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Mixed Brain Pathologies in Dementia: The BrainNet Europe Consortium Experience

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Key Words
Alzheimer disease · Synucleinopathy · Vascular pathology · Argyrophilic grain dementia

Abstract
Background: Dementia results from heterogeneous diseases of the brain. Mixed disease forms are increasingly recognized. ***Methods:*** We performed a survey within brain banks of BrainNet Europe to estimate the proportion of mixed disease forms underlying dementia and age- and gender-specific influences. ***Results:*** Data collected in 9 centres from 3,303 individuals were analysed. The proportion of patients with mixed diagnoses among all cases with Alzheimer disease (AD), vascular pathology (VP), argyrophilic grain dementia (AGD), and synucleinopathies, such as Lewy body dementia (LBD), Parkinson disease (PD) and synuclein pathology only in the amygdala, was 53.3%. Mixed pathology was more frequently reported with LBD, PD, AGD, and VP than with AD. The percentage of mixed diagnoses for AGD and VP significantly differed between centres. In patients younger than 75 years, synucleinopathies, and pure forms of AD, VP, and AGD were more frequent in men. Above 75 years of age, more women had pure AD and pure AGD. ***Conclusions:*** The most obvious neuropathological alteration should not terminate the diagnostic procedure since copathology is likely to be found. Neuropathological interpretation of AGD and VP has not been sufficiently established in a consensus. Pure forms of synucleinopathies are unlikely sole substrates for dementia.

Introduction

Dementia is a clinical syndrome resulting from heterogeneous diseases of the brain. The most common disorders comprise neurodegenerative diseases. These are characterized by selective neuronal loss and are accompanied by intra-, or extracellular deposition of conforma-

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Table 1. Summary of collected data

	Center									
	1	2	3	4	5	6	7	8	9	all
Country	Spain	Italy	Hungary	Sweden	Finland	UK	Germany	France	Austria	–
Case referral	CH	CJS	CH, CJS	BBD	CH, BBD	BBD	CH, BBD	CH, BBD, CJS	CH, CJS	–
Mean age, years	72.16	68.24	75.73	79.19	77.83	76.15	73.53	NA	71.92	74.1[1]
Women	74.43	69.66	78.15	79.71	80.2	78.9	75.28	NA	73.32	76.45[1]
Men	70.82	66.82	71.94	78.55	74.68	73.41	72.35	NA	70.5	71.82[1]
Number of cases included in this study										
Total	798	206	235	134	268	250	63	1,196	153	3,303
Women	273	103	143	72	153	124	25	697	77	1,667
Men	525	103	92	62	115	126	38	499	76	1,636

BBD = Brain bank donations; CH = community hospitals; CJS = CJD surveillance systems.
[1] Calculated from 2,107 cases.

tionally altered proteins [1]. Neuropathological classification depends on the evaluation of the anatomical distribution of neuronal loss and cellular/subcellular distribution of specific aggregated proteins [2]. Considerable overlap in the accumulation of different proteins questions whether the mere detection of a particular aggregated protein is really a substrate for dementia. In addition to neurodegenerative diseases, the presence and role of vascular pathology is also variably interpreted [3]. These observations underpin the need for detailed neuropathological evaluation and efforts to use common criteria. Multicentre autopsy series may increase the sample size and may provide more exact information regarding the frequency of pure and mixed forms of disorders, and furthermore give estimations of age- and gender-specific influences.

BrainNet Europe is a consortium of brain banks in mainland Europe and the UK, which commenced activities in 2001, expanding to the present grouping in 2004 (http://www.brainnet-europe.org/). In addition to promoting brain banking as a research resource for European neuroscience through the provision of high-quality human brain tissue samples, the major aims of BrainNet Europe include the development of gold standards for tissue handling and tissue quality control to best practice guidelines for brain banking.

In the present study, we performed a survey within brain banks of BrainNet Europe to estimate the proportion of mixed and pure disease forms underlying dementia syndromes and to estimate age- and gender-specific relative frequencies, and finally to compare neuropathological evaluations of mixed and pure disease forms. Our aim was to point out the importance of recognizing co-occurrence of various pathologies for the sake of clinico-pathological correlations and therapeutic measures.

