Mon, 23 h9.00 - Recent advances in standardisation

STANDARDIZATION OF CSF PROTEINS

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The Alzheimer's disease (AD) CSF biomarkers total tau (T-tau), phospho-tau (P-tau) and ß-amyloid (Aß42 and the Aß42/40 ratio) reflect central pathophysiological mechanisms. Increased secretion of T-tau to CSF reflects intensity of neurodegeneration, while P-tau reflects the phosphorylation state of tau protein, and is an AD-specific biomarker. Decreased CSF levels of Aß42 or Aß42/40 ratio (that also compensates for total brain amyloid production) show very high concordance with PET measures of cortical amyloid load. These CSF biomarkers have very high diagnostic performance to identify AD also early in the disease. Based on the solid clinical validation, these AD CSF biomarkers are central in the novel diagnostic criteria for the disease.

The IFCC-WG for CSF proteins is working on standardization, which is warranted due to the high between-lab and between-batch variability for current ELISA methods. The IFCC-WG for CSF proteins has developed mass spectrometry-based high-precision methods for CSF Aß42, which have been approved as Reference Measurement Procedures (RMP) by the JCTLM. These RMPs have been used for value assignment of Certified Reference Materials (CRMs) for CSF Aß42. The CRMs consist of aliquots of three large pools of CSF, with low, medium and high Aß42 levels, which will be available for distribution 2017 to harmonize assay readouts. Ongoing projects in the IFCC-WG include RMPs for CSF Aß40 (method fully validated and submitted to JCTLM) and CSF T-tau (method development ongoing with promising results), and value assignment of the CRM for CSF Aß40. Importantly, in parallel, Biotech companies have developed high-quality fully automated assays for CSF Aß42 (published in 2016), as well as T-tau, P-tau and Aß40. Data from the Alzheimer's Association quality control (QC) program show a dramatic improvement in performance, with between-lab CVs dropping from 15-20% for the ELISAs down to 3-4% for the fully automated Aß42 method. A large 2-site clinical study has been performed to align the clinical cut-offs for these assays with amyloid PET.

In summary, the extensive clinical validation, the standardization efforts, and the introduction of fully automated instruments will together serve as the basis for the large-scale introduction of CSF biomarkers in diagnostic routine. This will be of utmost importance for the patients given the promise of several disease-modifying drugs that now are in Phase III clinical trials.

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STANDARDIZATION OF PREGNANCY-ASSOCIATED PLASMA PROTEIN A

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Pregnancy-associated plasma protein A (PAPP-A) is commonly used for screening of Down syndrome pregnancies. PAPP-A is a large protein that is found in the circulation at least in two different forms, in complex with the proform of eosinophil major basic protein or in noncomplexed free form. For Down syndrome screening purposes PAPP-A is measured from blood in the first trimester of pregnancy and is combined with other determinants, such as nuchal translucency and circulating beta human chorionic gonadotropin, to estimate the risk of the fetus having Down syndrome. Many commercial assays are used to determine PAPP-A levels for Down syndrome screening. The Working Group on standardization of PAPP-A of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has previously worked on establishing an international reference material for PAPP-A based on recombinant protein or purified endogenous protein to enable standardization of PAPP-A measurements. Unfortunately, this approach was not successful, as commercial assays seemed to detect these preparations differently than the endogenous protein in pregnancy serum. The work of the Working Group has recently been reactivated with an aim to seek harmonization of the commercial assays with pregnancy serum based materials.