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COMMENTARY

Are cases with tau pathology occurring in the absence of Aβ deposits part of the AD-related pathological process?

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The current neuropathological diagnosis of clinically suspected Alzheimer's disease (AD) requires the presence of advanced neurofibrillary tangle (NFT) stages and of Aβ deposits in the brain [15]. Both abnormal proteins (intraneuronal forms of aggregated and hyperphosphorylated tau and extracellular Aβ) develop at different times at different predilection sites and progress gradually but inexorably during the pathological process by sequential spreading into previously uninvolved regions. Tau pathology develops prior to Aβ deposits [1, 5, 6]. In their position paper, Crary et al. [8] present arguments for distinguishing two processes: an 'AD-related process' and a non-AD-related 'primary age-related tauopathy' (PART). Both are characterized by the presence of 3R and 4R tau isoforms as well as paired helical filaments but they differ in that the first displays the combined presence of tau and Aβ pathologies, whereas the second is marked by the presence of tau pathology alone.

Nevertheless, application of the criteria required to confirm neuropathologically that the diagnosis of clinically manifest AD [15] does not warrant the disqualification of tau-only cases because the statement that "a diagnosis of AD neuropathologic changes requires at least a minimum threshold level of Aβ deposition" [8] is correct only in cases with clinically diagnosed AD but is inaccurate when applied to non-demented individuals. In the absence of Aβ deposits, tau pathology consisting of 3R and 4R isoforms that occurs in the same neuronal cell types as those known to be vulnerable to the pathological process underlying AD and only at the same predilection sites as the tau lesions that are present in individuals with Aβ and in fully developed AD can represent possible preclinical (early) stages of the AD-related pathological process. In other words, an interim or transient absence of a minimum of Aβ deposits is not an adequate or compelling rationale for excluding tau-only cases from the developmental spectrum of the AD-related process, nor is the existence of such cases in non-aged individuals (compare Table 3 here with Table 1 in [8]) consistent with the term 'primary age-related tauopathy.'

The authors claim that PART, in contrast to AD, is probably not APOE ε4 allele-driven. However, an earlier study showing that non-demented individuals with NFT stage I pathology displayed a significantly higher APOE ε4 allele frequency than controls [11] reached the opposite conclusion. That study was retrospective (cross sectional), but so were the studies in the supporting literature (13, 67, 70, 122, 150, 151) cited by Crary et al. [8], who have not incorporated into their thinking the implications of recent original findings showing that neuronal injury develops independently of Aβ in APOE ε4 allele carriers [7, 13].

The fundamental question whether 3R + 4R tau-only cases and cases with 3R + 4R tau plus Aβ deposits belong to essentially different pathological processes cannot be resolved without identifying potentially unique mechanisms for cases with tau-only pathology, e.g., by means of experimental models of tau seeding and neuron-to-neuron transmission [12], in which tau extracts are isolated not from AD brains but from brains of individuals with autopsy-confirmed 3R + 4R tau-only lesions. Biomarker-based research and positron emission tomography (PET) imaging of brain Aβ and of tau that can quantify abnormalities in AD-associated neurodegeneration [19] have the developmental potential to reach the point at which the presence and progression of both pathological proteins can

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be followed in prospective cohorts. Although the fluorodeoxyglucose-PET is still in its infancy [16–18, 22], the use of longitudinal PET imaging for both pathological proteins may one day make it possible to see whether individuals with early NFT stages but lacking Aβ plaques go on to develop them and full-blown AD, while at the same time making it possible to distinguish AD from non-AD-associated tauopathies [10].

The relationships between age and stages/phases of abnormal tau and Aβ deposition [20] are shown in Figs. 1 and 2. The columns represent decades and show the prevalence of stages/phases in a cross-sectional cohort ($n = 2{,}366$) of non-selected autopsy cases from our database ranging from 1 to 100 years of age [4]. Figure 1 depicts cases lacking tau pathology (Fig. 1a) as well as those with subcortical stage a through NFT stage VI (Fig. 1b–f; see also Tables 1, 2). The yellow columns represent cases without tau lesions. Red areas represent tau-only cases, whereas cases with Aβ deposits (irrespective of phase) plus tau pathology (by stage) appear in green. The numbers of individuals and their frequencies in each decade are shown in Tables 1 and 2. Blue columns in Fig. 2 indicate the presence of Aβ deposition (range of cases with phases 1–5) in the same cases depicted in Fig. 1. Yellow columns represent cases without Aβ deposits (Fig. 2a).