Materials and Methods

Collection of Data

The following data were requested from the participating centres: list of neuropathological diagnoses, gender, and age of patients who died due to a clinically documented dementing disorder evaluated during the last 3–5 years using immunohistochemical methods and current diagnostic neuropathological criteria (for a detailed list see: http://www.brainnet-europe.org/en/references-for-neuropathological-diagnoses.php). Types of case referral include brain bank donations (n = 6 centres), community hospitals (n = 6), or Creutzfeldt-Jakob disease (CJD) surveillance systems (n = 3) (table 1). For the evaluation of the frequency of mixed pathologies and the effect of gender and age, we used the following diagnoses with relevant numbers of cases: Alzheimer disease (AD), vascular pathology (VP), argyrophilic grain dementia (AGD), CJD, Parkinson disease (PD), Lewy body dementia (LBD), neurofibrillary tangle predominant form of dementia (TOD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and frontotemporal lobar degeneration with ubiquitin-only-immunoreactive neuronal inclusions (FTLD-U) or associated with motor neuron disease (FTLD-MND). In addition, all cases with any Lewy body pathology (e.g. LBD, PD, and cases with synuclein pathology only in the amygdala) were pooled in one group as synucleinopathies.

Statistical Analysis

The χ^2 test was used to compare the proportion of mixed and pure diagnoses in different centres, age and gender groups. The factorial ANOVA test was used to evaluate differences in age at death in different gender groups and diagnostic groups (pure or mixed).

