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Commentary Open Access

Commentary on the Paper "PART, a Distinct Tauopathy, Different from Classical Sporadic Alzheimer Disease"

Kurt A. Jellinger*

Institute of Clinical Neurobiology, Alberichgasse 5/13, A-1150 Vienna, Austria

***Corresponding author:** Kurt A. Jellinger, Institute of Clinical Neurobiology, Alberichgasse 5/13, A-1150 Vienna, Austria, Tel: +43-1-5266534; E-mail: kurt.jellinger@univie.ac.at

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Commentary

Alzheimer disease (AD) is a neurodegenerative disorder with a well-defined neuropathological background characterized by the accumulation of tau protein within neurons (neurofibrillary tangles; NFT) and the extracellular deposition of β amyloid (Aβ) (as plaques and amyloid angiopathy), which is associated with neuronal and synaptic loss [1]; yet some individuals at autopsy have NFTs in the absence of Aβ. When associated with cognitive impairment, this condition was previously termed tangle-only dementia (TOD) [2] or tangle-predominant dementia [3]. NFTs in the absence of Aβ pathology are also common in cognitively intact elderly individuals [4,5], while some ApoE ε4 non-carriers with mild to moderate dementia may have extensive NFT pathology and minimal Aβ plaques [6].

Recently, the term primary age-related tauopathy (PART) was coined to describe a poorly understood and under-recognized subtype of late-onset dementia that has a distinct constellation of features setting it apart from classical sporadic AD [7]. Involving 2-10% of very old adults, PART is defined by the presence of predominantly limbic NFT pathology up to Braak NFT stage IV [8], with no or only few isocortical tau pathology, but involvement of the nucleus accumbens [9], and the absence of neuritic plaques [7]. The NFTs in PART are essentially identical to those observed in classical AD. They are composed of similar tau isoforms (mixture of insoluble 3 and 4 repeat tau isoforms), form paired helical filaments and are concentrated within neurons [3]. PART brains show absence of Aβ deposits (Thal stages 0-2), and no elevated soluble Aβ was observed in this disorder [10]. Thus, PART does not meet the formal criteria for sporadic AD according to the NIA-AA guidelines [11]. The hypothetical correlation between PART and AD is given in Table 1. New consensus criteria place PART/TOD on a continuum with age-related NFTs that are universally observed in aged brains. They recommend subdividing of PART into "definite" (Braak stage ≤ 4, Thal Aβ stage 0) and "possible" (Braak ≤ 4 and Thal Aβ stage 1-2) [7].

Clinical features of PART are older age at onset and death with shorter disease duration than classical AD and a female preponderance increased at higher Braak stages [12]. Their cognitive impairment ranges from normal to moderate dementia, occasionally associated with depression, delusions, hallucinations, paranoid symptoms or parkinsonism [3,13]. There is evidence that PART is associated with progressive cognitive decline that is dependent on the degree of NFT pathology, while some subjects with severe cognitive impairment show mixed pathologies - cerebrovascular disease, TDP-43 or hippocampal sclerosis [14-16]. The location of tau pathology corresponds well with involved cognitive domains, but further work will be needed to determine the degree to which PART is associated with domain-specific or more general cognitive functions.

PART cases have a disproportionate number of ApoE ε2 and ε3 allele carriers, but are almost never associated with ApoE ε4 [3], but are strictly associated with MAPT H 1 haplotype, a genomic inversion also associated with other tauopathies that may be related to an Aβ-independent mechanism [10]. Recent genome-wide studies (GWAS) found a novel locus located near the gene encoding tau protein and a strong association between the MAPT H1 haplotype and AD in ApoE ε4 negative subjects [17], supporting an association between PART and the H1 haplotype [10,18] and indicating that it stems from an Aβ-independent mechanism.