In Fig. 1b, tau occurs at young ages in the locus coeruleus or there and in other nuclei with diffuse cortical projections (subcortical stages a–c). These stages are not accompanied by Aβ deposits [3, 5]. The frequency of such cases culminates in the second decade and slowly decreases thereafter (Fig. 1b; Tables 1, 2). The diagram in Fig. 1c shows stages 1a and 1b in which cortical tau pathology occurs at first in the form of pretangle material that preferentially appears in the transentorhinal region [2]. Stage 1a tau pathology is confined to the processes of nerve cells, whereas stage 1b cases show pretangle material in cortical pyramidal cells (mostly layer pre-α cells). All stage 1a and 1b cases also display subcortical lesions corresponding to those seen in stages a–c, i.e., cortical tau pathology does not occur in the absence of the previously seen subcortical tau pathology. Cases at stages 1a and 1b increase steadily up to the fourth decade and, thereafter, decrease up to the ninth decade. Some of these individuals also develop mild Aβ deposits (Fig. 1c; Tables 1, 2).

The presence of argyrophilic (Gallyas-positive) cortical lesions characterizes NFT stages I–VI (Fig. 1d), and subcortical nuclei also develop argyrophilic lesions during these stages. In stage I, argyrophilic NFT pathology occurs, again, predominantly in the transentorhinal region, and the numbers of involved neurons there increase. In stage II, the pathological process extends into layer pre-α of the entorhinal region and gains there a distinct priority. In some instances, in stage I/II cases, a few pyramidal cells in the first sector of the Ammon's horn also display Gallyas-positive staining