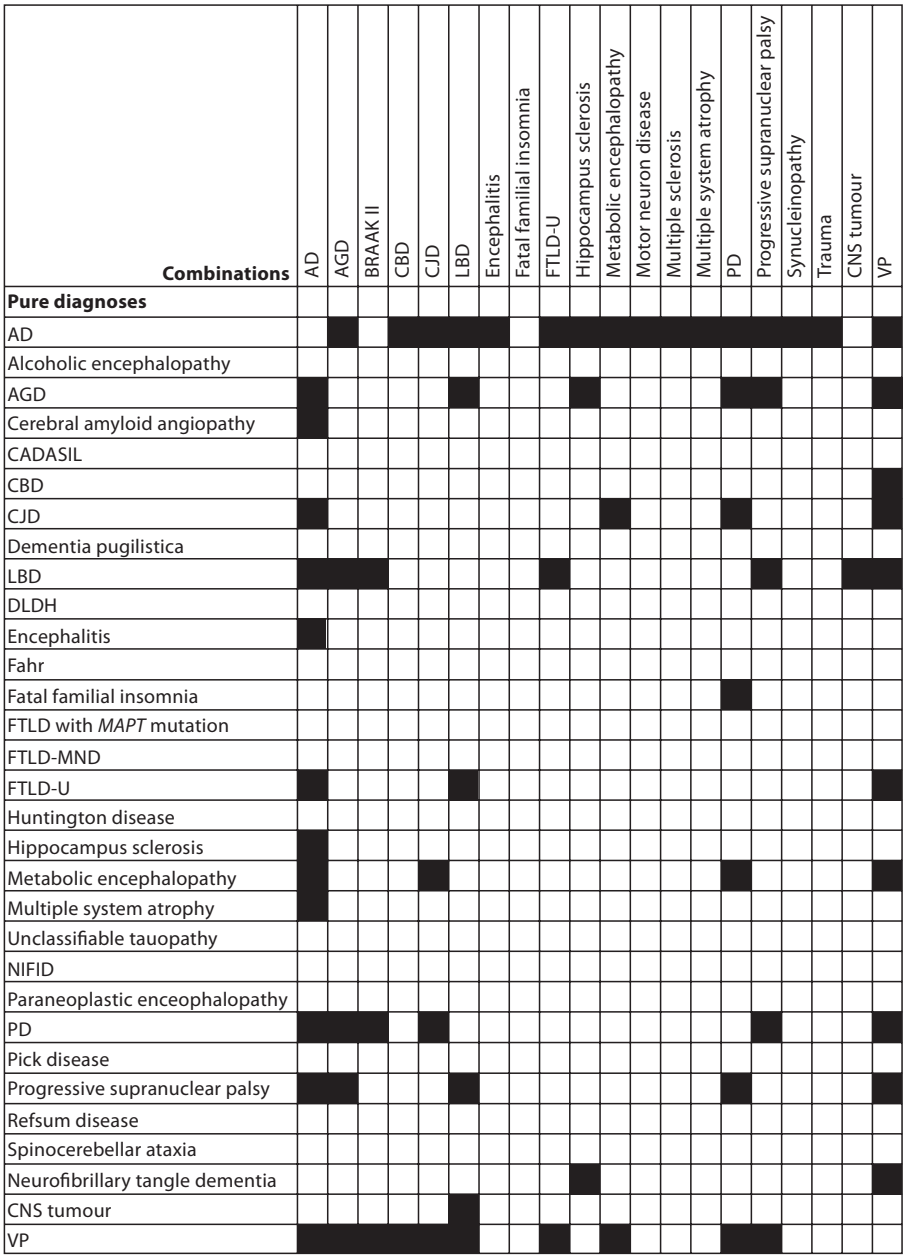

Fig. 1. Neuropathological diagnoses used in our cohort. Diagnoses which also appear in single ('pure') forms are listed in the column on the left, while combined diagnoses are listed in the horizontal row on top. The black boxes indicate which pure diagnoses may also be present in a combined form. CADASIL = Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; DLDH = dementia lacking distinctive histopathology; NIFID = neuronal intermediate filament inclusion disease; CNS = central nervous system.

Results

Data collected in 9 centres from 3,303 individuals (1,667 women and 1,636 men) were analysed (summarized in table 1). For the calculation of the effect of age, we used 2,107 cases. The age of individuals ranged between 18 and 99 years, with a mean age (± standard deviation) of 74.14 ± 12.07 years for all, 76.45 ± 12.29 years for women, and 71.82 ± 11.4 years for men. The number of neuropathological diagnoses, including combined ones, in clinically documented dementia cases was 88. The number of combined diagnoses was 54 (61.36%) (fig. 1). In the current paper, we focused on diagnoses with relevant numbers of cases (i.e. 1,138 cases with AD, 1,011 with CJD, 341 with VP, 207 with LBD, 25 with PD, a sum of 275 cases with the diagnosis of synucleinopathies, 90 with AGD, 42 with TOD, 36 with PSP, 32 with FTLD-U/MND, and 14 with CBD).

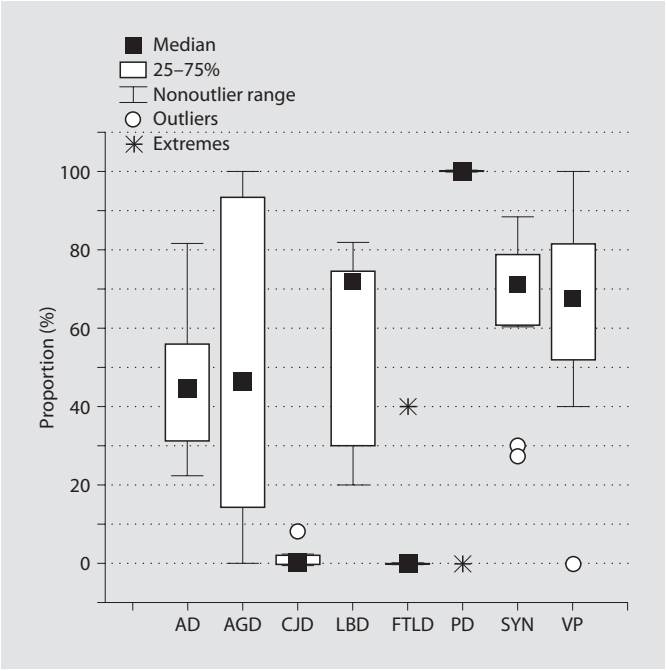

Fig. 2. Boxplot representation of the proportions of mixed forms of AD, AGD, CJD, LBD, FTLD (FTLD-U and FTLD-MND), PD, any type of synucleinopathy cases (SYN: this includes pooling of LBD, PD and cases with synuclein pathology only in the amygdala), and VP.

