Idiopathic normal pressure hydrocephalus pathophysiology

The full clinical triad is not prevalent in all of the cases and the pathophysiology of iNPH remains unclear.

For many years, the pathophysiology of idiopathic intracranial hypertension (IIH) was interpreted as “secondary intracranial hypertension,” and IIH was considered to be caused by brain edema due to obstructive sleep apnea. Another theory proposed cerebrospinal fluid (CSF) absorption impairment due to excessive medication with vitamin A derivatives. Other reports pointed out the importance of obesity, which may cause an impairment of intracranial venous drainage due to elevated right atrial pressure [1].

Kamalian et al. conducted an in-depth proteomics of cerebrospinal fluid (CSF) in 28 shunt-responsive idiopathic normal pressure hydrocephalus patients, 38 Mild Cognitive Impairment (MCI) due to Alzheimer's disease, and 49 healthy controls. Utilizing the Olink Explore 3072 panel, they identified distinct proteomic profiles in iNPH that highlight significant downregulation of synaptic markers and cell-cell adhesion proteins. Alongside vimentin and inflammatory markers upregulation, these results suggest ependymal layer and transependymal flow dysfunction. Moreover, downregulation of multiple proteins associated with congenital hydrocephalus (e.g., L1CAM, PCDH9, ISLR2, ADAMTSL2, and B4GAT1) points to a possible shared molecular foundation between congenital hydrocephalus and iNPH. Through orthogonal partial least squares discriminant analysis (OPLS-DA), a panel comprising 13 proteins has been identified as potential diagnostic biomarkers of iNPH, pending external validation. These findings offer novel insights into the idiopathic normal pressure hydrocephalus pathophysiology, with implications for improved idiopathic normal pressure hydrocephalus diagnosis [2].

Disturbed cerebrospinal fluid (CSF) dynamics are part of the pathophysiology of normal pressure hydrocephalus (NPH).

A study investigated the contribution of established CSF dynamic parameters to mean pulse amplitude (AMP), a prognostic variable defined as mean amplitude of cardiac-related intracranial pressure pulsations during 10 min of lumbar infusion test, with the aim of clarifying the physiological interpretation of the variable. AMP(mean) and CSF dynamic parameters were determined from infusion tests performed on 18 patients with suspected NPH. Using a mathematical model of CSF dynamics, an expression for AMP(mean) was derived and the influence of the different parameters was assessed. There was high correlation between modelled and measured AMP(mean) ($r = 0.98$, $p < 0.01$). Outflow resistance and three parameters relating to compliance were identified from the model. Correlation analysis of patient data confirmed the effect of the parameters on AMP(mean) (Spearman's $\rho = 0.58$-0.88, $p < 0.05$). Simulated variations of ±1 standard deviation (SD) of the parameters resulted in AMP(mean) changes of 0.6-2.9 SD, with the elastance coefficient showing the strongest influence. Parameters relating to compliance showed the largest contribution to AMP(mean), which supports the importance of the compliance aspect of CSF dynamics for the understanding of the pathophysiology of NPH [3].

1)

Miyachi S, Hiramatsu R, Ohnishi H, Takahashi K, Kuroiwa T. Endovascular Treatment of Idiopathic Intracranial Hypertension with Stenting of the Transverse Sinus Stenosis. Neurointervention. 2018 Sep;13(2):138-143. doi: 10.5469/neuroint.2018.00990. Epub 2018 Oct 1. PubMed PMID: 30196687; PubMed Central PMCID: PMC6132029.

2)

Kamalian A, Shirzadeh Barough S, Ho SG, Albert M, Luciano MG, Yasar S, Moghekar A. Molecular signatures of normal pressure hydrocephalus: a large-scale proteomic analysis of cerebrospinal fluid. Fluids Barriers CNS. 2024 Aug 8;21(1):64. doi: 10.1186/s12987-024-00561-5. PMID: 39118132.

3)

Qvarlander S, Malm J, Eklund A. CSF dynamic analysis of a predictive pulsatility-based infusion test for normal pressure hydrocephalus. Med Biol Eng Comput. 2014 Jan;52(1):75-85. doi: 10.1007/s11517-013-1110-1. Epub 2013 Oct 23. PubMed PMID: 24151060.

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