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Aging and cerebrovascular lesions in pure and in mixed neurodegenerative and vascular dementia brains: a neuropathological study

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Abstract

Introduction: *The prevalence of dementia is increasing in our aging population. Because of the complexity of disease pathology, dementia classifications remain controversial. The present post-mortem study investigates whether there are age differences between dementia brains with a single pure neurodegenerative or cerebrovascular disease and those with mixed pathological features. Also, the impact of these vascular lesions is compared.*

Material and methods: *A total of 132 dementia brains with a pure neurodegenerative or cerebrovascular disease and 84 with mixed features were examined. Main age and gender distribution were compared between the overall group of pure and of mixed dementia. Also, the most common subgroups were compared separately. In addition to the detection of macroscopic visible lesions, a whole coronal section of a cerebral hemisphere, at the level of the mamillary body, was taken for semi-quantitative microscopic evaluation of white matter changes (WMCs), cortical micro-bleeds (CoMBs), and cortical micro-infarcts (CoMIs).*

Results: *Overall, patients with mixed dementia were at death significantly older than those with pure dementia. According to the main diagnosis, the pure forms of Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD) were more common in the younger age groups while in the older ones the mixed form of Lewy body disease (LBD) predominated. Neuropathological examination revealed an increased severity of cerebral amyloid angiopathy (CAA), territorial infarcts, lobar haematomas, and CoMIs in the mixed AD group. In FTLD only CoMIs were increased in the mixed group, while in LBD no differences in severity of all cerebrovascular lesions were observed. Lacunar infarcts were more frequent in pure vascular dementia, while CAA predominated in the mixed one.*

Conclusions: *Mixed dementia during the aging process is mainly due to the severity of AD and LBD pathologies combined with CAA-related cerebrovascular lesions.*

Key words: *neuropathology, aging, cerebrovascular lesions, pure and mixed dementia syndromes, Alzheimer's disease, frontotemporal lobar degeneration, Lewy body disease, vascular dementia.*

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Introduction

The prevalence of dementia is increasing in our aging population. Because of the complexity of disease pathology, dementia classifications remain controversial [32]. Many distinct brain diseases other than Alzheimer's disease (AD) afflict older human patients and contribute to cognitive impairment [2,31]. Dementia of unknown aetiology increases with age [8]. Mixed brain pathologies account for most dementia cases in the elderly [25,34]. The most common mixed dementia is the coexistence of AD with cerebrovascular pathology [26]. Cerebral amyloid angiopathy (CAA) occurs with increasing age and is the cause that contributes most to this type of mixed dementia [25,27]. The second most frequent mixed dementia is the association of AD with Lewy body disease (LBD) [26]. Cerebrovascular lesions are also frequently observed in this type of mixed dementia [17,35].

The present post-mortem study investigates whether there are age differences between dementia brains with a single "pure" neurodegenerative or cerebrovascular disease and those with mixed pathological features. Also, the impact of cerebrovascular lesions is compared in the different pure and mixed disease entities.

Material and methods

A total of 216 demented patients, who had been followed up at the Lille University Hospital, underwent an autopsy. Early obtained informed consent of the patients, or from the closest family later, allowed the autopsy for diagnostic and scientific purposes. The brain tissue samples were acquired from the Neuro-Bank of Lille University, federated to the "Centre des Resources Biologiques", which acted as an institutional review board.

Table I. Percentage distribution of the different types of mixed dementia

Type of mixed dementia	%
Alzheimer's disease with cerebrovascular pathology	36
Alzheimer's disease with Lewy body pathology	24
Vascular dementia with Alzheimer pathology	15
Lewy body disease with Alzheimer pathology	14
Amyotrophic lateral sclerosis with frontotemporal lobe pathology	3
Frontotemporal lobe degeneration with Alzheimer pathology	3
Lewy body disease with cerebrovascular pathology	2
Frontotemporal lobe degeneration with cerebrovascular pathology	2
Progressive supranuclear palsy with cerebrovascular pathology	1

In total, 132 brains with a pure neurodegenerative or cerebrovascular disease and 84 with mixed features were examined. Main age and gender distribution were compared between the overall pure groups and between the most common subgroups according to their main diagnosis. The low number of patients with progressive supranuclear paralysis (PSP), amyotrophic lateral sclerosis (ALS) and corticobasal degeneration (CBD) did not allow a separate statistical comparison between the pure and the mixed cases. Table I shows the percentage distribution of the different types of mixed dementia.

