Dario Saracino

Neurofilaments as prognostic and stratification biomarkers in FTLD

Neurofilaments are cytoskeletal proteins highly expressed in axons, which are released in CSF and in blood following neuronal injury and axonal turnover. The levels of neurofilament light chain (NfL) and phosphorylated neurofilament heavy chain (pNfH) show an age-dependent increase under physiological conditions, and are significantly more elevated in several neurological diseases, notably in neurodegenerative disorders. In this talk, we will provide an overview about the contribution of NfL and pNfH dosage in FTD and ALS, and the current perspectives concerning their utilization in clinical practice and for research purposes. Briefly, neurofilaments are significantly elevated during the disease stage. In genetically determined FTLD, the causal gene has a major impact on NfL trajectories, with more sustained increases in GRN than in C9orf72 carriers. Their levels are associated with the severity of clinical phenotype, the overall disease intensity and the rate of cerebral atrophy. NfL and pNfH levels, and their change rates, can thus be employed as prognostic biomarkers for disease evolution. Additionally, neurofilament dosage can provide valuable information for the stratification of mutation carriers during the presymptomatic phase. Temporal dynamics differ between NfL and pNfH, the first showing noticeable increases up to 5 years before phenoconversion, the latter mostly increasing at the moment of the clinical onset. Globally, neurofilament dosage may significantly contribute to define of the boundaries of the prodromal stage, and can result in effective outcome measures usable in therapeutic trials. Current challenges for an optimal use of neurofilament dosage include the standardization of neurofilament measurement across centers, and the definition of consensus thresholds for the interpretation of values, in particular with respect to phenoconversion.