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Review

Suspected non Alzheimer's pathology – Is it non-Alzheimer's or non-amyloid?

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ABSTRACT

Neurodegeneration, the progressive loss of neurons, is a major process involved in dementia and age-related cognitive impairment. It can be detected clinically using currently available biomarker tests. Suspected Non Alzheimer Pathology (SNAP) is a biomarker-based concept that encompasses a group of individuals with neurodegeneration, but no evidence of amyloid deposition (thereby distinguishing it from Alzheimer's disease (AD)). These individuals may often have a clinical diagnosis of AD, but their clinical features, genetic susceptibility and progression can differ significantly, carrying crucial implications for precise diagnostics, clinical management, and efficacy of clinical drug trials.

SNAP has caused wide interest in the dementia research community, because it is still unclear whether it represents distinct pathology separate from AD, or whether in some individuals, it could represent the earliest stage of AD. This debate has raised pertinent questions about the pathways to AD, the need for biomarkers, and the sensitivity of current biomarker tests.

In this review, we discuss the biomarker and imaging trials that first recognised SNAP. We describe the pathological correlates of SNAP and comment on the different causes of neurodegeneration. Finally, we discuss the debate around the concept of SNAP, and further unanswered questions that are emerging.

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1. Introduction

Alzheimer's Disease (AD) is the commonest cause of dementia and cognitive impairment worldwide and leads to significant disability and death. While the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders) 1984 criteria are based on clinical factors, the National Institute of Ageing-Alzheimer Association (NIA-AA) diagnostic guidelines from 2011 incorporate the use of biomarkers into the diagnosis of Mild Cognitive Impairment (MCI), AD and preclinical disease (Albert et al., 2011; McKhann et al., 2011; Sperling et al., 2011). These biomarkers reflect amyloid (Aβ) deposition (reduced CSF Aβ or detection of amyloid fibrils with Positron Emission Tomography (PET)) and neurodegeneration (raised CSF tau, medial temporal lobe atrophy on MRI, hypometabolism on fluorodeoxyglucose (FDG) PET imaging). These operationalized biomarkers can classify the pre-clinical stages of the AD trajectory, allowing each stage to be characterized and examined in more detail – stage 1 (biomarker evidence of Aβ, but no neuronal injury), stage 2 (Aβ, and neuronal injury) and stage 3 (Aβ, neuronal injury, and subtle cognitive impairment, not reaching the criteria for Mild Cognitive Impairment) (Jack et al., 2012). These studies have consistently revealed a significant minority of individuals with biomarker evidence of neurodegeneration, but no evidence of amyloid deposition. This has been labelled Suspected Non Alzheimer Pathology (SNAP). Histopathologic data also suggest that a proportion of patients represent neurodegeneration positive, Aß negative 'mimics' of AD, and have different clinical and prognostic features from AD. There is debate about whether these 'neurodegeneration only' subjects form part of the spectrum of AD, with neurodegeneration occurring prior to amyloid deposition, or whether the non-amyloidogenic pathways reflect underlying tauopathy or other pathologies. Current tau PET imaging studies may help answer this. Importantly, the biomarker profiles associated with SNAP have different clinical and prognostic features from amyloid positive AD, and this carries both clinical and research implications.

In this review, we discuss the defining imaging and biomarker studies which have led to the conceptualization of SNAP, and implications for future work. We also describe possible pathological bases for SNAP, by describing conditions with positive biomarkers for neurodegeneration (cortical atrophy and cortical hypometabolism) in the absence of Aβ, and possible mechanisms of neurodegeneration in these subjects. We then discuss the pathological relationship between SNAP and the histopathological concept of PART (Primary Age-Related Tauopathy) and detail how their neurodegenerative patterns differ. Finally, we discuss whether these entities are a subgroup of AD, or represent entirely separate pathologies.

2. The emergence of suspected non amyloid pathology (SNAP) in biomarker and imaging studies

The sensitivity and specificity of clinical criteria in making a diagnosis of AD are widely recognised to be imperfect (Beach et al., 2012; Bradford et al., 2009). This was highlighted recently when a drug trial that was recruiting patients with a clinical diagnosis of AD revealed that 16% of patients were amyloid negative (Salloway et al., 2014). This finding has been corroborated by: (a) Pathological examination, which has shown that 14% of individuals with a clinical diagnosis of probable AD have no or few Aβ plaques at subsequent autopsy (Serrano-Pozo et al., 2014) (b) Imaging studies which show that 15% of clinical AD cases are amyloid negative on Positron Emission Tomography scans (Landau et al., 2016). These findings highlight the need for biomarkers in making a diagnosis of AD (as suggested in the NIA-AA criteria described above). However, the application of these guidelines by using imaging and CSF biomarkers has led researchers to find different combinations of biomarkers present in the ageing brain with and without cognitive impairment. The biomarkers that are currently used in the diagnosis of AD are those that reflect amyloid plaque deposition (detected by amyloid PET imaging or inferred by reduced CSF Aβ42 levels) and markers of neurodegeneration (hypometabolism detected on ^{18}F FDG PET, hippocampal atrophy measured with MRI, and raised phospho-tau and total tau measured in CSF). A two-feature biomarker classification system devised by Jack et al. (Jack et al., 2012; Jack et al., 2014) stratifies subjects according to their amyloid positivity or negativity (A+/A−) and neurodegeneration status (N+/N−). Using this stratification, a proportion of subjects are amyloid and neurodegeneration positive (A+N+, representing preclinical, prodromal, or clinical AD subjects); neurodegeneration positive in the absence of Aβ (A−N+, also known as Suspected Non Alzheimer Pathology, or SNAP); amyloid positive only (A+N−); and negative for both amyloid and neurodegeneration (A−N−). This framework acknowledges that not all patients are on a 'typical' recognised AD pathway (Jack et al., 2012), and challenges the Amyloid Cascade Hypothesis, which posits that neurodegeneration occurs as a downstream effect of amyloid deposition (Karran et al., 2011)

SNAP (Suspected Non Alzheimer Pathology) is a biomarker-defined syndrome that encompasses individuals across the cognitive spectrum with normal amyloid biomarkers, but evidence of neurodegeneration on CSF, MRI or FDG-PET (Jack et al., 2016a). It was first defined in 2012 by Jack et al. (2012) who evaluated the NIA-AA criteria for preclinical AD using 450 cognitively normal volunteers, and found that 23% of the sample had normal amyloid PET imaging but were positive for biomarkers of neurodegeneration (defined by hippocampal volume and FDG-PET). There was a lower prevalence of APOE ε4 carriers in this cohort compared to the preclinical AD (Aβ) group.

2.1. Prevalence

Following the initial classification described above by Jack et al. in 2012, several studies have followed, evaluating cognitively normal elderly subjects, individuals with MCI, and cases of clinically diagnosed dementia. These are summarized in Table 1 (cognitively normal subjects) and Table 2 (cognitively impaired subjects).

In the cognitively normal group, the prevalence ranged from 18 to 35%, the majority of studies (6 of 9) showing remarkable consistency at 22–25%. The age group of the SNAP subjects was 57–81 years. APOEε4 carriage amongst the SNAP subjects was 12–41%, consistently lower than in the A+N+ subjects (range 41–71%)(Burnham et al., 2016; Jack et al., 2012; Knopman et al., 2012, 2013, 2016; Mormino et al., 2014, 2016; Soldan et al., 2016; Vos et al., 2013, 2016).

In the MCI group, prevalence ranged from 16.6% to 35%, with higher variability of prevalence between cohorts than the cogni-