Apoptosis-associated speck-like protein containing a CARD (ASC) as a potential biomarker of dementia in cerebrospinal fluid

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Dementia impacts about fifty-five million individuals world-wide, and this number is expected to double every twenty years according to the World Health Organization. Though amyloid beta plaques and neurofibrillary tangles comprised of the hyperphosphorylated microtubule-associated protein tau are established hallmarks of dementia, inflammation is critical to its pathology. In a pathological state, microglia, which are the innate immune cells of the brain, assemble a multiprotein complex called the inflammasome. The inflammasome is composed of the NACHT, LRR, and PYD domain-containing protein 3 (NLRP3); the adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC); and inflammatory caspase 1 (cysteine-dependent aspartate-directed protease 1). The ASC and pro-caspase 1 components of the complex lead to the activation of caspase-1, which can facilitate the cleavage of IL-1β and IL-18. Upon labeling for ASC, the inflammasome complex appears as a speck. This visualized "ASC-speck" is approximately 1 μm in diameter, secreted into the extracellular space, and is capable of cross-seeding in a prionoid-manner. Our recent study in a small patient population (PMID: 34551296) detected ASC-specks in the cerebrospinal fluid (CSF) of patients with tauopathies. However, it is unclear if ASC-specks could serve as a potential biomarker in a larger patient cohort. To determine if ASC is a feasible biomarker of disease, flow cytometry was utilized to quantify ASC specks in CSF. Here, we report for the first time to our knowledge that levels of ASC specks are significantly increased (p= 0.0033) in the CSF samples of dementia patients (n=18;1.9x104 specks/μL ± 1918) in a group primarily comprised of AD patients compared to community member controls (n=11; 1x104 specks/μL ± 1756). Preliminary investigations suggest that the amount of ASC in the CSF correlates with phosphorylated threonine 181 tau (pT181+ tau). Together, these studies suggest that ASC-speck levels could serve as a valid inflammatory biomarker for dementia diagnosis and supplement pT181+ tau levels in the CSF.