EDITORIAL

Cause of Suspected Non-Alzheimer Disease Pathophysiology
If Not Tau Pathology, Then What?

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Suspected non-Alzheimer pathophysiology (SNAP) is a biomarker-based concept suggested as a complement to the new National Institute on Aging–Alzheimer Association (NIA-AA) research criteria of preclinical Alzheimer disease (AD).[1] The NIA-AA classifies individuals with preclinical AD into 1 of the following 3 stages: biomarker evidence of β-amyloid (Aβ) but no brain injury (stage 1), biomarker evidence of Aβ and brain injury (stage 2), and biomarker evidence of Aβ and brain injury, with subtle cognitive changes (stage 3). The term *SNAP* was introduced to capture cognitively normal individuals with evidence of AD-like brain injury in the absence of amyloidosis. As the name suggests, this group was initially hypothesized to have a non-AD pathophysiological process such as vascular disease or other types of neurodegenerative diseases.[1]

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SNAP and preclinical AD concepts rely on the presence or absence of Aβ, as evidenced by high positron emission tomography (PET) radiotracer binding and/or low cerebral spinal fluid Aβ levels, as well as the presence or absence of brain injury (called *neurodegeneration* in most publications). The latter is typically defined by high cerebrospinal fluid tau levels, magnetic resonance imaging atrophy in AD-vulnerable regions, and/or PET hypometabolism in AD-vulnerable regions.[1] The proportion of SNAP among cognitively normal older individuals is remarkably consistent across cohorts (approximately 25%) and is independent of the biomarkers being used to define this group.[2] Also, studies have consistently reported that apolipoprotein E (*APOE*) ε4 carriers are less common in SNAP than in preclinical AD. Individuals with SNAP also tend to be older, and men are often overrepresented in comparison with preclinical AD.[2]

The underlying causes of SNAP are not well understood. In this issue of *JAMA Neurology*, Mormino et al[3] used a new PET ligand (fluorine 18–labeled AV1451, previously named T807) to examine whether tau pathology is a major contributor of SNAP. This study was motivated by autopsy studies showing that neurofibrillary tangles are often observed in the medial temporal lobes of older adults, even in the absence of amyloidosis.[4] The presence of tau pathology in the absence of Aβ has been referred to as *primary age-related tauopathy* (PART). Similar to SNAP, PART is typically associated with reduced frequency of *APOE* ε4 carriers and medial temporal lobe atrophy. These parallels between SNAP and PART suggest that Aβ-independent tau pathology may be an underlying cause of the SNAP biomarker-based concept.[5]

Assessing whether tau pathology is a main contributing factor of SNAP is of interest because PART has been proposed, not without controversy,[5] to be part of the AD pathologic spectrum.[6] Although Aβ is a prerequisite in the NIA-AA research criteria for entering the preclinical AD stages, one might argue that AD is a multidetermined disease and that individuals can enter the AD preclinical stages via pathways that are independent of Aβ.[7,8] This perspective is consistent with the observation that tau pathology can develop before, and independently of, Aβ pathology.[4] This idea does not exclude the possibility that Aβ can potentiate tau toxicity and propagation; it suggests that Aβ might not be the only upstream driver of the AD cascade leading to AD-related neurodegeneration. Indeed, although tau deposition is necessary but not sufficient for clinical expression of AD, the same principal probably applies to Aβ, because not all individuals with Aβ deposition may develop the clinical symptoms related to AD dementia. Furthermore, the interaction between Aβ and tau—and neither one alone—may to be required for the clinical expression of AD.

To investigate whether tau pathology (PART or other sorts of tauopathy) is a major candidate of SNAP, Mormino et al[3] evaluated 247 individuals from the Harvard Aging Brain Study, of whom 80 underwent tau-PET scanning using the AV1451 tracer. They assessed Aβ status using Pittsburgh Compound B (PiB) PET, and neurodegeneration was defined using regional cerebral glucose metabolism in AD-vulnerable regions and/or hippocampal volumes adjusted for intracranial volume. In accordance with other studies, they found that 25.9% of cognitively normal older adults were classified as having SNAP. Among the other groups studied, 26.7% were classified as having preclinical AD stages 1 and 2, while 47.4% had no abnormal biomarkers.