Frequency of Mixed and Pure Diagnoses

The proportion of patients with mixed diagnoses in the group of cases with AD, VP, AGD, and synucleinopathies was 53.3%. In cases where combined diagnoses were indicated, AD was found in 89.6% ($p < 0.01$), VP in 52.6%, synucleinopathies in 50%, and AGD in 11.4%. The percentage of mixed diagnoses for the group of patients with AD, VP, LBD, PD, synucleinopathies, AGD, CJD, and FTLD-U/MND varied between centres (fig. 2); this was significant for AGD and VP. Mixed pathology was significantly more frequently reported with PD (92%), LBD (61%), AGD (67%), and VP (65%) than with AD (43%), while in PSP (22%), CBD (21%), and in particular in FTLD-U (9%) and CJD (2%) mixed pathology was significantly less frequently documented as compared to AD, LBD, PD, and VP.

Influence of Age and Gender

We observed significant ($p < 0.05$) differences in age at death and distribution of diagnoses: while FTLD-U/MND and CJD were more frequent in younger patients below 75 years, AD, AGD and combined diagnoses were more frequent in elderly patients (fig. 3a).

In the total cohort, LBD (also combined with AD) and any type of synucleinopathy were more frequent in men. In women, only AD with VP was significantly more frequent (fig. 3b). In younger patients (<75 years), the detection of some kind of synucleinopathy as a pure or combined diagnosis was significantly more frequent in men. In addition, AD, VP, TOD, and AGD were more frequent in men (fig. 3c). However, among the patients above 75 years of age, more women were found with pure AD, pure AGD, mixed VP and AD combined with VP (fig. 3d). More detailed age grouping indicated a female predominance among patients with TOD aged above 81 years (table 2).

Discussion

In this study, we summarized the results of a survey within neuropathological centres of BrainNet Europe. The following implications may be emphasized: (1) the first and most obvious neuropathological alteration should not terminate the diagnostic procedure since copathology is likely to be found; (2) the frequency of AGD and VP as a combined diagnosis is significantly different between brain banks; (3) morphological evidence of a Lewy body type of synucleinopathy, including LBD and in particular PD, is unlikely the sole neuropathological substrate for dementia; (4) neuroscientists using tissue from brain banks should be aware of the high probability of mixed alterations, in particular in brains of individuals above age 75, thus exclusive disease-specific results should be interpreted with caution; (5) influence of gender may be considered in AD, synucleinopathies, AGD, or TOD.

Our study shows that α-synuclein and/or vascular pathology frequently accompanies different disorders. After the widespread recognition of LBD as a disease entity, several autopsy surveys demonstrated a frequency of LBD of 20% [4–11]. Due to bias in the recruitment of subjects to the brain banks involved in this survey, the current study has limitations from an epidemiological viewpoint; it is not representative, and cannot give reliable estimations of the relative frequencies of brain disorders. However, it shows that mixed pathology is common and thus is in line with recent studies emphasizing the role of mixed brain pathologies accounting for most dementia cases in community-dwelling older persons [12], as well as supports the findings of other population-based and consecutive autopsy series [13–15].

Interestingly, combined diagnosis was rarely reported in CJD or FTLD-U/MND cases. In patients with CJD,