	No AD/ no PART	Asymptomatic PART	p - preAD	NFT-predominant Dementia (symptomatic PART)	Symptomatic AD
Aβ Phase	0	0-2	1-5	0-2	3-5
Braak-NFT-Stage	0	I-IV	0-VI	III, IV	III-VI
Degree of AD pathology	no AD	no or low AD	Low-high AD	no AD or low	Intermediate-high AD
Clinical signs of dementia or cognitive decline	no	no	no	yes	yes
PART *vs.* AD: Symptomatic PART and Symptomatic AD can be distinguished by Aβ Pathology. Asymptomatic PART and p-preAD overlap in those cases with initial Aβ pathology (Aβ phases 1, 2).					

Table 1: Hypothetical correlation between PART and AD.

Some investigators have suggested that PART and AD should not be differentiated [19,20], presupposing that all PART subjects will eventually develop Aβ plaques had they lived long enough, but the fact that the burden of amyloid pathology decreases in centenarians does not support this conclusion [21]. PART subjects are usually very old, have an end stage tauopathy with ghost tangles, marked atrophy and gliosis in restricted distribution, indicating that they are not early stages of AD but rather the end stage of their disease course [14]. The usage of the PART diagnosis would include individuals who do not have dementia and who are not at risk for AD. As some evidence supports the tenet that tau pathology occurs downstream of Aβ deposition, it seems reasonable to consider PART as a separate disease process not necessarily related to Aβ. Following this view, the early stages of NFT pathology may not always be the forerunner of diffuse tau changes and AD [22]. Without causality established, it is impossible to know that these representing two distinct processes rather than different manifestations of a common "dual" pathway [23].

There is increasing evidence indicating that AD is a heterogenous disorder with various phenotypes, some preferentially affect the hippocampus in older cohorts ("limbic-predominant AD"), while in younger ones there is poor hippocampal tau pathology in comparison to the neocortex ("hippocampal sparing AD") [18,24,25]. Since atypical cases are increasingly recognized to constitute subtypes of AD, one should not speak of "AD" as a uniform disorder with a predictable course, and the nosological position of PART should be proven by further genetic, clinical, neuroimaging and pathologic evidence.

Overall PART clinical syndrome is similar to AD, probably due to dominance of NFTs causing cognitive impairment. However, the findings of several comparative studies of PART and classical AD indicate that both types are somewhat different from each other, and there are clear sets of differentiating neuropathological features [3]. The cognitive and non-cognitive or other clinical features of both subtypes are similar and do not serve as indicators for prognosis, but older age (>80 years), lack of ApoE ε4 allele and less severe cognitive impairment may allow some differentiation [13]. Since currently no biomarkers are available for PART to enable an *in vivo* diagnosis, the majority of cases is detected postmortem [3,13]. The frequency of PART may be higher when the whole clinicopathological spectrum is considered, but further investigation is required to determine whether PART is a unique neuropathological condition, reflects membership in the spectrum of AD, or is a result of the pathological consequences of aging. Given the commonality of NFT deposition in older adults without amyloid pathology and the reported cognitive findings, it is possible that PART is an important contributor to age-related decline. Emergent tau-PET imaging techniques may enhance our ability to study this condition *in vivo* [26,27]. Should PART be an amyloid-independent form of AD-like dementia, it may be an exception that helps to confirm or modify the amyloid cascade hypothesis [28,29]. Should the PART hypothesis withstand further experimental studies, it would represent a shift in the way a subset of subjects with AD-like neuropathological changes is classified and has the potential to reevaluate or reject the amyloid cascade hypothesis [14,30,31]. There appear to be links between PART and SNAP (suspected non-Alzheimer pathology) in normal or mildly cognitively impaired oldest individuals with normal brain Aβ but abnormal biomarkers of neurodegeneration (Aβ–/ND+), also having low ApoE ε4 levels [32,33].

In conclusion, PART is considered a distinct and interesting group of age-related tauopathies that do not meet the current morphological criteria for sporadic AD. However, the question whether it represents either a unique age-related condition or a distinct variant of AD that requires separate classification for multiple reasons, including a different age pattern, genetic predilections, negative Aβ pathology, with signs of neurodegeneration particularly in the temporal lobe requires further investigations that may allow *in vivo* diagnosis and may consider emerging therapies targeting tau in age-associated neurodegenerative diseases.

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