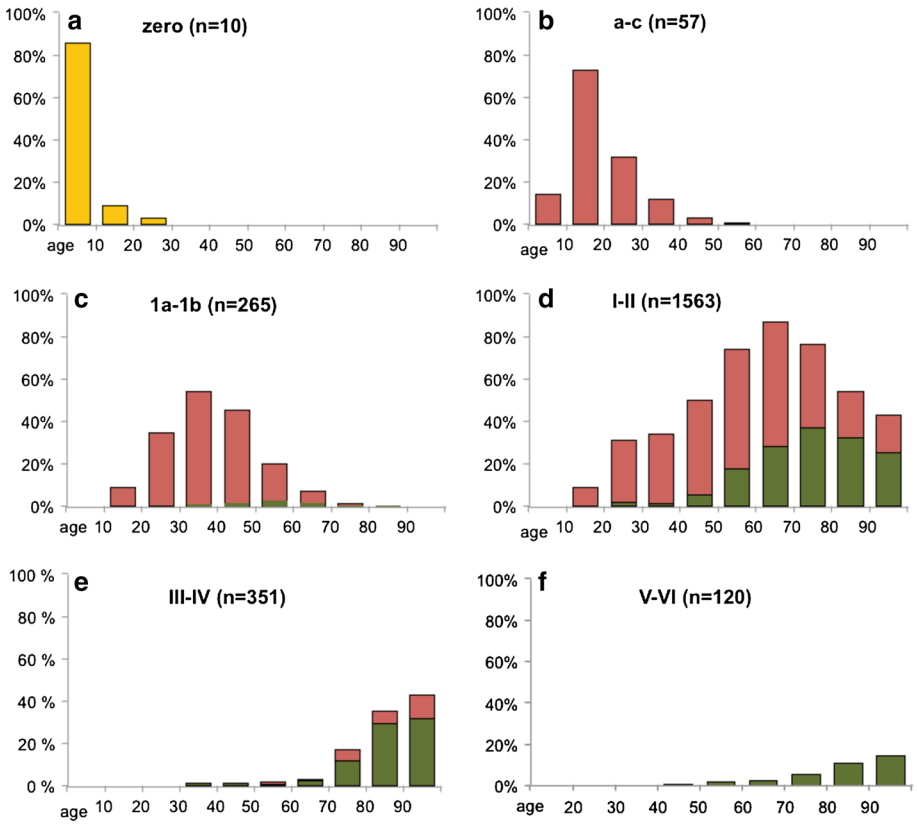

Fig. 1 Development of tau pathology ($n = 2{,}366$) by decade (ages of cohort 1–100). Columns show the frequency of cases in relation to the total number of cases in the respective age categories. **a** The diagram summarizes the prevalence of cases lacking tau inclusions (*yellow*). **b** Non-argyrophilic (Gallyas-negative) tau pathology in subcortical stages *a–c* (*red*). **c** Initial cortical non-argyrophilic tau pathology characterizes stages *1a* and *1b* (*red*). During these stages, some cases also display a combination of tau pathology and Aβ deposition (*green*). **d** The presence of argyrophilic (Gallyas-positive) neurofibrillary (NFT) lesions in cortical nerve cells mark NFT stages *I* and *II*. **e**, **f** Frequencies of argyrophilic tau pathology in NFT stages *III–IV* (**e**) and *V–VI* (**f**)

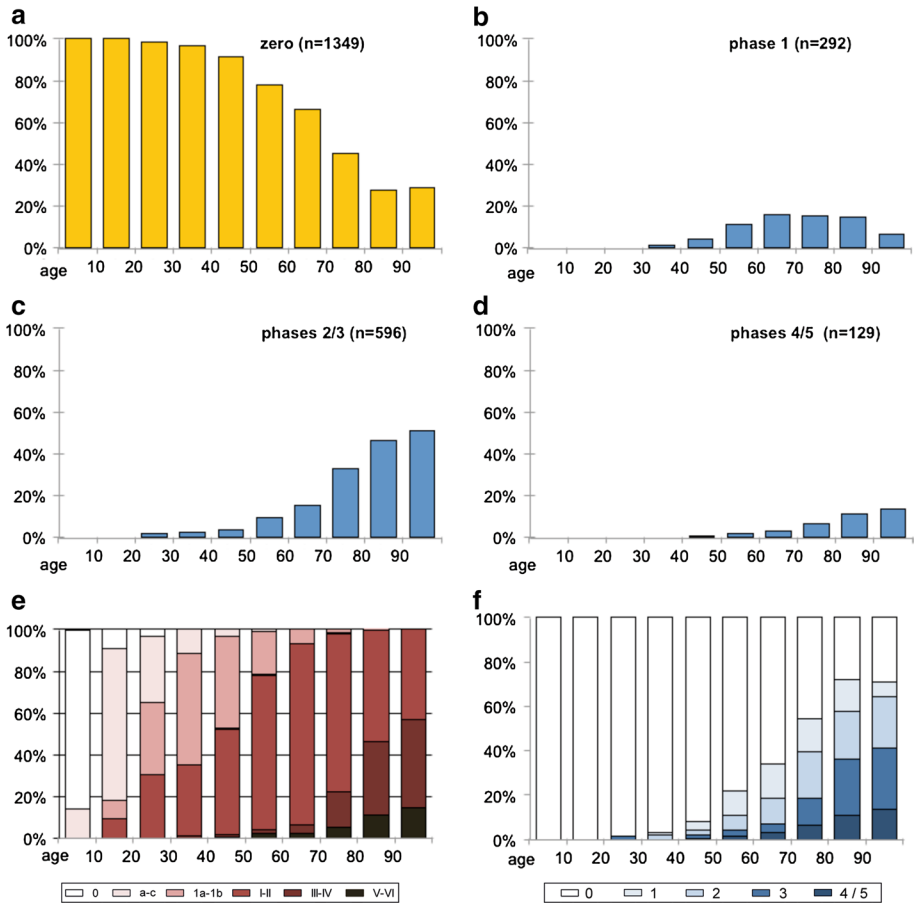

Fig. 2 Development of Aβ deposits in $n = 2{,}366$ cases by decade (ages of cohort 1–100). **a** The diagram summarizes the prevalence of cases lacking Aβ deposits (*yellow*). **b**–**d** These graphs show the prevalence of Aβ deposition (phase 1) (**b**), phases 2–3 (**c**), and phases 4–5 (**d**) (see also Table 2). **e**, **f** Frequency of all tau-only stages (*red*) juxtaposed with all phases of Aβ deposits (*blue*) by decade. Cases devoid of tau pathology (**e**) and those without Aβ deposits (**f**) are indicated in *white*. Note the relatively late appearance of Aβ