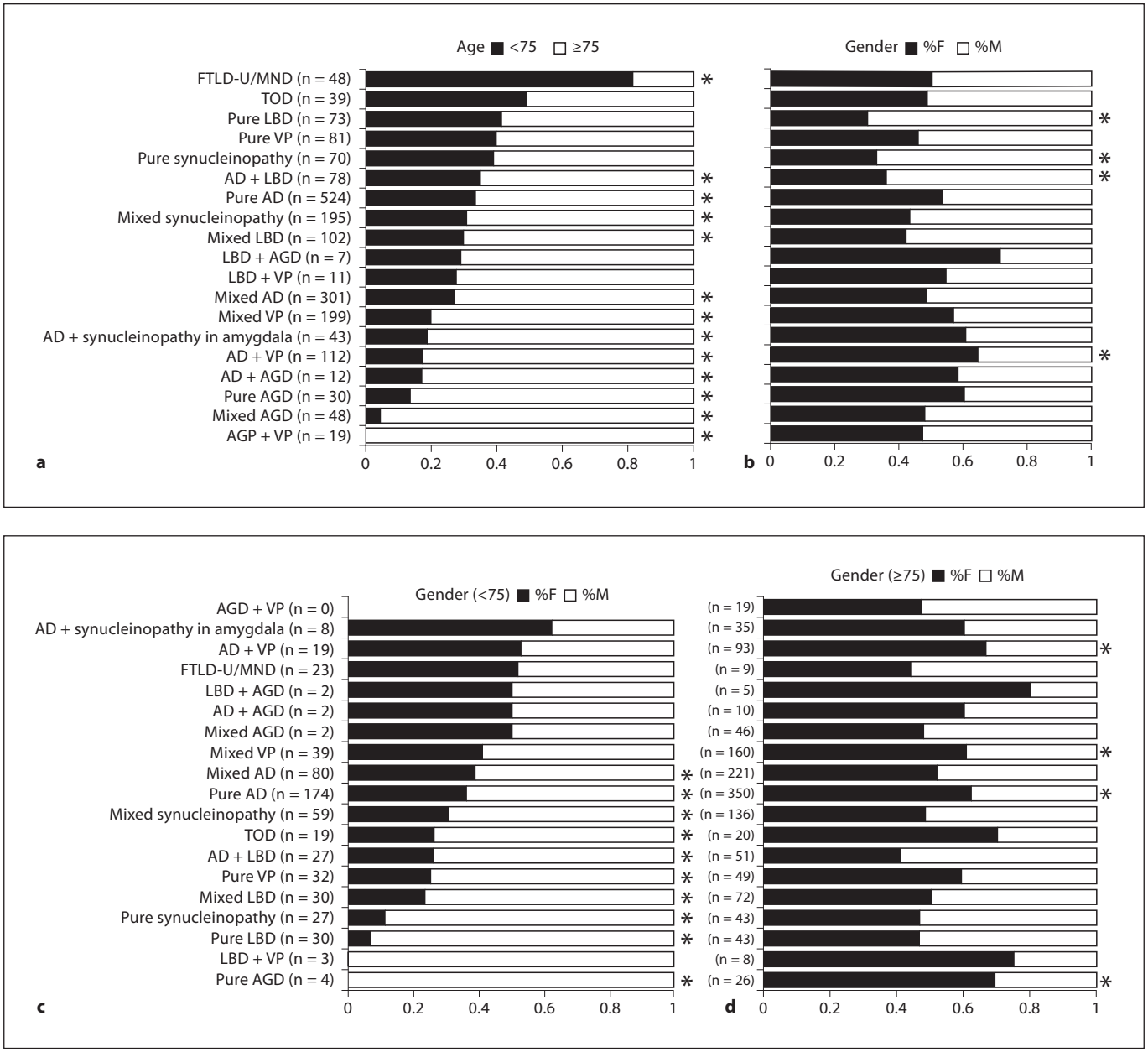

Fig. 3. Age- and gender-specific proportions of pure and mixed diagnoses. Asterisks on the right side of column bars indicate significant difference ($p < 0.05$). Synucleinopathy: LBD, PD, and cases with synuclein pathology only in the amygdala pooled in one group. F = Female; M = male.

detailed neuropathological examination is usually terminated after the detection of spongiform change and deposition of the disease-associated prion protein in brain tissue, which may hinder the exact evaluation of copathology. In addition, age at onset is generally lower (around 10 years) compared to the aforementioned diseases. Previously some cases of FTLD-U/MND may have been overlooked when showing prominent tau or α-synuclein pathology due to the more difficult interpretation of ubiquitin-immunoreactive structures. Recent criteria and the introduction of TDP-43 immunostaining may help give exact frequencies of copathology [16]. Indeed, overlap with AD or Lewy body pathologies is already noted [17, 18].

