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Decrease in Olfactory Cortex Volume and Alterations in Caspase Expression in the Olfactory Bulb in the Pathogenesis of Alzheimer's Disease

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Abstract : Introduction: Alzheimer disease (AD) is a chronic disorder that affects millions of individuals worldwide. Symptoms include memory dysfunction, and also alterations in attention, planning, language and overall cognitive function. Olfactory dysfunction is a common symptom of several neurological disorders including AD. Studying the mechanisms underlying the olfactory dysfunction may therefore lead to the discovery of potential biomarkers and/or treatments for neurodegenerative diseases. Objectives: To determine if olfactory dysfunction predicts future cognitive impairment in the aging population and to characterize the olfactory system in a murine model expressing a genetic factor of AD. Method: For the human study, quantitative olfactory tests (UPSIT and OMT) have been done on 93 subjects (aged 80 to 94 years) from the Quebec Longitudinal Study on Nutrition and Successful Aging (NuAge) cohort accepting to participate in the ORCA secondary study. The telephone Modified Mini Mental State examination (t-MMSE) was used to assess cognition levels, and an olfactory self-report was also collected. In a separate cohort, olfactory cortical volume was calculated using MRI results from healthy old adults (n=25) and patients with AD (n=18) using the AAL single-subject atlas and performed with the PNEURO tool (PMOD 3.7). For the murine study, we are using Western blotting, RT-PCR and immunohistochemistry. Result: Human Study: Based on the self-report, 81% of the participants claimed to not suffer from any problem with olfaction. However, based on the UPSIT, 94% of those subjects showed a poor olfactory performance and different forms of microsmia. Moreover, the results confirm that olfactory function declines with age. We also detected a significant decrease in olfactory cortical volume in AD individuals compared to controls. Murine study: Preliminary data demonstrate there is a significant decrease in expression levels of the proform of caspase-3 and the caspase substrate STK3, in the olfactory bulb of mice expressing human APOE4 compared with controls. In addition, there is a significant decrease in the expression level of the caspase-9 proform and caspase-8 active fragment. Analysis of the mature neuron marker, NeuN, shows decreased expression levels of both isoforms. The data also suggest that Iba-1 immunostaining is increased in the olfactory bulb of APOE4 mice compared to wild type mice. Conclusions: The activation of caspase-3 may be the cause of the decreased levels of STK3 through caspase cleavage and may play role in the inflammation observed. In the clinical study, our results suggest that seniors are unaware of their olfactory function status and therefore it is not sufficient to measure olfaction using the self-report in the elderly. Studying olfactory function and cognitive performance in the aging population will help to discover biomarkers in the early stage of the AD.

Keywords : Alzheimer's disease, APOE4, cognition, caspase, brain atrophy, neurodegenerative, olfactory dysfunction
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