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PART, a distinct tauopathy, different from classical sporadic Alzheimer disease

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The relationship between primary age-related tauopathy (PART) and Alzheimer's disease (AD) is currently a matter of discussion. Recently the term PART was referred to cases characterized by mainly allocortical neurofibrillary (NF) pathology (Braak stages 0–IV) with only few or no amyloid (Aβ) deposits (Thal Aβ phases 0–2) [49]. In addition, no elevated soluble Aβ was detected in this disorder [9, 46]. PART cases that lack any Aβ do not meet formal criteria for sporadic AD according to the NIA–AA guidelines [35]. These neurofibrillary tangle (NFT)+/Aβ-brains are commonly observed in extreme old age [9, 15, 19]. When associated with a high density of NFTs in the same distribution and some cognitive deficits, the disorder has been referred to as tangle-predominant senile dementia (TPSD) [27] or "tangle-only dementia" [55].

The new neuropathologic criteria recommend subdividing PART cases into "definite" (Braak stage ≤IV, Thal Aβ phase 0) and "possible" (Braak stage ≤IV, Thal Aβ phase 1–2) [9]. The frequency of PART is higher when the whole clinico-pathologic spectrum is considered and can reach 30–40 % [Alafuzoff, personal communication]. Since the selection criteria, number of included subjects and methods employed varied, the obtained percentages are not fully comparable. Introduction of the concept of PART will help to provide more correct frequencies. This kind of tau pathology is also seen in other

neurodegenerative disorders such as Huntington's disease, motor neuron disease, or Guam parkinsonism–dementia complex, where NFTs can be present in the same brain regions, especially in late-onset/longer surviving cases, in the (total or relative) absence of Aβ plaques [11, 41]. These cases might be considered as "coincidental" PART. Thus, further studies are essential to understand the relationship among PART, AD, and other tauopathies [9]. Patients that are symptomatic from PART pathologic change (i.e., PART dementia) correspond to those who were considered TPSD (Table 1).

Another group argued that there are no clinical, genetic, and morphological characteristics that permit the differentiation between AD and PART, and that PART merely represents an early stage of an inevitable AD process associated not only with NFTs, but also (eventually) Aβ deposits [13]. They emphasized that NF tau pathology in the entorhinal cortex and hippocampus belongs to the AD continuum, that at the early stages of AD, only the tau component may be apparent, and a combination of tau and Aβ pathologies develops later with progression of the AD-related process. This does not take into consideration the fact that for the "symptomatic" form of PART (TPSD), NFTs are numerous, including extracellular tangles and that quantitative approaches have clearly shown much higher densities than detected in early stages of the process that culminates in AD [21, 40]. It was argued that the asymptomatic cases without or with low Aβ plaque pathology, but with significant NFTs are not different from classical AD. Due to an overlap of the PART and presymptomatic AD, a certain number of the asymptomatic cases categorized as "coincidental" PART may eventually develop Aβ pathology, but many others likely will not progress to AD. Given that Braak et al. [5] reported initial tau pathology in every individual aged 40 years or older and given the finding of the same study that only ~80 % of all individuals that reach 90–100 years of age develop Aβ plaques, there are a significant number of individuals (~20 %) that will not develop AD although they presumably had tau pathology earlier in life. Accordingly, we think it is more informative to classify cases with medial temporal NFT pathology and no evidence of Aβ deposition as PART, since it is currently impossible to predict which will progress to AD and which will either remain with a limited medial temporal NFT (asymptomatic PART) or progress to symptomatic PART or another tauopathy.

Further points arguing in favor of the concept of PART are as follows:

1. The quality and quantity of neuropathological changes differs between the oldest-old (>90 years of age) and the younger old age groups [18, 37], and a certain number of oldest-old individuals do not get "plaque and tangle" dementia [5, 6, 19, 34]. These data indicate that the characteristic plaque + tangle AD peaks in the 8th and 9th decades and declines thereafter, while other disease processes (e.g., hippocampal sclerosis of the elderly [12, 38] and cerebrovascular pathology) are more prevalent in the final segment of the aging spectrum (see [42]).
2. In the absence of Aβ plaques, the presence of medial temporal NFTs is insufficient to predict that such an individual will progress to AD or another type of tauopathy, such as TPSD, the core form of PART, even though the NF tau pathology of AD, PART and TPSD is immunohistochemically, biochemically and ultrastructurally similar, if not identical [4, 9, 19, 34]. The correlation between cortical Aβ burden

