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Does NPH equal ischemia?

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Background

It has been postulated that NPH equals pressure- and distortion-induced ischemia. Such a postulate fails to take into consideration the high co-incidence of AD and cerebrovascular disease (CVD) with NPH; as well as the observation that ischemia persists despite resolution of the elevated CSFP and ventriculomegaly [1,2]. We offer an alternate postulate, that NPH is a multi-factorial disease and that defective metabolite clearance, e.g., amyloid-beta peptides (Aβ) and Tau protein, via the CSF and across the blood-brain barrier (BBB), play a significant role in the dementia and ischemia of NPH.

Materials and methods

Aged Sprague-Dawley rats (12 mos) had hydrocephalus induced by intracisternal kaolin injection [3]. Brains were harvested at two, six and 10 weeks post-induction, n = 4–6 for each experimental group. The brains were stained for Aβ, hyperphosphorylated Tau (hpTau), and the Aβ transporters LRP-1, Pgp and RAGE (receptor for advanced glycation end products) by immunohistochemistry (IHC). Three epitopes of hpTau were used: pT231, pS262 (intraneuronal) and AT100 (extraneuronal). Cerebral microvessel isolations (MVIs) were performed and the extracted RNA and protein were assayed for the Aβ transport proteins. Western blots and ELISA were used to assay Aβ and Tau accumulation. Aged matched non-operated rats serves as controls.

Results

On IHC, Aβ accumulated in cortex and hippocampus with increasing hydrocephalus, particularly around microvessels and in and around neurons. HpTau, pT231, was seen in neurons in a typical AD pattern: loss of dendritic hpTau and accumulation and margination of hpTau granules in the cell soma. Extracellular hpTau, AT100, was also seen to accumulate around blood vessels. The Aβ transport proteins were significantly altered in the MVIs compared to controls: LRP-1 and Pgp were down-regulated whereas RAGE was up-regulated.

Conclusion

These studies show that induction of hydrocephalus (increased resistance to CSF absorption and decreased CSF production and turnover) leads to defective CSF and BBB metabolite clearance, and to the accumulation of Aβ and hpTau, similar to what is seen in AD [4,5]. The localization of Aβ, a known vasoconstrictor, and hpTau to cerebral blood vessels suggests that these toxins may play a role in the persistent ischemia and CVD seen in NPH. Hydrocephalus in aged animals, therefore, causes severe metabolic dysfunction, due to a progressive inability to clear metabolites, and is likely a major cause of the pathology in NPH.

References

1. Golomb J, Wisoff J, Miller DC, Boksay I, Kluger A, Weiner H, Salton J, Graves W: **Alzheimer's disease comorbidity in normal pressure hydrocephalus: Prevalence and shunt response.** *J Neurol Neurosurg Psychiat* 2000, **68:**778-781.

2. Momjian S, Owler BK, Czosnyka Z, Czosnyka M, Pena A, Pickard JD: **Pattern of white matter regional cerebral blood flow and autoregulation in normal pressure hydrocephalus.** *Brain* 2004, **127:**965-972.
3. Klinge PM, Samii A, Muhlendyck A, Visnyei K, Meyer G-J, Walter GF, Silverberg GD, Brinker T: **Cerebral hypoperfusion and delayed hippocampal response after induction of adult kaolin hydrocephalus.** *Stroke* 2003, **34:**193-199.
4. Augustinack JC, Schneider A, Mandelkow E-M, Hyman BT: **Specific tau phosphorylation sites correlate with severity of neuronal cytopathology in Alzheimer's disease.** *Acta Neuropathol* 2002, **103:**26-35.
5. Donahue JE, Flaherty SL, Johanson CE, Duncan JA III, Silverberg GD, Miller MC, Tavares R, Yang W, Wu Q, Sabo E, Hovanesian V, Stopa EG: **RAGE, LRP-1, and amyloid-beta protein in Alzheimer's disease.** *Acta Neuropathol* 2006, **112:**405-415.