Increased PCSK9 cerebrospinal fluid concentrations in Alzheimer's disease

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Background: Alzheimer's disease (AD) is a progressive and multifactorial neurodegenerative disease characterized by a progressive cognitive impairment. A large number of studies have shown a correlation between cholesterol homeostasis and AD and also some cholesterol-related genes are involved in AD. The trafficking of cholesterol in the CNS is mediated by HDL-like particles present in the cerebrospinal fluid (CSF) that have a crucial role in maintaining cholesterol trafficking between astrocytes and neurons. Adult neurons in facts progressively loose their cholesterol synthesis capacity and almost exclusively rely on cholesterol produced from astrocytes to maintain neuronal development and synaptic plasticity. Proprotein convertase subtilisin/kexin type 9 (PCSK9) promotes the degradation of the hepatic low density lipoprotein receptor (LDLr) and is a key regulator of LDL-cholesterol plasma level. However, PCSK9 is also present in the brain and is detectable in the CSF of healthy subjects. PCSK9 degrades the apoE neuronal receptors, which internalize the astrocytes-derived cholesterol. Thus, PCSK9 disturbances might in principle be involved in the alteration of brain cholesterol trafficking and lipoprotein homeostasis and in AD pathogenesis.

Objective: The objective of the present study was to measure PCSK9 levels in CSF of AD patients and to look at correlations with total apoE and apoE4.

Methods: CSF from non-AD (n=17) and sex and age-matched AD patients (n=21) was collected by lumbar puncture for routine diagnosis. CSF PCSK9, total apoE and apoE4 levels were measured by ELISA.

Results: AD patients showed the typical CSF neurobiomarker (amyloid β 1-42, Tau and phosphor-tau levels) pattern and impaired cognitive performances, as indicated by the score of the minimental state examination (MMSE) test. The analysis of CSF revealed that AD patients have higher levels of PCSK9 than non-AD subjects (+1.65 fold; p=0.0106). CSF total apoE concentrations were similar between the two groups, while apoE4 levels were higher in AD subjects (+ 2.61 fold; p=0.0453). Considering all samples, PCSK9 concentration correlated with CSF levels of the apoE4 isoform (r=0.4450; p=0.0065). Interestingly, CSF PCSK9 levels were higher in APOE ?4 carriers, reaching statistical significance in the AD group (+1.53 fold; p=0.05).

Conclusion: These results suggest, for the first time, an alteration of PCSK9 levels in CSF of AD patients and a link between PCSK9, apoE4 and AD.