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POLYMORPHISMS IN GENES OF PROTEINS INVOLVED IN CHOLESTEROL METABOLISM: EVIDENCE FOR ALZHEIMER'S DISEASE?

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Cholesterol is suggested to be involved in the pathogenesis of Alzheimer's disease (AD). This commentary discusses the relevance of the polymorphisms in genes involved in cholesterol metabolism for the risk of AD, and explains why a greater number of and larger sample sizes are needed to provide solid evidence on whether such genes are involved in the pathogenesis of the disease.

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by an increased production of the amyloid precursor protein (APP) and of β-amyloid (Aβ) plaques. APP is expressed ubiquitously, cleavage of β- and γ-secretases results in the formation of Aβ. Patients with early-onset AD often present with mutations in the APP, PS1 or PS2 genes; that increase the production of Aβ (see: http://molgen-www.uia.ac.be/ADMutations/introduction.cfm). However, carriers of these mutations are rare (below 5% of all AD cases). Consequently, it is still unclear, why the majority of patients not carrying these mutations also present with an increased production of APP and Aβ.

A high cholesterol content of the membrane promotes the production of Aβ.[1] Recent research revealed a relevance of cholesterol metabolism in the pathogenesis of AD:

(1) increased midlife plasma cholesterol level might act as a risk factor for AD.[2,3]
(2) levels of the cholesterol oxidation product, 24S-hydroxycholesterol, are altered in AD.[4]
(3) modulation of cholesterol levels *in vitro* and *in vivo* affects the production of Aβ and thus may alter CSF levels of Aβ and the risk of AD.[1,5-9]
(4) brain cholesterol is synthesized locally, not imported into the brain.[10] Thus it appears unlikely, that circulatory cholesterol affects the risk for AD; however, different groups reported on the effect of high plasma cholesterol levels on AD brain pathology.[11-13]
(5) cholesterol affects synaptic plasticity,[14] neurotransmission[15] and cholesterol metabolites, such as 24S-hydroxycholesterol. Cholesterol may also cause neuronal cell death *in vitro*.[16] Thus, it might influence AD pathology by a mechanism different from Aβ metabolism.

Since cholesterol is a risk factor for AD, it might be suggested, that genes whose products are involved in cholesterol metabolism are good candidates for AD risk factors. In agreement, the ε4 allele of the apolipoprotein E (ApoE) gene, which is relevant for cholesterol transport,[17] is the strongest known risk factor for late-onset AD.[18] Again, presence of an ApoE ε4 allele only accounts for less than 50 % of all late onset AD cases,[18] suggesting the existence

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of additional risk factors. Other polymorphisms in genes related to cholesterol metabolism were investigated, such as in the lipoprotein receptor related protein associated protein (LRP), yielding conflicting results.[19,20]

Since the elimination of cholesterol from the brain into blood is critical for brain cholesterol metabolism,[21,22] and conversion of cholesterol in 24S-hydroxycholesterol is catalyzed by the cholesterol 24S-hydroxylase (CYP46), we screened this gene for polymorphisms. Two polymorphisms in the region of the exons 2 and 3 have been detected. The C-allele of a IVS3+43C→T polymorphism was associated with an increased risk for AD in a case control study and with an increased CSF ratio of 24S-hydroxycholesterol/cholesterol,[23] suggesting a reduced clearance of cholesterol from the brain. The other polymorphism (rs755814 or IVS2-150A→G) did not show an association with AD. These data are in line with Desai *et al.*,[24] but in contrast to Papassotiropoulos *et al.*, who reported on an increased risk and an increased Aβ load in the brain of AA genotype carriers.[25] Even though the data on CYP46 polymorphism and AD are not consistent, they still suggest a role of such polymorphisms in the pathogenesis of AD.

Wavrant-De Vrieze reported on additional polymorphisms in the genes encoding for HMG-CoA reductase, lipoprotein a (Lp(a)) and ABCA1 transporter. They found no association of HMG-CoA reductase polymorphism with AD, but polymorphism in ABCA1 was associated with AD in ApoE ε2 allele carriers.[26] Wollmer *et al.* also investigated polymorphisms in ABCA1 and found one polymorphism to influence the age at onset of AD, but not the risk of AD.[27] The Lp(a) polymorphism in the Kringle-IV region of the gene was also associated with AD in apoE ε2 allele carries.[28]

These data are encouraging and suggest a role in AD for genes whose products are involved in cholesterol metabolism. However, currently available data have to be discussed carefully, since the number of studies and probands is low. Results might be false positive due to α-errors, but on the other hand the sample sizes might also be too low to identify the likely interactions between different genes involved in cholesterol metabolism.

CONCLUSION

A greater number of and larger studies are needed to provide solid evidence whether polymorphisms in genes (other than ApoE) involved in cholesterol metabolism are associated with the pathogenesis of Alzheimer's disease.

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