Alzheimer's disease features were classified according to the Braak and Braak criteria [3]. The main diagnosis of AD was retained when stages V and VI were reached. In mixed dementia groups, beneath the main diagnosis, additional AD features were retained when stages II to IV were already reached. The CERAD criteria were used to evaluate the severity of CAA [20]. The degree of CAA was evaluated semi-quantitatively on four cortical samples and graded from 0 to 3. The post-mortem diagnosis of frontotemporal lobar disease (FTLD) was made according to the neuropathological diagnostic and the nosological criteria of the Consortium for FTLD [5]. FUS histochemistry was performed in tau- and TDP-negative cases. LBD was diagnosed according to the report of the consortium on DLB international workshop [31]. Progressive supranuclear palsy (PSP) was retained according to the NIND criteria [22]. The neuropathological criteria proposed by Cruz-Sánchez *et al.* were used for the diagnosis of ALS [7]. The diagnosis of CBD was made according to the recommendations of an international consortium group [1]. Staging of the cerebrovascular pathology in pure and mixed vascular dementia (VaD) was performed according to the recommendations of the vascular dementia group [30].

In addition to the detection of macroscopic visible lesions such as haematomas, and territorial and lacunar infarcts, a whole coronal section of a cerebral hemisphere, at the level of the mamillary body, was taken for semi-quantitative microscopic evaluation of the small cerebrovascular lesions such as white matter changes (WMCs), cortical micro-bleeds (CoMBs), cortical

micro-infarcts (CoMIs), and lacunes. The mean values of WMCs were the average of the ranking scores: no change (R0), a few isolated (R1), frequently scattered in the corona radiata (R2), and forming confluent lesions (R3) of myelin and axonal loss. For the other cerebrovascular lesions their mean values corresponded to their average numbers in the individual brains [21].

Univariate comparisons of unpaired groups were performed with the Fisher's exact test for categorical data. The non-parametric Mann-Whitney *U*-test was used to compare continuous variables. The significance level, two-tailed, was set at ≤ 0.05 for moderately significant, at ≤ 0.01 for significant, and at ≤ 0.001 for highly significant.

Results

Overall, patients with mixed dementia were, at death, significantly older than those with pure dementia, with 77 (SD = 10) years in the former and with 72 (SD = 11) years in the latter group ($p \leq 0.01$), while male gender distribution was similar: 52% compared to 57%. According to the age distribution, the mixed group consisted mainly of the oldest old ($p \leq 0.05$), while adults were more frequent in the pure group ($p \leq 0.05$). According to the main diagnosis FTLD was more common in the pure group ($p \leq 0.05$) and LBD in the mixed group ($p \leq 0.01$). The mixed dementia cases were mainly composed of an association of AD with VaD and with LBD features. By comparing the cerebrovascular lesions between the overall pure and mixed groups, CAA ($p \leq 0.001$) was found to be more severe and territorial infarcts ($p \leq 0.01$), lobar haematomas ($p \leq 0.01$), and CoMIs ($p \leq 0.01$) were more frequent in the latter group (Table II).