[1, 14, 21]. The occurrence of stage I/II cases rises steadily up to the seventh decade (Fig. 1d). Beyond that point, these stages occur more infrequently, only to be replaced by higher neurofibrillary stages. NFT stage I often is accompanied by Aβ deposition, mostly phase 1, but also up to and including phase 4 (Fig. 1d; Tables 1, 2, 3). Stage II cases more frequently display Aβ deposits than stage I cases, with most having phase 2; but, again, many reach phase 4 (Tables 1, 2, 3). Individuals with tau pathology corresponding to stages a–II do not manifest AD-related symptoms or possibly fall below the clinical detection threshold when tested using the currently available diagnostic tools.

The existence of many elderly individuals with NFT stages I–II shows that it is possible to reach old age with mild lesions (Fig. 1d; Tables 1, 2, 3). It is also remarkable that the rates of progression differ considerably from one individual to another (Fig. 1d): Some reach stages I–II as teenagers or in early adulthood, others have to be over 90 years of age to do so. This indicates that the pathological process underlying AD does not inevitably lead to dementia [9] but, instead and as a rule, it does not reach dimensions that result in clinically recognizable symptoms. At the present time, these marked inter-individual differences cannot be adequately explained. Thus, more research into the factors that determine or can influence the tempo and pathogenicity of the process is urgently needed [4].

During NFT stage III, the pathological process moves into the basal temporal neocortex and, in stage IV, it progresses into limbic regions of the cortex (proneocortical regions of the insula and frontal lobe and temporal high-order sensory association areas). Cases with NFT stages III/IV begin to occur in the third decade and increase in frequency up to the ninth decade. The majority of these cases also show Aβ deposition (Fig. 1e; Tables 1, 2, 3).

Neurofibrillary lesions encroach upon nearly all sensory and prefrontal association areas in stage V and, during stage VI, even extend into the primary areas of the neocortex. The prevalence of these late stages rises with age (Fig. 1f). All stage V and VI cases have Aβ deposits corresponding to phase 2 or higher (Tables 1, 2, 3). In general, individuals with a growing burden of pathology display a shift toward higher age categories and, thus, the AD-related pathological process appears to progress continuously from tau stage a to NFT stage VI and from Aβ phase 1 to phase 5 (Figs. 1, 2; Tables 1, 2, 3). The extensive over-regional impairment of the neocortex usually leads beyond the threshold to manifest symptoms, thereby making the clinical diagnosis of AD possible.

Table 1 Development of tau pathology ($n = 2{,}366$) by decade (ages of cohort 1–100), including both tau-only cases and those with Aβ deposits (*n*/*n*)

