

CHOLESTEROL EFFLUX CAPACITY OF CEREBROSPINAL FLUID IS IMPAIRED IN ALZHEIMER'S DISEASE

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Introduction: Alterations of cholesterol homeostasis in the central nervous system (CNS) have been associated to various neurodegenerative disorders, including Alzheimer's disease (AD). CNS cholesterol trafficking is mediated by HDL-like particles identified in the cerebrospinal fluid (CSF) and mainly containing apolipoprotein E (apoE). apoE, initially produced by astrocytes, interacts with membrane cholesterol transporters such as ABCA1 and ABCG1 to convey cholesterol from astrocytes to neurons. This cholesterol supply is essential for neuronal plasticity maintenance, function and regeneration after injury. The objective of the present study was to establish whether the cholesterol transport mediated by brain HDL-like particles is defective in AD. In order to achieve this aim we measured the ability of CSF to promote cell cholesterol efflux specifically through the transporters ABCA1 and ABCG1 (CSF cholesterol efflux capacity, CSF-CEC).

Materials and methods: CSF from AD patients (n=37), from patients with dementia not related to AD (non-AD DEM, n=16) and control subjects (n=39) were collected by lumbar puncture. CSF apoE and apoE4 levels, as well as AD neurobiomarkers were measured by ELISA assay. CSF-CEC was assessed by cell-based radioisotopic techniques.

Results: AD patients showed the typical neuromarker profile with reduced CSF A β 1-42, increased total- and phospho-Tau and higher frequency of apoE4 genotype. ABCA1- and ABCG1-mediated CSF-CEC were markedly reduced in AD (-73% and -33%, respectively), but not in non-AD DEM, where a reduced passive diffusion CEC (-47%) was observed. Only non-AD DEM patients displayed lower CSF apoE concentrations (-24%) compared to controls. No differences in CSF-CEC were found by stratifying CSF-CEC for apoE4 status. ABCG1 CSF-CEC positively correlated with A β 1-42 ($r=0.305$, $p=0.025$), while ABCA1 CSF-CEC inversely correlated with total- and phospho-Tau ($r=-0.348$, $p=0.018$ and $r=-0.294$, $p=0.048$ respectively).

Conclusions: Our results indicate that, despite no change in CSF apoE concentrations, possibly reflecting no change in HDL concentration, an impairment of CSF capacity to promote cholesterol efflux specifically occurs in AD. These findings, together with the correlations found with the typical neurobiomarkers, reinforce the idea that alterations of brain cholesterol transport may play an important role in AD pathogenesis and may represent novel pharmacological target for the treatment of the disease.