Research Highlights

Highlights from the latest articles in biomarkers

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Study bridges the gap between advanced mass spectrometry and immuno-based multiplex assays

Evaluation of: Zhang J, Sokal I, Peskind ER *et al.*: CSF multianalyte profile distinguishes Alzheimer and Parkinson diseases. *Am. J. Clin. Pathol.* 129, 526–529 (2008).

A recent study validates the results from an explorative proteomics study using an immuno-based multiplex assay.

The field of general proteomics in neurodegenerative diseases is in great need of standardization and replication studies. A consensus is emerging that general proteomics findings should be replicated in independent populations, and, if possible, using independent techniques. A recent study published in the *American Journal of Clinical Pathology* has managed to take findings from two explorative proteomics studies one step further to establish a multiplex assay, using a technique based on flow cytometric separation of antibody-coated microspheres that are labeled with a specific mixture of two fluorescent dyes. After binding of a biotinylated reporter

antibody, quantification is made by binding of a third fluorochrome coupled to streptavidin. The technique allows for simultaneous measurement of several analytes in the same tube and may be possible to use in a clinical routine laboratory. The study included cerebrospinal fluid samples from 48 patients with probable Alzheimer's disease, 40 patients with probable Parkinson's disease and 95 control individuals. A panel of ten candidate biomarkers identified in earlier proteomic studies, in addition to the two well established Alzheimer biomarkers, tau and A β 42, differentiated the three groups with accuracies between 73 and 96%. This is a major step forward and paves the way for the introduction of candidate biomarkers identified by advanced mass spectrometric studies into the clinical routine. The next step would be to determine assay characteristics (e.g., intra- and inter-day coefficients of variation), as well as the intraindividual stability of the different markers and confounding factors.

Is cerebrospinal fluid antithrombin III a novel marker for CNS lymphomas?

Evaluation of: Roy S, Josephson SA, Fridlyand J *et al.*: Protein biomarker identification in the CSF of patients with CNS lymphoma. *J. Clin. Oncol.* 26, 96–105 (2008).

An explorative study identifies antithrombin III as a candidate cerebrospinal fluid (CSF) biomarker for CNS lymphomas but forgets the blood–brain barrier (BBB).

A well-known feature of CNS lymphomas is impaired BBB function [1]. A recent state-of-the-art proteomics study on CSF protein changes associated with CNS lymphomas report decreased levels

of several normal brain-derived proteins as well as increased levels of antithrombin III, which is concluded to be an accurate biomarker for CNS lymphomas. However, the study fails to take into account that antithrombin III is a plasma protein normally present at 300–400-times higher concentration in plasma than in CSF. Even a minor disturbance in the BBB function would result in elevated levels of antithrombin III in CSF. The original finding of elevated levels of antithrombin III in CSF from CNS lymphoma patients prompted the researchers to analyze tumor tissue for antithrombin III expression and also

to investigate the relationship between antithrombin III levels and CNS lymphoma progression. However, as long as routine neurochemical characterization of the CSF is missing it is impossible to interpret the results. What if the authors have identified antithrombin III as a sensitive marker for BBB function?

Reference

1. Ernerudh J, Olsson T, Berlin G, von Schenck H: Cerebrospinal fluid immunoglobulins and β 2-microglobulin in lymphoproliferative and other neoplastic diseases of the central nervous system. *Arch. Neurol.* 44, 915–920 (1987).