Age (*n*)	Zero (AT8)	a–c (AT8)	1a–1b (AT8)	NFT I–II (Gallyas)	NFT III–IV (Gallyas)	NFT V–VI (Gallyas)
0–9	6 (6/0)	1 (1/0)	0	0	0	0
$n = 7$	85.7 (85/0) %	14.3 (14/0) %	0 %	0 %	0 %	0 %
10–19	2 (2/0)	16 (16/0)	2 (2/0)	2 (2/0)	0	0
$n = 22$	9.1 (9/0) %	72.7 (72/0) %	9.1 (9/0) %	9.1 (9/0) %	0 %	0 %
20–29	2 (2/0)	21 (21/0)	23 (23/0)	20 (19/1)	0 (0/0)	0
$n = 66$	3.0 (3/0) %	31.8 (32/0) %	34.8 (35/0) %	30.3 (29/1) %	0 %	0 %
30–39	0	11 (11/0)	51 (50/1)	32 (31/1)	1 (0/1)	0
$n = 95$	0 %	11.6 (12/0) %	53.7 (53/1) %	33.7 (33/1) %	1.1 (0/1) %	0 %
40–49	0	5 (5/0)	76 (73/3)	86 (77/9)	2 (0/2)	1 (0/1)
$n = 170$	0 %	2.9 (3/0) %	44.7 (43/2) %	50.6 (45/5) %	1.2 (0/1) %	0.6 (0/1) %
50–59	0	3 (3/0)	68 (60/8)	242 (184/58)	7 (4/3)	6 (0/6)
$n = 326$	0 %	0.9 (1/0) %	20.9 (18/2) %	74.2 (56/18) %	2.1 (1/1) %	1.8 (0/2) %
60–69	0	0	34 (28/6)	424 (287/137)	18 (7/11)	11 (0/11)
$n = 487$	0 %	0 %	6.9 (6/1) %	87.0 (59/28) %	3.7 (1/2) %	2.3 (0/2) %
70–79	0	0	10 (8/2)	430 (220/210)	94 (27/67)	30 (0/30)
$n = 564$	0 %	0 %	1.8 (2/0) %	76.2 (39/37) %	16.7 (5/12) %	5.3 (0/5) %
80–89	0	0	1 (0/1)	282 (113/169)	185 (32/153)	57 (0/57)
$n = 525$	0 %	0 %	0.2 (0/0.2) %	53.7 (22/32) %	35.2 (6/29) %	10.9 (0/11) %
90–100	0	0	0	45 (19/26)	44 (11/33)	15 (0/15)
$n = 104$	0 %	0 %	0 %	43.3 (18/25) %	42.3 (10/32) %	14.4 (0/14) %
Totals $n = 2{,}366$	10 (10/0) <1 (0.4/0) %	57 (57/0) 2 (2/0) %	265 (244/21) 11 (10/1) %	1,563 (952/611) 66 (40/26) %	351 (81/270) 15 (4/11) %	120 (0/120) 5 (0/5) %

The green portions of the columns in Fig. 1 trace the development of cases with combinations of tau pathology and Aβ plaques. The earliest Aβ deposits begin to develop in some individuals during stages 1a–1b (Table 3). It is important that none of the cases in the cohort display Aβ deposits in the absence of tau pathology. In the following NFT stages, the number of individuals with Aβ deposition steadily increases. In stages V and VI, all cases are accompanied by phase 2 Aβ deposition or higher (Tables 1, 2, 3).

These findings have a considerable bearing on the interpretation of tau-only cases within the collective spectrum of what is, in our view, an AD-related process. The initial appearance of cases with Aβ versus the cessation of tau-only cases is not unimportant. We see that Aβ deposits inevitably develop in brains that, according to Crary et al. [8], display lesions associated with a 'non-AD-related' tauopathy. Our data indicate that tau-only cases consistently evolve into cases with Aβ plaques. Aβ deposition occurs initially (phase 1) in some stage 1a/1b cases and increases considerably during stages I/II, and phase 1 becomes more infrequent in stages III and IV (Table 3).

Subsequently, tau-only cases decrease during NFT stages III/IV, and beginning in NFT stage V tau-only cases no longer exist. If Crary et al. [8] are correct in their thinking about a form of primary tauopathy that is non-AD related, we would anticipate that such cases should cease already during the course of stages III–IV. This process should be obvious in that pretangles decrease while, at the same time, tombstone tangles increase. This did not occur, however, in the present cohort. For this reason, we think that the gradual decrease of tau-only cases can be best explained in that they undergo a transformation into cases with Aβ deposition. As such, the data (Fig. 1; Tables 1, 2, 3) do not give occasion to postulate the existence of a 'non-AD-related tauopathy' alongside of an AD-related process. At the same time, however, the clinically bland but remarkably large group of tau-only individuals (1,334 of 2,366 cases) bears closer study to clarify, among other issues, why Aβ deposits develop relatively late during the preclinical phase of AD.