The main finding of this new study is that tau-PET uptake in the medial and inferior temporal lobes was indistinguishable between individuals with SNAP and those with no abnormal biomarkers (stage 0). Furthermore, the SNAP group showed lower tau-PET uptake than individuals with Aβ plus brain injury (stage 2). This finding is extremely important because it does not support the hypothesis that Aβ-independent tau pathology accounts for most SNAP cases. Given the inherent limitations of tau imaging, neuropathologic studies comparing individuals with SNAP with those without abnormal biomarkers and those with preclinical AD will be needed to definitively refute the hypothesis that SNAP does not reflect Aβ-independent tau pathology. For example, levels of some tau species that are not detectable with AV1451 radiotracer may be

elevated in SNAP. Also, low levels of tau may be difficult to detect using tau tracers.

Another proposed hypothesis is that some individuals with SNAP have significant brain Aβ deposition,[2] but at levels that do not reach conventional thresholds for Aβ positivity. Indeed, although SNAP and preclinical NIA-AA AD stages are based on numeric cutoffs, no uniform agreement exists regarding the optimal Aβ cutoff.[9] To address this issue, Mormino et al[3] explored whether individuals with SNAP had increased subthreshold Aβ levels, which were defined as higher values within the Aβ-negative group. They found that compared with individuals with stage 0, those with SNAP were not more likely to have significant subthreshold Aβ values.

Other proposed explanations for SNAP include vascular pathology, α-synucleinopathy, argyrophilic grain disease, 43-kDa transactive response DNA-binding proteinopathy, and hippocampal sclerosis.[2] Shortly after the term *SNAP* was introduced, clinical and imaging features of cerebrovascular disease and Lewy body disease were described in 430 clinically normal individuals from the Mayo Clinic.[10] Cardiovascular risk factors, cerebrovascular disease, and clinical features associated with α-synucleinopathy were found to be increased in cases with SNAP when compared with individuals without abnormal biomarkers, but not when compared with those categorized as having preclinical AD. A study from the Berkeley Aging Cohort[11] further reported an association in cognitively normal older adults between white matter hyperintensities, a proxy of cerebrovascular disease, and brain injury in AD-vulnerable regions. These results suggest that cerebrovascular disease and α-synucleinopathy may play a role in the expression of SNAP. Given the fact that individuals with SNAP and preclinical AD seem to be indistinguishable with regard to these pathologies, cerebrovascular disease and α-synucleinopathy probably do not account for all SNAP cases.

Together, these results imply that, in cognitively normal individuals, SNAP represents a biomarker-based concept of which the underlying causes are not yet understood. As mentioned by Mormino et al,[3] SNAP probably represents a heterogeneous group, which may explain in part our difficulties understanding its nature. Another explanation, which is not mutually exclusive, is that SNAP is not solely related to neurodegenerative pathologies. The NIA-AA biomarkers used to assess neurodegeneration are based on only 1 time point, which does not allow assessing the rate of progression over time. The few studies[12] that have assessed brain changes in individuals with SNAP over time suggest that, even if the brain biomarker(s) use to define neurodegeneration start out as abnormal in those with SNAP, they do not worsen over time. Longitudinal studies also suggest a reduced rate of cognitive decline in SNAP individuals compared with those with Aβ and brain injury.[2,12] In the study by Mormino et al,[3] only individuals with Aβ and brain injury showed rapid cognitive decline. The SNAP group showed a diminished practice effect when compared with the stage 0 group, an observation partly driven by 2 individuals with subthreshold Aβ values presenting a deep cognitive decline.

Given that the cognitive and brain profile of most SNAP individuals are stable over time, some authors have suggested that neurodegeneration should not be a defining feature of SNAP, particularly because the assessment of neurodegeneration is based on cross-sectional data. This perspective opens the SNAP construct to other possible causes, including faster biological aging, and/or developmental differences. The passage of time, in the absence of detectable neurologic disease, is implicated in some degree of brain atrophy and cognitive decline.[13] In opposition to most neurodegenerative disease, age-related atrophy and cognitive decline progress slowly. Age-related changes do not occur at the same rate in all individuals, possibly owing to differences in biochemical, genetic, or environmental factors. The use of arbitrary cutoffs for brain injury (or neurodegeneration) opens the possibility that part of what we capture as SNAP represents a tail of the normal aging distribution. Although the concept of aging itself needs to be better understood, increasing evidence suggests that AD-vulnerable regions are targeted by late-life neurodegenerative diseases (including non-AD pathologies) and normal aging.[14,15]

The study by Mormino et al[3] strongly suggests that SNAP is a heterogeneous condition that may not be attributable solely to tau pathology. To understand the nature of this heterogeneity, a better comprehension of the biomarkers used to characterize SNAP will be important, with an awareness of the limitations of bimodal markers, especially those with cutoffs that do not have a biological basis.

ARTICLE INFORMATION

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