No evidence of Alzheimer's disease-associated changes in adolescents carrying genetic risk factors

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Two studies published in the *Journal of Alzheimer's Disease* indicate that some of the pathologic changes associated with Alzheimer's disease in older individuals are not apparent in young people who carry the apolipoprotein (APOE) genetic risk factor for developing the disease. In the first study, no differences were found in hippocampal volume or asymmetry between cognitively normal adolescent carriers and non-carriers of the ApoE ε4 or ε2 allelles. The second study reports no differences in plasma concentrations of amyloid-β peptides among young adult ε4, ε3 or ε2 carriers.

Carriers of the apolipoprotein (ApoE) ε4 allele are at greater risk for developing late-onset Alzheimer's disease (AD), develop AD at an earlier age, and experience a more severe cognitive decline and shorter survival times. The ε4 allele has also been linked to the severity of hippocampal atrophy and pathological alterations in the neocortex. The ε2 allele is thought to exert protection against the disease.

"Atrophy of the hippocampus, a region of the brain crucial for memory, is a common feature of AD, although it may also be detected in asymptomatic individuals as well as healthy adult carriers of the ApoE ε4 allele," explained Andy Simmons, PhD, of the Department of Neuroimaging of the Institute of Psychiatry of King's College London. "Whether young people genetically at risk for AD manifest early changes is an important question for those interested in interventions or

treatments designed to slow or stop the progression of the disease."

To address the question, 1412 adolescents underwent MRI imaging and had blood samples tested for DNA analysis in order to determine their ApoE status. "Contrary to some recent studies, no hippocampal volume differences were observed between carriers and non-carriers of the ApoE ε4 allelle," said Dr. Simmons. The investigators also looked for other potential changes, such as hippocampal asymmetry or gene dose-dependent effects on volume, but could find no associations with genetic status.

In addition to structural changes in the brain, patients with AD typically show an increase in the brain load of amyloid-β (Aβ) peptides and a decrease in cerebrospinal fluid (CSF) concentration of Aβ peptides. Similar changes are found in almost all persons with mild cognitive impairment at risk of conversion to AD. "These changes represent the earliest diagnostic tools in AD," explains Professor Dr. med. Piotr Lewczuk, head of the Lab for Clinical Neurochemistry and Neurochemical Dementia Diagnostics, at the Department of Psychiatry and Psychotherapy, Universitätsklinikum Erlangen and Friedrich-Alexander-Universität Erlangen-Nürnberg. Since to some extent alterations of the concentrations of Aβ peptides are also observed in the blood, his research group explored differences in plasma levels of Aβ peptides among young adult ε4, ε3 or ε2 carriers.

To see whether these changes associated with AD are present at an early age, before clinical symptoms are apparent, investigators measured Aβ peptide concentrations in the plasma of 175 cognitively normal young adults. 40 individuals (22.9%) had at least one ε4 allele and were considered "at risk" for AD, 111 (63.4%) had the ε3/ε3 genotype and were considered "neutral," and 24 (13.7%) in the "protective: group had at least one ε2 allele.

The investigators measured four Aβ peptides and found that no significant differences in plasma levels of any of the Aβ peptides were found among the three genetic groups.

"The lack of differences of the Aβ concentrations reported in this study between the groups with and without increased genetic risk of AD does not mean that ongoing pre-clinical neurodegeneration can be fully excluded in all young subjects," says Dr. Lewczuk. He also notes that around 40% of AD patients are not carriers of the ε4 allele. However, he believes that both Dr. Simmons' findings concerning hippocampal volume and his study on plasma Aβ concentrations suggest that the AD-suggestive alterations begin perhaps 20-30 years before the onset of clinical symptoms, but most probably not earlier.

More information: "No Differences in Hippocampal Volume between Carriers and Non-Carriers of the ApoE ε4 and ε2 Alleles in Young Healthy Adolescents." Wasim Khan, Vincent Giampietro, Cedric Ginestet, Flavio Dell'Acqua, David Bouls, Steven Newhouse, Richard Dobson, Tobias Banaschewski, Gareth J. Barker, Arun L.W. Bokde, Christian Büchel , Patricia Conrod, Herta Flor, Vincent Frouin, Hugh Garavan, Penny Gowland, Anreas Heinz, Bernd Ittermann, Hervé Lemaîitre, Frauke Nees, Tomas Paus, Zdenka Pausova, Marcella Rietschel, Michael N. Smolka, Andreas Ströhleh, Jean Gallinat, Eric Westman, Gunther Schumann, Simon Lovestone, Andrew Simmons, and the IMAGEN consortium (www.imagen-europe.com). *Journal of Alzheimer's Disease*, Volume 40/Issue 1 (March 2014). DOI: 10.3233/JAD-131841.

"Plasma Concentrations of the Amyloid-β Peptides in Young Volunteers: The Influence of the APOE Genotype." Ruediger Zimmermann, Ellen Huber, Christine Schamber, Natalia Lelental, Barbara Mroczko, Sebastian Brandner, Juan Manuel Maler, Timo Oberstein, Maciej Szmitkowski, Manfred Rauh, Johannes Kornhuber

and Piotr Lewczuk. *Journal of Alzheimer's Disease*, published online ahead of issue, Volume 40/Issue 4 (May 2014). DOI: 10.3233/JAD-132687.