The columns in Fig. 2a–d show the prevalences of all phases of Aβ deposition for $n = 2{,}366$ cases (Table 2). Aβ plaques generally begin to develop (phase 1) in the fourth decade of life and peak in the eighth decade. Beyond that point, phase 1 cases decline in frequency and are replaced by cases with more advanced phases (Fig. 2b). Aβ plaques then appear in previously uninvolved regions, reaching phases 2–3 (Fig. 2c) and, in some instances, phases 4 and 5 (Fig. 2d). Once again, the diagrams show a continuum, with a shift towards higher age categories, beginning with

the occurrence of Aβ plaques in basal portions of the temporal neocortex and peaking in the late phases. Early Aβ phases are seen predominantly in younger individuals, whereas the more advanced phases occur at higher ages, i.e., the mean of Aβ deposition phases increases with age (Table 3).

Table 2 Development of Aβ plaques ($n = 2{,}366$) by decade (ages of cohort 1–100)

Age (n)	Zero	Phase 1	Phases 2 + 3	Phases 4 + 5
0–9	7	0	0	0
$n = 7$	100 %	0 %	0 %	0 %
10–19	22	0	0	0
$n = 22$	100 %	0 %	0 %	0 %
20–29	65	0	1	0
$n = 66$	98 %	0 %	2 %	0
30–39	92	1	2	0
$n = 95$	97 %	1 %	2 %	0 %
40–49	156	7	6	1
$n = 170$	92 %	4 %	3 %	1 %
50–59	254	37	30	5
$n = 326$	78 %	11 %	9 %	2 %
60–69	322	76	74	15
$n = 487$	66 %	16 %	15 %	3 %
70–79	256	86	186	36
$n = 564$	45 %	15 %	33 %	7 %
80–89	145	78	244	58
$n = 525$	28 %	15 %	46 %	11 %
90–100	30	7	53	14
$n = 104$	30 %	7 %	51 %	12 %
Totals $n = 2{,}366$	1,349 57 %	292 12 %	596 25 %	129 6 %

The summary Fig. 2e illustrates the proposed continuum of the intraneuronal pathology from subcortical stages a–c to the wide regional distribution pattern that is characteristic of NFT stage VI [1, 4, 5]. The extraordinarily long time span over which the lesions develop, together with the observation that they occur in a very large proportion of the human population do not detract from their insidious nature. If stages a–c, 1a, 1b, and I–III are incorporated into the 'natural history' of tau pathology, it can be postulated that the preclinical (early) phase of sporadic AD is virtually a lifelong process. Yet, this also implies that the AD-related process offers a much larger window of opportunity for disease-modifying interventions than previously imagined.

Figure 2e and f juxtapose the development of tau pathology and Aβ plaques. Only a proportion of all cases exhibit Aβ deposition and, notably, all of these cases also have tau pathology. Tau inclusions corresponding to stages a–1b develop approximately two decades prior to the initial development of Aβ deposits [4, 6].

In conclusion, the absence of Aβ in individuals of all ages with 3R and 4R tauopathy does not mean that such tauopathy does not belong to a larger pathological process ultimately leading to AD, during which Aβ plaques develop but do so after pretangles and NFTs are present in neurons and brain predilection sites associated with the AD process. The absence of Aβ deposits is not an adequate rationale for excluding tau-only cases from the developmental spectrum of the AD-related process.

Table 3 Mean ages in years of Aβ phases and tau stages ($n = 2{,}366$)

Aβ phases	Tau zero	Tau stages a–c	Tau stages 1a–1b	NFT stage I	NFT stage II	NFT stage III	NFT stage IV	NFT stage V	NFT stage VI
Zero	10	57	244	687	265	76	5	0	0
	9.7	27.4	45.8	61.4	72.4	78.7	86.6	–	–
1	0	0	12	141	103	35	2	0	0
	–	–	59.5	67.2	75.6	78.8	84	–	–
2	0	0	9	128	135	54	11	3	0
	–	–	60	70.3	79.2	80.6	85.3	76.7	–
3	0	0	0	22	74	100	39	24	1
	–	–	–	69.9	77.6	81.4	82.1	85.3	57
4	0	0	0	2	6	10	18	36	15
	–	–	–	68.5	78.2	79.4	83	79.9	73.4
5	0	0	0	0	0	1	0	37	4
	–	–	–	–	–	75	–	78.7	83.8
Totals	10	57	265	980	583	276	75	100	20
Mean age	**9.7**	**27.4**	**46.9**	**63.6**	**75.3**	**80.1**	**83.1**	**80.7**	**74.7**

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