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# Is SNAP a Preclinical State of Alzheimer's Disease?

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## Keywords

Preclinical Alzheimer's Disease; SNAP (Suspected Non-Alzheimer Pathophysiology); PART (Primary Age-Related Tauopathy); Biomarkers; National Institute on Aging–Alzheimer's Association (NIA-AA) Criteria

The National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for preclinical Alzheimer's disease (AD) proposed ordered stages for cognitively normal individuals without amyloid markers and/or markers for neurodegeneration (A-N-) as stage 0; those with amyloid but negative neurodegenerative markers (A+N-) as stage 1, those with both amyloid and neuronal injury markers (A+N+) as stage 2, and subtle cognitive changes as stage 3 [1].

Besides these stages, the nosological entity of suspected non-Alzheimer pathophysiology (SNAP) was described, characterized by abnormal total (t) tau or phosphorylated (p) tau in the presence of normal Aβ-42 (Table 1, Fig. 1). SNAP is a biomarker-based concept for individuals with normal levels of brain amyloid (Aβ) but abnormal biomarkers of neurodegeneration. It was applied to clinically normal individuals and those with mild cognitive impairment (MCI), but it is also applicable to any Aβ-negative and neurodegeneration-positive individual regardless of the clinical status. SNAP is present in about 23% of clinically normal subjects aged≥ 65 years and about 25% of MCI individuals [3]. APOE ε4 is underrepresented in SNAP subjects, and high APOE ε2 carrier prevalence may account for the differences in neurodegeneration patterns between A-N+ and A+N+ cases independent from the neuroimaging biomarker modality used to define neurodegeneration associated with AD [4]. Combined PET, MRI and CSF studies support the general framework of the NIA-AA staging, and most individuals classified as SNAP showed no elevated AD-related pathologies. Longitudinal follow-up of 174 cognitively normal subjects showed that SNAP (A-D+) subjects did not demonstrate differences in rates of Aβ accumulation or loss of hippocampal volume compared with stage 0 participants, while subjects with stage 1 and 2 had accelerated Aβ accumulation and hippocampal volume loss compared with SNAP individuals [5]. Increasing Aβ deposition over time occurred in a SNAP cohort, and some of these individuals later became Aβ-positive. The rate of accumulation and the frequency of biomarker conversion in SNAP individuals were similar to those without any pathology at baseline. This suggested that non-AD pathology is likely. It may represent comorbid pathology rather than emerging AD [5]. Individuals with SNAP have been shown to have worse clinical/cognitive outcomes over time compared with stage 0 [6]. The high progression rate (around 20%) for SNAP subjects is intriguing, as the biomarker profile suggests that non-AD pathology is likely. SNAP subjects who progressed to AD-type dementia had CSF Aβ-42 levels just above the cut-off. Alternatively, these subjects could have co-morbidities so that less amyloid is necessary to process to AD-type dementia. SNAP could also be an atypical form of AD with less pronounced Aβ pathology [7]. In a study of 212 cognitively normal volunteers (age range 45-88 years), at baseline 21% had preclinical AD based on CSF and 28% based on neuroimaging markers. Between modalities, staging was concordant in only 47%, indicating disparity between biomarkers which may lead to different NIA-AA staging classifications [8]. These data and those of another cohort of clinically suspected amyloid-negative AD patients showing heterogenous clinical presentations at follow-up, highlighted the need for a clinical terminology to define these patients who may have underlying limbic-predominant, non-amyloid related pathologies [9].

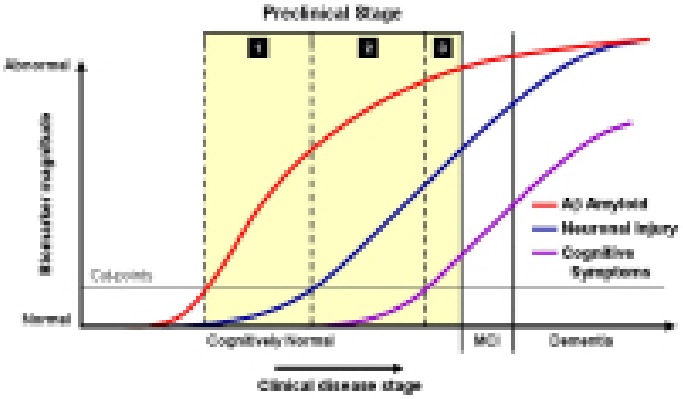


**Figure 1:** Alzheimer's disease preclinical stages 1 to 3 (from [2]).

**Table 1:** Classification of prodromal AD according to NIA-AA criteria (2011).

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|---|
| • A–N– : NIA-AA preclinical stage 0 |
| • A+N– : NIA-AA preclinical stage 1 |
| • A+N+ : NIA-AA preclinical stages 2 and 3 |
| • A–N+ : SNAP |

A-amyloidosis; N-neurodegeneration; NIA-AA-National Institute on Ageing-Alzheimer disease Association; SNAP-suspected non-Alzheimer disease pathophysiology.

A new classification for biomarkers in AD and cognitive aging research is based on grouping them into three categories (ATN groups): amyloid deposition (A), tauopathy (T) and neurodegeneration or neuronal injury (N). Assessment of these biomarkers in a large cohort of elderly subjects was used in order to better characterize the heterogeneous pathological profiles in the elderly population. Both amyloid-dependent and -non-dependent pathological profiles can be identified in cognitively unimpaired people, while the prevalence of each ATN group changes substantially with age, with progression towards more biomarker abnormalities among individuals who remained cognitively unimpaired [10].

The etiology of SNAP as a marker of early AD is unclear. A recent autopsy study of 11 people who had been diagnosed with SNAP showed that none of them fulfilled the NIA-AA pathological criteria for AD. Seven of them had moderate to severe arteriosclerosis and white-matter lesions, while one had

hippocampal sclerosis, four argyrophilic grain disease (AGD), and six fulfilled criteria for PART (primary age-related tauopathy) [11], that is considered a distinct tauopathy different from classical sporadic AD [12], in which tau aggregation influences cognition in the absence of Aβ [13].

These data suggest that SNAP may be a heterogenous condition which may overlap with PART considered an Aβ-independent subgroup of AD or it may be related to severe hippocampal atrophy [6]. From the perspective that SNAP is not definite AD, however, it is consistent with the concept of preclinical AD, although there is a debate as whether PART is an early stage or variant of AD. According to a recent autopsy study, PART differs considerably from typical AD by relatively low frequency of APOE ε4, TD-43, Lewy bodies, and hippocampal sclerosis [13].

## Conclusion

SNAP is a biomarker-based concept denoting AD-like degeneration in clinically normal elderly people or those with MCI without brain Aβ-deposition (A-) but positive neurodegeneration markers (N+). It does not fall into the NIA-AA stages of preclinical AD, but may have tau PET in temporal lobes/hippocampus. Both SNAP and PART (Braak stage ≤ 4 and Thal Aβ phase ≤ 2 or 0 ) have low prevalence of APOE ε4 and greater conversion rate to dementia than A-N- (stage 0) cases. Autopsy studies revealed low level AD pathology (neuritic plaque score 0), AGD, PART or white matter lesions, indicating comorbid features rather than early AD. SNAP may be a heterogenous condition, which may overlap with Aβ-independent PART or may be related to hippocampal atrophy. There is a debate as to whether PART is an early stage or a variant of AD, but recent studies suggest that it differs from typical AD. Further studies should subclassify SNAP and the concordance of its markers, and determine the biological correlates of neurodegeneration markers among SNAP and their relations to PART and atypical AD.

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