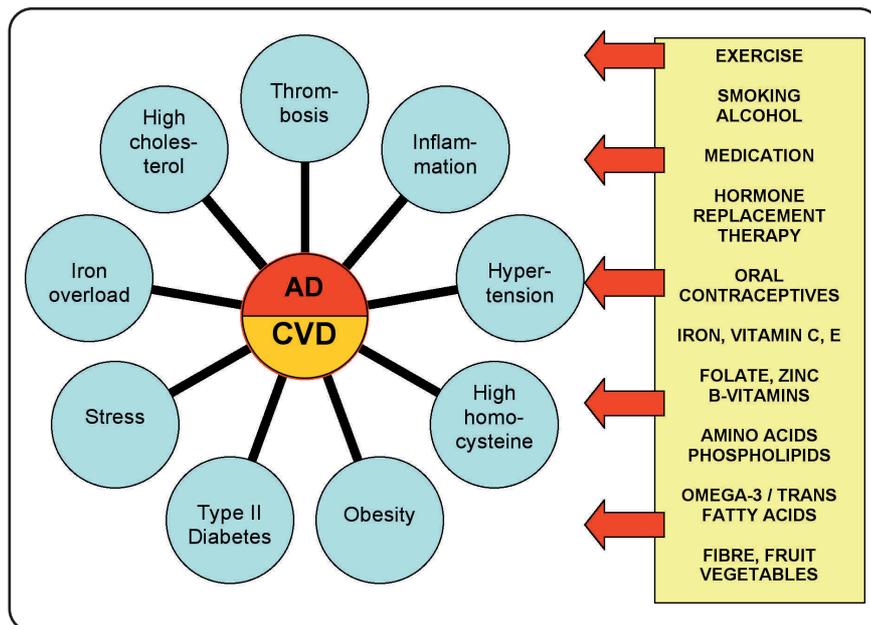
The common E4 allele (30-40% in different ethnic groups) of the apolipoprotein E (Apo E) polymorphism has a significant

cholesterol-raising effect, as also confirmed in the general South African population.⁴ The lifetime risk of developing AD is approximately 15% for persons with no family history and increases to nearly 30% in carriers with at least one E4 allele, compared with less than 10% for those without the E4 allele.⁵ Apo E4 is more susceptible to oxidation than the E2 and E3 isoforms and in mice it was shown that atherosclerosis is reversible by dietary vitamin E supplementation.⁶ It has been shown that the risk of dementia increases significantly with increasing alcohol consumption in individuals with the Apo E4 allele.

Genetic testing for optimised treatment

Magnetic resonance imaging studies have demonstrated increased hippocampal atrophy in the presence of the Apo E4 allele, which

Figure 1: Co-inheritance of multiple genetic risk factors in the presence of environmental triggers has a significant impact on the development of clinical conditions associated with the development of cardiovascular disease (CVD) and/or Alzheimer's disease (AD). Environmental factors that may be either harmful or beneficial (right column) in the context of their direct effect on genetic factors underlying the high-risk clinical conditions highlighted in the circles on the outside, can potentially be manipulated to prevent the conversion of genetic risk factors into disease.



emphasises the importance of early intervention before cognitive decline becomes apparent. Therapeutic responses may be genotype specific and this could contribute to the apparent inability of presently available drugs to alter the course of AD for some patients. Approximately 15% of AD cases with adverse response to treatment are associated with a defective CYP2D6 gene which can be assessed genetically.⁷

The key to disease prevention lies in a better understanding of gene-environment interactions underlying CVD and AD and effective intervention based on this knowledge (Figure 1). Genetic testing enables the dissection of complex conditions into treatable subtypes; for example to distinguish between hypercholesterolaemics with familial hypercholesterolaemia (FH) requiring long-term drug treatment and those with the Apo E4 allele who respond well to specific dietary and

lifestyle changes without the use of medication.⁸

Conclusions

Genetic testing has the potential to translate into improved health outcomes in patients with cognitive impairment and their at-risk family members. Since the deleterious effects of the Apo E4 allele is mediated through diet and oxidation processes, its detection highlights the importance of smoking cessation and a healthy diet with regular intake of foods that offer neuroprotection. Contrary to previous belief, identification of modifiable genetic risk factors for AD does not result in increased worrying and depression⁹ because lifestyle changes can delay the onset and severity of dementia.¹⁰ Genetic testing for multiple CVD risk factors (Figure 1, more information available on request) in conjunction with nutrition and cognitive assessment empowers patients to take the necessary steps to improve their health.

References

- Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* 2005; 64:277-81.
- Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP Jr, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *Br Med J* 2005;330:1360 (epub ahead of print).
- Ravaglia G, Forti P, Maioli F, Martelli M, Servadei L, Brunetti N, Porcellini E, Licastro F. Homocysteine and folate as risk factors for dementia and Alzheimer disease. *Am J Clin Nutr* 2005; 82:636-43.
- Kotze MJ, de Villiers WJS, Steyn K, Kriek JA, Marais AD, Langenhoven E, Herbert JS, Graadt van Roggen JF, van der Westhuyzen DR, Coetzee GA. Phenotypic variation among familial hypercholesterolemics heterozygous for either one of two Afrikaner founder LDL receptor mutations. *Arterioscler Thromb* 1993; 13: 1460-1468.
- Seshadri S, Drachman DA, Lippa CF. Apolipoprotein E E4 allele and the lifetime risk of Alzheimer's disease. What physicians know, and what they should know. *Arch Neurol* 1995; 52: 1074-1079.
- Pratico D, Tangirala RK, Rader DJ, Rokach J, FitzGerald GA. Vitamin E suppresses isoprostano generation in vivo and reduces atherosclerosis in Apo E-deficient mice. *Nat Med* 1998; 4: 1189-1192.
- Cacabelos R. The application of functional genomics to Alzheimer's disease. *Pharmacogenomics*. 2003; 4:597-621.
- Kotze MJ, Kriegshäuser G, Thiar R, de Villiers JNP, Scholtz CL, Kury F, Moritz A, Oberkanins C. Simultaneous detection of multiple familial hypercholesterolaemia mutations facilitates an improved diagnostic service in South African patients at high risk of cardiovascular disease. *Mol Diagn* 2003; 7: 169-74.
- Romero LJ, Garry PJ, Schuyler M, Bennahum DA, Qualls C, Ballinger L, Kelly V, Schmitt C, Skipper B, Ortiz IE, Rhyne RL. Emotional responses to APO E genotype disclosure for Alzheimer disease. *J Genet Couns* 2005;14:141-50.
- Potocnik FCV, Bouwens C, van Rensburg SJ. Neurological ageing factors: Neurobiology of ageing and prevention of dementia. *CME* 2005; 23: 307-309.