and NFTs is under discussion [5, 10]. Nevertheless, the stages of the pathological process in AD show considerable age-related variance. Whereas NF tau pathology increases in centenarians (up to 90 %), the development of Aβ plaques often reaches a plateau or even may regress with time, depending on the balance of production and clearance, which may be why some very old AD patients have relatively fewer plaques (20–25 % of people over age 90 years have Thal stage 0 Aβ) [5, 6, 50]. Other tauopathies, such as Pick disease or corticobasal degeneration have age spectra that peak at a given age group, decrease in more advanced ages [51] and may argue in favor of the possibility of a decrease of a given neurodegenerative disorder after reaching a "critical" age. In other words, around 20 % of people had PART by age 60 over and may never develop Aβ plaques had they lived to a greater age, which refutes the idea that PART inevitably leads to AD but may represent a tauopathy with an age spectrum similar to that of AD as defined according to current criteria. What will happen with longer survival is currently unknown.

3. Understanding why individuals die with relatively high medial temporal lobe NFTs without Aβ, and in some cases without dementia, is extremely important. There may be genetic factors that protect some from and predispose others to form plaques. The fact that PART has a disproportionate number of ε2 and ε3 allele carriers, but is almost never associated with ε4 [2, 20], Alafuzoff, Beach, Thal, personal communications], significantly differs from early onset AD and may explain age-related differences in the association between the ε4 allele and NFTs [16]. Although the association between PART and limbic-predominant AD [25] and the MAPT H1 haplotype appears to be non-specific [14, 36], some studies suggest that a specific variant in the MAPT 3′ UTR may be related to an Aβ-independent mechanism in PART [46]. Recent re-analysis of genome-wide study (GWAS) data from the International Genomics of Alzheimer's Project (IGAP) Consortium found a novel AD locus located near the gene encoding tau protein and a strong association between MAPT H1 haplotype and AD in ApoE ε-negative subjects [29]. Hence, the genetic data differentiating PART from preclinical/early AD need further elucidation.

4. Neuritic plaques (NPs) made up by a central Aβ core surrounded by swollen abnormal tau-positive neurites, some of them showing presynaptic axonal terminals with synaptic vesicles [48], are not observed in "definite" PART and related disorders [1, 9, 13, 27, 30, 37], while they are obvious even in early stages of AD [18]. This may be explained by the absence of Aβ in these cases, which probably have not yet reached loss of Aβ homeostasis seen in AD. Their absence in "possible" PART cases (Braak tangle stage ≤IV and Thal Aβ phase 1–2) needs further elucidation. However, NP-related and NP-independent tauopathies may occur in the same brain as parts of a coordinated process or could manifest uniquely in subgroups of elderly subjects [45], whereas, like Aβ, NP-related NFT pathology may develop preclinically. In so doing, NPs restricted to AD pathology, distinguish PART and AD cases including most of its preclinical stages. Further analyses are required to understand the temporal spread of NFTs better.

5. It should be looked at whether molecular imaging studies Aβ (e.g., PiB) or tau imaging (e.g., T807) in conjunction with markers of neurodegeneration (FDG-PET or MRI) can be used to provide information about PART in living subjects. In particular, a subset of elderly individuals has evidence of neurodegeneration (e.g., medial temporal atrophy on MRI) yet no Aβ on PiB PET. These subjects have been considered to have "suspected non-Alzheimer pathophysiology" (SNAP). Whether a subset of SNAP also has PART remains to be seen [22, 23, 31] but appears to be very likely. At this point in the introduction of molecular imaging for tau (tau PET), SNAP has not been addressed; however, there are CSF studies on both Aβ and tau that have come to largely the same conclusions of the imaging biomarker studies [44, 52–54]. Thus, PART likely represents a subgroup of SNAP cases whereas preclinical and symptomatic AD cases are expected to exhibit Aβ-related AD biomarkers. In the Mayo Clinic Study of Aging, a community cohort is systematically followed with antemortem brain MRI, Aβ PET and FDG PET imaging to address the issue of the neuropathological basis of SNAP. The ability to follow these individuals over time to determine if they progress to AD will help address the controversy.

