

SYMPOSIUM 9 - Biomarkers of the Brain: Past and Future

TRAUMATIC BRAIN INJURY BIOMARKERS: CURRENT AND FUTURE

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Traumatic Brain Injury (TBI) biomarkers are crucial for accurate diagnosis, prognosis, and treatment monitoring. This talk will cover the definition, importance, and criteria for effective TBI biomarkers, along with their role in clinical management. The categorization of TBI biomarkers by severity and source will be highlighted along with key examples of TBI biomarkers. Future directions in TBI biomarkers will also be discussed.

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PRACTICAL USE OF MTBI BLOOD BIOMARKERS: FEEDBACK, APPLICATIONS TO SPECIFIC POPULATIONS AND PERSPECTIVES

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Mild traumatic brain injuries (mTBI) account for 80-90% of all TBI, with acute repercussions (intracranial lesions in 5-10% of cases) and/or chronic ones (post-traumatic syndrome). Several cellular and molecular events occur during mTBI, but current practical options are in favour of the development of blood protein biomarkers. These biomarkers have been incorporated into clinical and radiological decision-making algorithms to reduce the time of patient' management and reduce the need for ionizing radiation exposure.

After years of research and development, three main biomarkers have emerged: two astrocytic (S100B and GFAP) and one neuronal (UCH-L1). The clinical performance of these biomarkers varies according to their specific characteristics, and users must be aware of these characteristics to optimize their use in the general population. There are specific populations where the use of these biomarkers must be adapted, such as patients on anticoagulants, athletes, and pediatric and geriatric patients. In addition, there is a need to validate complementary strategies to increase the specificity of these three blood biomarkers (taking neuroinflammation into account, for example) and extend their current diagnostic uses to prognostic purposes.

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TOWARDS A BIOLOGICAL DEFINITION OF PARKINSON'S DISEASE: CSF AND BLOOD BIOMARKERS

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Current diagnostic criteria for Parkinson's Disease (PD) rely on the clinical characterization of the disease. This approach allows for diagnosis only once the motor signs have become apparent, which makes it unable to detect the long pre-motor phase that characterizes the earliest stages of the disease. Early and accurate diagnosis can only be achieved using objective measures that identify key pathophysiological features of the disease, similar to the use of fluid biomarkers in Alzheimer's Disease (AD) to detect amyloidosis, tau phosphorylation, and neuronal damage.

Following the example set by AD, a biological definition of PD has emerged, with two innovative proposals published in 2024: the NSD-ISS and the SyNeurGe systems. These biological classification systems for PD, and more broadly for neuronal synucleinopathies, were made possible by advancements in fluid biomarkers of α -synucleinopathy. To date, CSF α -synuclein seed amplification assay is the most recognized biomarker for detecting α -synuclein pathology. However, synucleinopathy is not the only mechanism that characterizes PD. Both the NSD-ISS and SyNeurGe systems recognize this, emphasizing the necessity of identifying dopaminergic denervation. This mechanism, currently detectable only by nuclear medicine techniques, is set to be recognized by a specific fluid biomarker: DOPA decarboxylase (DDC), whose concentration in CSF shows promise in reflecting dopaminergic neuron loss specific to PD. Furthermore, the measurement of biomarkers for amyloidosis, tau phosphorylation, and axonal damage in both CSF and plasma can enable the in vivo detection of AD copathology in PD, serving as reliable indicators for a clinical course at higher risk for cognitive decline.

In conclusion, we are experiencing a profound transformation in the way PD is identified, as fluid biomarkers offer the promise of more accurate and earlier diagnoses. These biomarkers will also become essential tools for initiating therapies that can more effectively control the symptoms of the disease and, crucially, for testing the biological effects of new treatments aimed at modifying disease progression.

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USE OF FLUID BIOMARKERS FOR DEMENTIAS IN THE ERA OF UPCOMING TREATMENTS

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Plasma biomarkers for Alzheimer's disease (AD) are promising tools due to their high accuracy and application ease. They can fill an important need in the current era of application of disease modifying therapies and boost in therapy development.

In this latter context, development and validation of fluid biomarkers are getting more and more important. They are crucial as objective outcome measures of clinical trials, yet more biomarkers need to be developed: we observed in a systematic analysis that only one-third of the recently conducted clinical trials for Alzheimer's disease applied fluid biomarkers as outcomes.

I will discuss the road towards swift development of fluid biomarkers for diagnostic, prognostic, prediction of response to therapy, monitoring therapeutic responses and safety (e.g. to predict and monitor ARIA) fluid biomarkers, and show new data for all these purposes in drug development programs. Next, biomarkers are needed for multiple forms of dementia. Among the highlights is the biomarker development of CSF dopamine decarboxylase for dementia with Lewy bodies, or acetylated Tau in frontotemporal dementia, and proteins measured in extracellular vesicles. In this increasing wealth of measurement options, education and interpretation support tools are needed. All these efforts will ultimately lead to a rich armory to improve treatment and care of patients with dementia.