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Editorial

Expanding the ATN Framework to Further Personalize Therapies

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Aging-related dementias are resultant from multiple pathophysiological processes, Alzheimer's disease (AD) and cerebrovascular disease being the dominant ones. Clifford Jack and colleagues advanced the field by proposing the ATN-based research definition of AD to describe the three pathological features of AD in populations and individuals (1). In principle, this framework is open to the incorporation of additional pathological processes such as those for cerebrovascular disease and other protein aggregates such as 3 repeat tau pathology, 4 repeat tau pathology, TAR DNA-binding protein 43 (TPD-43), alpha-synuclein and others. As developments in AD biomarkers are rapidly scaling towards assessing non-ATN brain abnormalities, one should start examining the readiness of biomarkers to expand the present ATN system.

The ATN research definition of AD has provided a useful framework for randomized clinical trials (RCT) at different biological and clinical stages of AD, as demonstrated by encouraging results using aducanumab (2) and lecanemab (3) in ATN-characterized participants in 'early AD', and there are ongoing RCT in asymptomatic A (+) persons (4). On the other hand, the clinical efficacy of monotherapy using anti-amyloid monoclonal antibodies may have reached a ceiling, at least in early symptomatic AD, and combinations in sequence or in addition are being initiated, such as lecanemab and drugs acting on tau pathology in early onset familial AD (5).

Post-mortem studies indicate in aging brain multiple pathologies potentially associated with dementia (6). Beyond amyloid and tau, other avenues of treatment are openly discussed, including vascular and neuroinflammatory factors (7). The invited reviews in this series examine the à-propos of adding V and I to the ATN definition. Despite the rapid progress in the field, it remains premature at this time. On a more positive note, the review about tau spreading demonstrated using PET and second-generation tau ligands expand the original definition of T beyond a (+) or (-) dichotomous score.

We offer evidence that the original ATN factors can be fine-tuned to fully understand the pathophysiology of AD and the biological response to therapy.

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