Cerebrospinal fluid proteomics for hydrocephalus

- Neuroinflammation in an optimized model of lysophosphatidic acid (LPA)-induced post-hemorrhagic hydrocephalus
- Proteomic profiling in cerebrospinal fluid reveal biomarkers for shunt outcome in idiopathic normal-pressure hydrocephalus
- Applying machine learning to high-dimensional proteomics datasets for the identification of Alzheimer's disease biomarkers
- Unbiased CSF Proteomics in Patients With Idiopathic Normal Pressure Hydrocephalus to Identify Molecular Signatures and Candidate Biomarkers
- Neuroinflammatory pathways and potential therapeutic targets in neonatal post-hemorrhagic hydrocephalus
- Identification of CSPG4 as a Biomarker and Therapeutic Target for Infantile Post-Hemorrhagic Hydrocephalus via Multi-Omics Analysis
- Alzheimer's disease CSF biomarkers correlate with early pathology and alterations in neuronal and glial gene expression
- Molecular signatures of normal pressure hydrocephalus: a large-scale proteomic analysis of cerebrospinal fluid

Cerebrospinal fluid proteomics is a powerful technique used to study the protein composition of cerebrospinal fluid, offering valuable insights into the underlying mechanisms of various neurological disorders, including hydrocephalus.

Role of CSF Proteomics in Hydrocephalus Research

Biomarker Discovery:

CSF proteomics helps identify potential biomarkers that could aid in the diagnosis, prognosis, and monitoring of hydrocephalus. Changes in the protein composition of CSF can reflect underlying pathophysiological processes, such as neuroinflammation, neural damage, or altered CSF production and absorption.

Understanding Pathophysiology:

By analyzing the proteomic profile of CSF in hydrocephalus patients, researchers can gain insights into the molecular mechanisms driving the disease. This includes identifying proteins involved in CSF dynamics, ventricular enlargement, and brain tissue damage.

Kamalian et al. conducted an in-depth proteomic study 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 pathophysiology of iNPH, with implications for improved diagnosis [1)].

Therapeutic Targets:

Proteomics can help identify potential therapeutic targets by uncovering proteins or pathways that are dysregulated in hydrocephalus. This information could be used to develop new treatments aimed at restoring normal CSF flow or protecting brain tissue from damage.

Differentiating Hydrocephalus Types:

CSF proteomics can assist in distinguishing between different forms of hydrocephalus, such as congenital, normal-pressure, or secondary hydrocephalus. Each form may have a distinct proteomic signature, which could guide more personalized treatment approaches.

Predicting Shunt Response:

In patients undergoing shunt surgery to relieve hydrocephalus, CSF proteomics might predict the likelihood of a positive response to the treatment. Certain protein markers may correlate with better outcomes, helping to optimize patient selection for this invasive procedure.

Techniques and Challenges

Techniques: CSF proteomics typically involves mass spectrometry (MS) techniques, such as liquid chromatography-tandem mass spectrometry (LC-MS/MS), for the identification and quantification of proteins. Protein extraction and sample preparation are crucial steps, as CSF is a low-protein-content fluid, making sensitive detection methods essential.

Challenges: One of the primary challenges in CSF proteomics is the low protein concentration and the presence of abundant proteins like albumin and immunoglobulins, which can obscure less abundant proteins. Additionally, variability in CSF sampling and processing can affect the reproducibility of results.

Current Findings: Recent studies have identified several proteins in CSF that may be associated with hydrocephalus, including inflammatory markers, proteins related to extracellular matrix remodeling, and those involved in cellular stress responses. However, more research is needed to validate these findings and to understand how they can be translated into clinical practice.

In summary, CSF proteomics is a promising tool for advancing our understanding of hydrocephalus, with the potential to improve diagnosis, treatment, and patient outcomes. However, further research is necessary to overcome technical challenges and to fully harness the potential of this approach.

By applying an unbiased proteomic approach, Rostgaard et al. aimed to search for cerebrospinal fluid (CSF) protein biomarkers distinguishing between obstructive hydrocephalus and communicating hydrocephalus in order to improve appropriate surgical selection for endoscopic third ventriculostomy vs. shunt implants. The second study's purpose was to look for potential CSF biomarkers distinguishing between patients with adult chronic hydrocephalus benefitting from surgery (responders) vs. those who did not (non-responders).

Methods: Venthydrocephalusricular CSF samples were collected from 62 patients with communicating hydrocephalus and 28 patients with obstructive hydrocephalus. CSF was collected in relation to the patient's surgical treatment. As a control group, CSF was collected from ten patients with unruptured aneurysms undergoing preventive surgery (vascular clipping).

Results: Mass spectrometry-based proteomic analysis of the samples identified 1251 unique proteins. No proteins differed significantly between the communicating hydrocephalus group and the obstructive hydrocephalus group. Four proteins were found to be significantly less abundant in CSF from communicating hydrocephalus patients compared to control subjects. A PCA plot revealed similar proteomic CSF profiles of obstructive and communicating hydrocephalus and control samples. For obstructive hydrocephalus, ten proteins were found to predict responders from non-responders.

They show that the proteomic profile of ventricular CSF from patients with hydrocephalus differs slightly from control subjects. Furthermore, they find ten predictors of response to surgical outcome (endoscopic third ventriculostomy or ventriculoperitoneal shunt) in patients with obstructive hydrocephalus [2].

1)
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.
2)
Rostgaard N, Olsen MH, Lolansen SD, Nørager NH, Plomgaard P, MacAulay N, Juhler M. Ventricular CSF proteomic profiles and predictors of surgical treatment outcome in chronic hydrocephalus. Acta Neurochir (Wien). 2023 Oct 19. doi: 10.1007/s00701-023-05832-y. Epub ahead of print. PMID: 37857909.