Comparing age and gender distribution in the subgroups, the main age of the mixed AD group was

Table II. Comparison of age distribution with standard deviation (SD), percentage main diagnosis, and severity of cerebrovascular features between pure and mixed dementia cases

Items	Pure disease (*n* = 132)	Mixed disease (*n* = 84)
Overall average age (years)	72 (SD = 11)	77 (SD = 10)**
% subgroups		
Adult	29	–
Young old	42	–
Middle old	21	32
Oldest old	8	27*
Male gender (%)	57	52
Main disease (%)		
Alzheimer disease	41	56
Frontotemporal lobar degeneration	19*	7
Lewy body disease	5	19**
Progressive supranuclear palsy	9	8
Amyotrophic lateral sclerosis	9	8
Corticobasal degeneration	3	0
Vascular dementia	14	13
Cerebrovascular pathology		
White matter changes	0.7 (0.9)	1.0 (1.1)
Cerebral amyloid angiopathy	0.3 (0.7)	1.2 (1.3)***
Lacunar infarcts	0.1 (0.3)	0.3 (0.7)
Territorial infarcts	0.0 (0.2)	0.3 (0.6)*
Lobar haematomas	0.0 (0.2)	0.3 (0.6)*
Cortical micro-infarcts	0.2 (0.7)	1.0 (2.1)**
Cortical micro-bleeds	0.0 (0.3)	0.2 (0.7)

*p*** ≤ 0.001: highly significant, **p ≤ 0.01: significant, *p ≤ 0.05: moderately significant*

greater than that of the pure group with, respectively, 77 (SD = 10) years and 69 (SD = 10) years ($p \leq 0.001$), predominantly in the middle old group ($p \leq 0.0.5$). A similar age difference was observed between the FTLD groups with, respectively, 87 (SD = 6) and 66 (SD = 10) years ($p \leq 0.001$). Also, according to the age classification, mixed FTLD occurred more frequently in the middle and oldest old patients ($p \leq 0.05$) and more in the adult and the young old of the pure group ($p \leq 0.001$). No average age differences were observed between the pure and the mixed LBD, with, respectively, 78 (SD = 3) years and 81 (SD = 7) years, predominantly in the middle and oldest old of both groups. Also, in VaD no age differences were

Table III. Comparison of age with standard deviation (SD) and percentage of age subgroups and gender distribution according to the main diagnosis between the pure and the mixed dementia cases

Items	Pure disease (n = 132)	Mixed disease (n = 84)
Alzheimer's disease	72 (SD = 11)	77 (SD = 10)**
Overall age (years)	69 (SD = 10)	77 (SD = 10)**
% subgroups		
Adult	21	15
Young old	32	21
Middle old	26	43*
Oldest old	21	21
Male gender (%)	66	40
Frontotemporal lobar degeneration		
Overall age (years)	66 (SD = 10)	87 (SD = 6)***
% subgroups		
Adult	32***	0
Young old	64***	0
Middle old	4	33*
Oldest old	0	67**
Male gender (%)	65	66
Lewy body disease		
Overall age (years)	78 (SD = 3)	81 (SD = 7)
% subgroups		
Adult	0	0
Young old	0	0
Middle old	67	50
Oldest old	33	29
Male gender (%)	100	71
Vascular dementia		
Overall age (years)	76 (SD = 7)	77 (SD = 19)
% subgroups		
Adult	0	0
Young old	31	33
Middle old	53	34
Oldest old	16	33
Male gender (%)	69	100

*p*** ≤ 0.001: highly significant,**p ≤ 0.01:significant, *p ≤ 0. 05: moderately significant*

observed, with 76 (SD = 7) years in the pure and 77 (SD = 19) years in the mixed cases. Gender distribution was similar in all the disease subgroups, except for the pure AD patients, in which a male predominance was seen ($p \leq 0.05$) (Table III).

The neuropathological examination revealed an increased severity of CAA ($p \leq 0.001$) and of territorial infarcts ($p \leq 0.01$), lobar haematomas ($p \leq 0.01$), and CoMIs ($p \leq 0.001$) in the mixed AD group with no differences in the severity of lacunar infarcts, WMCs, and CoMBs. In FTLD only CoMIs were increased in the mixed group ($p \leq 0.05$). In LBD no differences in severity of all cerebrovascular lesions were observed. In pure VaD the number of lacunar infarcts was sig-

Table IV. Comparison of the severity of cerebrovascular features between subgroups of pure and mixed dementia cases

