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CORRESPONDENCE

Neuropathological subtypes of Alzheimer's disease

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Murray et al. [9], among 889 cases of autopsy-verified Alzheimer's disease (AD) recently compared clinical and neuropathological features between typical and atypical AD cases, thus separating distinct clinicopathological subtypes. Based on the density of neurofibrillary tangles (NFT) in various brain regions, using thioflavin-S fluorescence microscopy [11] but not immunohistochemistry as suggested more recently [3], cases were classified as hippocampal-sparing with lower NFT counts in hippocampus (11%), limbic-predominant forms with lower cortical NFT counts (14%), and typical AD forms (75%). In a smaller AD validation cohort ($n = 113$), 71% were typical AD, while limbic-predominant and hippocampal-sparing type showed different frequencies (21 and 8%, respectively). Hippocampal-sparing cases were younger at death and a higher proportion of them were men, whereas those with limbic-prominent AD were older and had a higher proportion of women. Additional vascular pathology ranging from 16 to 36% was highest in limbic-predominant and lowest in hippocampal-sparing cases, while Lewy body pathology (11–26%) was lowest in the hippocampal-sparing form, but did not differ between limbic-predominant and typical AD cases. Disease duration was similar, while final Mini-Mental score (MMS) was lowest in hippocampal-sparing form but did not differ from typical AD.

Some major pathological data of this extensive study can be confirmed from a personal study in 933 autopsy-confirmed cases of AD (all with neurofibrillary tangle stage of more than Braak IV) from the brain bank of the Institute of Clinical Neurobiology, Vienna, Austria (1989–2008). All cases underwent standardized neuropathological assessment including immunohistochemistry for tau (using antibody AT-8—Innogenetics, Ghent, Belgium, and not Thioflavin-S fluorescence microscopy as by Murray et al. [9]), β-amyloid and α-synuclein (methods see [7]). Tangle distribution was assessed using Braak neurofibrillary tangle stage [2, 3]. The classification of the different subtypes of AD followed those by Murray et al. [9], however, without performing local NFT counts, but using detailed histological description of NFT distribution. Cerebrovascular disease was assessed with a simple scheme [5], and Lewy body pathology by immunohistochemistry, as previously described [6].

The age at onset, duration of disease, initial MMS score, essential clinical data, APOE genotype, and brain weight were not systematically assessed in our series; final MMS score was only assessed in a rather small percentage of patients (10.1–25.3%).

The major results are summarized in Table 1. Typical AD in our cohort was more frequent than in the Mayo series (82.5 vs. 75%), while both hippocampal sparing (8.2%) and limbic-predominant including tangle-predominant cases [4, 8] were less frequent (8.9%), the latter being similar to its frequency in their smaller validation AD cohort [9]. As stated by Murray et al. [9], the limbic-predominant AD cases share several morphologic characteristics with the subtype of late onset dementia, referred to as tangle-predominant dementia (TDP, [4, 8]), in which NFTs are frequently limited to allocortical regions with rather few isocortical NFTs, similar to the limbic-predominant AD. The major difference between the two subtypes is the virtual absence of neuritic plaques in TPD [8], whereas in the Mayo cohort the senile plaques (detected by thioflavin-S-fluorescence, non-differentiating the plaque types) showed little differences in their density

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Table 1 Major characteristics of AD subtypes

Characteristics	Hippocampal-sparing AD ($n = 79$, 8.2%)	Limbic-predom. AD ($n = 85$, 8.9%)	Typical AD ($n = 769$, 82.5%)	P value
Women	$n = 47$, 59.5%	$n = 55$, 64.7%*	$n = 520$, 67.5%*	* versus HS $P < 0.01$
Age at death	76.3 ± 8.6	84.9 ± 3.8*	81.3 ± 9.2*	* versus HS $P < 0.01$
Age at onset	68.0 ± 10.0	73.8 ± 6.4*	79.7 ± 3.8*	$P < 0.01$; * versus HS <0.001
Disease duration	7.4 ± 3.6**	4.8 ± 2.6***	9.1 ± 4.3*	***$P < 0.001$; ** versus HS $P < 0.001$
MMSE final (mean)	10 ($n = 20$)	11.5 ($n = 16$)	4.6 ($n = 78$)*	* versus other forms $P < 0.01$
Braak NFT stage (mean)	4.5 (2–5)	4.5 (3–5)	5.6 (5–6)	
Cerebrovascular pathology	27 (34.2%)*	35 (41.1%)	286 (36.4%)*	* versus. LP $P < 0.01$
Lewy body pathology	19 (24.9%)*	3 (3.5%)	63 (8.2%)	* versus. other forms $P < 0.001$

between the three AD subtypes [9]. Despite several clinical similarities (more frequent involvement of females, shorter disease duration, older age at death, less severe cognitive impairment than in typical AD), another difference between the limbic-predominant AD and TPD was the higher proportion of ApoE ε4 allele in the former but increased ε2 and ε3 in TDP irrespective of age [1]. In the Vienna series, the proportion of females was highest in typical AD (67.5%) and lowest in hippocampal-sparing forms (59.5%). Similar to the Mayo series, age at onset and death was significantly higher in limbic-predominant forms than in classical AD ($P < 0.01$), and significantly lower in the hippocampal-sparing type. Disease duration was longest in typical AD and shortest in limbic-predominant forms, the differences in our cohort being more expressed than in the Mayo series. Final MMS score was lowest in classical AD, while it did not essentially differ between the two other types, whereas in the Mayo series the final MMS scores were lowest in the hippocampal-sparing form and slightly higher in the typical AD cases. However, it is to be considered that in our cohort, MMS was evaluated only in a minority of patients. The mean Braak NFT stages in our cohort were slightly higher in typical AD cases, but lower in the two other subgroups than in the Mayo series. Among other/superimposed pathologies, additional cerebrovascular lesions were more frequent in our cohort (34.2–41.1%, respectively), most frequent in limbic-predominant forms. Lewy body pathology was highest in hippocampal-sparing forms (24%, due to frequent association with dementia with Lewy bodies), and much lower in the two other subtypes (3.5–8.2%, respectively), thus being less frequent than in the Mayo series. Limitations of this study are the lack of exact clinical and evaluation and follow-up studies, so exactly performed in the Mayo series.

Despite several differences and shortcomings of our material, the results of these two series and of another recent study of 1,677 dementia cases from the National Alzheimer's Coordinating Center Registry, separating "tangle intensive" and "plaque intensive" cases from "classic AD" [10], emphasize the need of further studies on both the pathological subclassification of AD subtypes and their distinct clinical presentations that should be considered in the design and interpretation of future biomarker and therapeutic studies.

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