Cerebrospinal fluid hypersecretion

Hydrocephalus, despite its heterogeneous causes, is ultimately a disease of disordered CSF homeostasis that results in pathological expansion of the cerebral ventricles. Our current understanding of the hydrocephalus pathophysiology is inadequate but evolving. Over this past century, the majority of hydrocephalus cases have been explained by functional or anatomical obstructions to bulk cerebrospinal fluid flow. More recently, hydrodynamic models of hydrocephalus have emphasized the role of abnormal intracranial pulsations in disease pathogenesis.

Karimy et al. reviewed the molecular mechanisms of CSF secretion by the choroid plexus epithelium, the most efficient and actively secreting epithelium in the human body, and provide experimental and clinical evidence for the role of increased CSF production in hydrocephalus. Although the choroid plexus epithelium might have only an indirect influence on the pathogenesis of many types of pediatric hydrocephalus, the ability to modify CSF secretion with drugs newer than acetazolamide or furosemide would be an invaluable component of future therapies to alleviate permanent shunt dependence. Investigation into the human genetics of developmental hydrocephalus and choroid plexus hyperplasia, and the molecular physiology of the ion channels and transporters responsible for CSF secretion, might yield novel targets that could be exploited for pharmacotherapeutic intervention [1].

Posthemorrhagic hydrocephalus (PHH) often develops following hemorrhagic events such as intraventricular hemorrhage (IVH) and subarachnoid hemorrhage (SAH). Treatment is limited to surgical diversion of the cerebrospinal fluid (CSF) since no efficient pharmacological therapies are available. This limitation follows from our incomplete knowledge of the molecular mechanisms underlying the ventriculomegaly characteristic of PHH. Here, we aimed to elucidate the molecular coupling between a hemorrhagic event and the subsequent PHH development, and reveal the inflammatory profile of the PHH pathogenesis.

Methods: CSF obtained from patients with SAH was analyzed for inflammatory markers using the proximity extension assay (PEA) technique. We employed an in vivo rat model of IVH to determine ventricular size, brain water content, intracranial pressure, and CSF secretion rate, as well as for transcriptomic analysis. Ex vivo radio-isotope assays of choroid plexus transport were employed to determine the direct effect of choroidal exposure to blood and inflammatory markers, both with acutely isolated choroid plexus and after prolonged exposure obtained with viable choroid plexus kept in tissue culture conditions.

Results: The rat model of IVH demonstrated PHH and associated CSF hypersecretion. The Na+/K+-ATPase activity was enhanced in choroid plexus isolated from IVH rats, but not directly stimulated by blood components. Inflammatory markers that were elevated in SAH patient CSF acted on immune receptors upregulated in IVH rat choroid plexus and caused Na+/K+/2Cl- cotransporter 1 (NKCC1) hyperactivity in ex vivo experimental conditions.

Cerebrospinal fluid hypersecretion may contribute to PHH development, likely due to hyperactivity of choroid plexus transporters. The hemorrhage-induced inflammation detected in CSF and in the choroid plexus tissue may represent the underlying pathology. Therapeutic targeting of such pathways may be employed in future treatment strategies towards PHH patients [2].

1)

Karimy JK, Duran D, Hu JK, Gavankar C, Gaillard JR, Bayri Y, Rice H, DiLuna ML, Gerzanich V, Marc Simard J, Kahle KT. Cerebrospinal fluid hypersecretion in pediatric hydrocephalus. Neurosurg Focus. 2016 Nov;41(5):E10. doi: 10.3171/2016.8.FOCUS16278. PMID: 27798982.

2)

Lolansen SD, Rostgaard N, Barbuskaite D, Capion T, Olsen MH, Norager NH, Vilhardt F, Andreassen SN, Toft-Bertelsen TL, Ye F, Juhler M, Keep RF, MacAulay N. Posthemorrhagic hydrocephalus associates with elevated inflammation and CSF hypersecretion via activation of choroidal transporters. Fluids Barriers CNS. 2022 Aug 10;19(1):62. doi: 10.1186/s12987-022-00360-w. PMID: 35948938.