Cerebrospinal Fluid Research

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Volume transmission of CSF: complications in aging and Alzheimer's disease

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In advanced aging and Alzheimer's disease (AD), there are many degenerative changes in the choroid plexus-CSF system which have adverse effects on CNS nutrient delivery, pharmacokinetics of drug disposition, and the removal of organic anions and proteins from ventricular CSF. The choroid plexus is a key locus for the failure in CSF dynamics, because fluid output from the epithelial cells is compromised following biochemical (oxidations of cellular membrane components and extracellular deposition of Ig complexes) and histological damage. Heat shock protein expression in the choroid plexus is also altered in AD, with HSP 90 showing the greatest elevation of several stress proteins analyzed. The reduced CSF formation, coupled with the ventriculomegaly, results in lower fluid turnover in the normal pressure hydrocephalus (NPH). As CSF turnover decreases, and the transport interfaces become less efficient, there is accumulation of proteins (such as amyloid beta) and deleterious catabolites in the brain interstitium. The compromised volume transmission (or bulk flow) of the CSF through the ventricular system also leads to a diminished supply of micronutrients and growth factors to the brain. In advanced stages of AD, the blood-brain barrier as well as the blood-CSF barrier are more permeable, and so CSF homeostasis can be disrupted. As more attention is focused on investigating the bi-directional transport processes at the CNS barrier systems, and on the chemical composition and volume of the CSF in AD, and in dementia, it should be possible to get a clearer picture of the effects of extracellular (brain interstitial) fluid dynamics on the progressive deterioration of neuronal function. Our histochemical and immunocytochemical analyses of autopsied human brain and choroidal specimens also support the hypothesis that disruptions in the CNS barriers lead to exacerbation of AD pathology.

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