Items	Pure disease	Mixed disease
Alzheimer disease		
White matter changes	0.8 (0.9)	1.2 (1.1)
Cerebral amyloid angiopathy	0.4 (0.1)	1.7 (1.3)***
Lacunar infarcts	0.1 (0.4)	0.2 (0.9)
Territorial infarcts	0.0 (0.1)	0.4 (0.5)**
Lobar haematomas	0.0 (0.1)	0.3 (0.5)**
Cortical micro-infarcts	0.1 (0.3)	1.5 (2.7)***
Cortical micro-bleeds	1.0 (0.9)	1.2 (1.1)
Frontotemporal lobar degeneration		
White matter changes	1.0 (1.0)	1.0 (1.0)
Cerebral amyloid angiopathy	0.0 (0.0)	0.0 (0.0)
Lacunar infarcts	0.2 (0.5)	0.7 (0.6)
Territorial infarcts	0.0 (0.0)	0.0 (0.0)
Lobar haematomas	0.0 (0.0)	0.0 (0.5)
Cortical micro-infarcts	0.0 (0.0)	0.7 (0.6)*
Cortical micro-bleeds	0.8 (0.9)	1.0 (1.0)
Lewy body disease		
White matter changes	0.0 (0.0)	0.9 (1.2)
Cerebral amyloid angiopathy	0.0 (0.0)	0.9 (1.2)
Lacunar infarcts	0.0 (0.0)	0.1 (0.4)
Territorial infarcts	0.0 (0.0)	0.1 (0.3)
Lobar haematomas	0.0 (0.0)	0.1 (0.5)
Cortical micro-infarcts	0.3 (0.6)	0.7 (1.6)
Cortical micro-bleeds	1.7 (1.2)	1.2 (1.3)
Vascular dementia		
White matter changes	1.4 (1.4)	1.4 (1.2)
Cerebral amyloid angiopathy	0.2 (0.4)	1.6 (0.7)**
Lacunar infarcts	1.6 (1.7)***	0.2 (0.4)
Territorial infarcts	0.8 (1.0)	0.7 (0.8)
Lobar haematomas	0.2 (0.4)	0.0 (0.0)
Cortical micro-infarcts	1.4 (2.1)	1.2 (1.3)
Cortical micro-bleeds	1.7 (0.9)	1.4 (0.5)

*p*** ≤ 0.001: highly significant, **p ≤ 0.01: significant, *p ≤ 0.05: moderately significant*

nificantly increased ($p \leq 0.01$) while CAA predominated in the mixed form ($p \leq 0.001$) (Table IV).

Discussion

The present study confirms that, overall, patients with mixed dementia are older than those with a pure neurodegenerative or cerebrovascular disease [24]. However, there are differences according to the disease type: mainly patients with AD and FTLD, who are the most frequent in this series, display this age difference, but not those with LBD and VaD.

AD with VaD or LBD features are the most frequent types of mixed dementia [4,17,28].

The increase of CAA with age is the leading cause of mixed AD group in elderly patients, leading to more frequent cerebral infarcts and lobar haematomas [10,14,16-18,21,24].

Brains with FTLD display a low incidence of cerebrovascular lesions [11]. The reason why patients with FTLD and ALS have a favourable vascular risk profile is unknown [19]. The severe frontotemporal WMCs are related to the neurodegenerative disease itself and are not of vascular origin [12]. The increased number of CoMIs in the mixed form, compared to the pure form of FTLD, is probably related to the much older age of the former [6].

Our study confirms that pure and mixed forms of LBD mainly occur in the middle old and the oldest old patients [34]. Pure and mixed LBD brains show a high incidence of CoMIs [14,17]. Additional AD features and CAA contribute less to the small cerebrovascular in LBD pathology [13,15,35].

Different types of cerebrovascular lesions have already been described in pure VaD and mixed AD-VaD brains, with mainly lacunar infarcts in the former and severe CAA in the latter [16,17].

In conclusion, the older age of mixed dementia cases is mainly due the combination of the severity of the AD and LBD pathologies, and to CAA-related cerebrovascular lesions. This study argues again that mixed AD-VaD has to be considered as the end stage of AD [16].

Disclosure

The authors report no conflict of interest.

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