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CEREBROSPINAL FLUID, HYPOSMIA AND DEMENTIA IN ALZHEIMER DISEASE: INSIGHTS FROM DYNAMIC PET AND A HYPOTHESIS

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I read with great interest Dr de Leon and colleagues' recent paper (*1*). Using dynamic PET techniques, they demonstrate elegantly that ventricular Cerebrospinal Fluid (CSF) clearance is significantly lower in patients with Alzheimer Disease (AD) and that this correlates inversely with amyloid deposition. Nasal CSF egress is described in vivo for the first time and shown to be greatly reduced in patients with AD (*1*). Despite some minor technical limitations of the study which they describe, it is hereby lauded as an excellent proof of concept that amyloid deposition impedes CSF circulation. Certain previous models linking impaired CSF turnover with the pathophysiology of AD may be thus corroborated (*2, 3*).

These findings are interesting and important for several reasons. Hyposmia is an extremely common symptom in AD, experienced by nearly 100% of patients (*4*). Rhinencephalon and olfactory bulb amyloid distribution has previously been implicated. Cells of the human olfactory apparatus are replenished and replaced by a population of endogenous neural stem cells, and this neuroregenerative system has been shown to be disrupted in AD (*5, 6*). Indeed, preventing this neuroregenerative impediment or enhancing neurogenesis is being investigated as a treatment strategy in AD (*5*). Neurogenesis in the brain is closely linked with the flow of CSF as new neurons migrate along CSF flow gradients (*7*). Amyloid plaques have been shown to disrupt the process of endogenous neurogenesis (*5*). It could be thus hypothesized that hyposmia in Alzheimer Disease could be secondary to disturbances in CSF flow secondary to amyloid deposition leading to impaired neurogenesis.

In addition to olfaction, endogenous neurogenesis in the hippocampus plays an important role in learning and memory (*8*). Taken together, I propose the hypothesis that amyloid deposition in Alzheimer Disease impedes ventricular CSF drainage which in turn impairs endogenous neuroregenerative mechanisms. Impaired neuroregeneration thence contributes to dementia, hyposmia and neuronal loss in Alzheimer Disease.

While the suggestion that neurodegeneration may include an element of neuroregenerative failure is not new (*9*), the symptom combination of dementia and hyposmia applies to virtually all neurodegenerative diseases albeit to different degrees (*4*). Using similar dynamic PET studies it would be interesting to evaluate if CSF circulation could contribute to their pathophysiology. Furthermore, while CSF diversion through ventriculoperitoneal shunting was not found to be efficacious in AD in a randomized study (*10*), it would be interesting to learn if similar CSF circulation problems exist in normal pressure hydrocephalus (which is amenable to CSF diversion procedures). Additionally, the role of paravascular glymphatic pathways in the clearance of CSF remains to be elaborated. Further studies are indicated and the authors are once again congratulated on an interesting paper.

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