Table 2. List of diagnoses in age and gender groups

Diagnosis	Age group							
	≤60		61–70		71–80		≥81	
	male	female	male	female	male	female	male	female
AD	20	17	*57*	*19*	79	92	*69*	*153*
AD + VP	0	0	4	2	19	23	*17*	*47*
AD + LBD	2	1	*12*	*2*	19	13	17	12
AD + synucleinopathy[1]	0	0	1	1	8	7	*4*	*14*
AD + AGD	0	0	0	0	0	0	4	5
AD + other	2	2	8	3	25	16	12	15
LBD	2	1	*12*	*0*	*24*	*7*	8	14
LBD + VP	0	0	1	0	2	1	1	5
LBD + AGD	0	0	0	0	0	0	1	3
LBD + other	0	0	1	1	2	1	1	1
AGD	0	0	2	0	2	2	*6*	*16*
AGD + VP	0	0	0	0	0	0	7	6
AGD + other	0	0	0	0	0	0	2	0
VP	3	1	*15*	*2*	15	17	11	17
VP + other	1	1	2	2	8	3	4	5
FTLD-U/MND	9	7	8	2	7	8	0	0
FTLD-U + other	0	1	0	0	0	0	0	0
TOD	1	1	8	3	11	4	*0*	*11*
Other	*82*	*54*	88	73	82	72	*31*	*57*
Sum	125	87	224	113	308	269	200	386

Italic numbers indicate that $p < 0.05$ (χ^2 statistics).
[1] Unclassified Lewy body synucleinopathy (e.g. in the amygdala).

Our results reflect a lack of neuropathological diagnostic criteria for AGD and VP, while such criteria are more widely accepted and used for AD, LBD and PD. AGD is a sporadic 4R tauopathy that is considered in the differential diagnosis of late-onset dementias and some features may be observed associated with mutations in the *tau* gene [19–21]. The detection of argyrophilic grains is not uncommon in aged human brains and AGD accounts for around 5% of dementias (see recent review of Ferrer et al. [22]). Whether the presence of argyrophilic grains per se represents a distinct disease process causing dementia or whether it lowers the threshold for dementia is a matter of debate [23]. In our cohort, AGD also appears as a pure diagnosis. Thus the constellation of main neuropathological abnormalities including oligodendroglial coiled bodies and tau-positive pretangles in limbic projection neurons, in addition to argyrophilic grains [19, 22], may be interpreted as a morphological entity. Since the appearance of argyrophilic grains is associated with ageing [24] that increases the frequency of comorbidity, pure forms of AGD may be rarely detected in individuals with dementia. Copathology is underestimated in particular in AD cases with neuropil threads in the same regions where grains are detected. A more exact evaluation may be obtained by using anti-4R tau immunohistochemistry [25]. Our results are in line with the variability of reported frequency of VP in autopsy series [4–11], as well as with a recent survey performed amongst neuropathologists about VP [3] pointing out the lack of detailed guidelines indicating what should be looked for at autopsy in cases of suspected vascular cognitive impairment. With regard to VP, the lack of quantification of the various lesions, as well as an account of their location, is a limitation of this study in terms of information on potential vascular correlates of dementia.

Earlier studies noted that cerebrovascular disease and Alzheimer-related pathology frequently occur in subjects with PD showing cognitive decline [26, 27]. Our results support the notion that pure forms of synucleinopathies are unlikely to be the sole cause of dementing disorder. This is exemplified by the amygdala-synuclein variant of AD [28]. PD with dementia more likely shows copathol-

ogy as compared to LBD. A recent study revealed severer Alzheimer-related pathology in PD with dementia than in LBD [27]. The clinical relevance of α-synuclein pathology in relation to dementia is debated, although some studies indicate a causative role [29–31]. It is of note that a recent study based on neuropathological findings also emphasized that abundant α-synuclein pathology in cortical and subcortical regions may be detected in many subjects without notable signs of dementia [32, 33].

Earlier observations indicated that women are at higher risk of developing AD than men [4, 34]. Our neuropathology-based results in a large series indicate that this influence of gender depends on the age group, and is generally true only for patients above 75 years. Our study supports the notion of a male predominance among patients with LBD [4], and we emphasize this in younger age groups. We point out that TOD is more frequent in younger men, whereas in elderly women the frequency is reversed, and that AGD also shows female predominance. While these observations could suggest a gender difference in the pathogenesis of neuronal tau pathology, it may also be explained by the increased mortality of men [35].

In summary, our survey supports the notion of a high frequency of combined pathologies as a morphological substrate for dementia and urges the establishment of commonly used neuropathological criteria for AGD and VP. Knowledge of gender- and age-specific differences may serve as a rationale for patient selection in therapeutic trials.

Acknowledgement

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