6. The involvement of subcortical and brainstem areas by tau pathology has been incompletely described in published cases of PART. As far as data are available, rather rare subcortical tau in medulla oblongata (up to 34.7 %), substantia nigra and locus ceruleus [37], but no definite involvement of spinal cord have been described [27].

7. An important unresolved problem is the role of soluble Aβ in PART. Reviewing data of six cases of the control group of Rijal Upadhaya et al. [43] fulfilling the criteria of definite PART did neither exhibit detectable amounts of soluble Aβ nor of dispersible, membrane-associated and formic acid-soluble plaque-associated Aβ, whereas preclinical cases did. Despite the synergistic roles of Aβ and tau in AD [39] it has to be shown whether tau propagates or spreads in a prion-like manner from the medial temporal lobe in the absence of abnormal fractions of Aβ. Recent studies to accomplish this include injecting enriched pathological tau from PART brains into tau transgenic mice to determine whether this pathology represents a distinct strain of abnormal tau that propagates differently from pathological tau in AD and other tauopathies [3, 8]. The proposed existence of PART would suggest that this does not occur, but there might be a specific tau strain that causes PART. If there is none, the low likelihood of PART spreading out of the medial temporal lobe could be an important clue as to why the combination of Aβ abnormalities and medial temporal tauopathy is fundamentally a more aggressive and expansive disorder than PART. Alternatively, the accumulation of other proteins associated with frontotemporal degeneration (e.g., TDP43) might play a role and future studies will be needed.

8. One can suggest the following: (a) medial temporal tauopathy is a critical ingredient of sporadic late-onset AD (LOAD) but because of the much earlier appearance of abundant Aβ, neuritic plaques, cerebral amyloid angiopathy and Lewy bodies [26, 47] in chromosomal (e.g., Down syndrome), sporadic young-

onset AD or autosomal dominant forms of AD (ADAD), medial temporal tauopathy may play a minor role in the latter forms of AD [33]; (b) in LOAD medial temporal tauopathy arises independently and earlier than β-amyloidosis; (c) sporadic LOAD may be thought of as a confluence of two independent processes, NF tau degeneration and β-amyloidosis; (d) the co-occurrence of β-amyloidosis and medial temporal tauopathy in both ADAD and LOAD accelerates medial temporal tauopathy and induces transneuronal spread of tauopathy outside of the medial temporal lobe [7]. This model has also been presented recently [24, 32].

9. There is increasing neuropathological evidence indicating that AD is a heterogenous disorder with various phenotypes, some of which preferentially affect the hippocampus in an older cohort ("limbic-predominant AD") and others where the hippocampus has a paucity of NF pathology in comparison to the neocortex ("hippocampal sparing AD"), often in younger ones [25, 36] who may present clinically as frontotemporal degeneration [51]. Moreover, there are subtypes of AD with plaque-predominant pathology, often associated with Lewy bodies [17, 28]. Therefore, it is not correct to speak of "Alzheimer disease" as a uniform disorder with a predictable course. Atypical cases are increasingly recognized to constitute a significant minority of AD. Whether or not PART should ultimately be considered a subtype of AD is yet to be proven by further genetic, clinical, neuroimaging or pathological evidence.

In addition to synergy during progression, there seems to be something more: people with Down syndrome or with PS1 mutations (and other such) develop NFTs in medial temporal lobes at far younger ages than would be expected, so to the extent that those processes are driven by Aβ, the development of entorhinal tangles is also accelerated by Aβ, making it different than an "independent process". This does not rule out the possibility that NFTs also can develop NFT through an independent process, but one can suggest that the synergy is stronger than is implied by a "co-existing" pathology hypothesis.

There are several ongoing projects on the genetics and pathology of PART, which may throw more light into the complex problems of PART in the near future, and we are looking forward to seeing progress emerge in this fascinating domain of age-related neurodegenerative pathologies.

In conclusion, PART, in our opinion, describes a distinct and interesting group of tauopathy cases that are worth of further studies because they do not meet the morphological criteria for sporadic AD according to current consensus criteria. They represent either a distinct separate pathology or a very distinct variant of AD that requires separate classification for multiple reasons, including a different age pattern, genetic predilections, and an expectation to be Aβ PET-negative with signs of neurodegeneration in the medial temporal lobe. Such cases would normally drop out of the clinical diagnosis of AD and probably deserve specific diagnostic and therapeutic modalities.

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Table 1

Hypothetical correlation between PART and AD

	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)