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ORIGINAL COMMUNICATION

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The impact of cerebrovascular lesions in Alzheimer disease

A comparative autopsy study

Abstract *Background* Recent epidemiological and clinico-pathological data suggest overlaps and some synergistic effects between Alzheimer disease (AD) and cerebrovascular pathology, but the results of studies of the relationship between the two types of lesion have been controversial. *Objective* Comparison of the frequency of cerebral infarcts, hemorrhages and minor cerebrovascular lesions in AD and age-matched control brains. *Subjects and methods* 730 consecutive cases of autopsy-proven AD and 535 age-matched controls were compared using current routine and immunohistochemical methods. *Results* The total prevalence of cerebrovascular pathology in AD was significantly higher than in controls (48.0 vs 32.8 %, $p < 0.01$). Minor to moderate cerebrovascular lesions (lacunes, amyloid angiopathy with and without minor vascular lesions) were more frequent in AD than in controls (31.6 vs 23.4 %), the frequency of severe vascular pathology (old and recent infarcts and hemorrhages) in AD was significantly higher than in controls (16.7 % and 7.4 % vs 2.1 % and 3.2 %, respectively, $p < 0.01$). There was no correlation between the severity of cerebral amyloid angiopathy with minor to severe subcortical lacunes and Ammon's horn sclerosis or to acute and old ischemic infarcts. On the other hand, acute and old cerebral hemorrhages were significantly correlated with severe amyloid angiopathy. The brain weight and severity of cognitive decline did not correspond to the degree of vascular pathology, but higher neuritic Braak scores and reduced brain weight contributed to the production of cognitive impairment. *Conclusion* In accordance with previous findings in AD and in Parkinson disease, our data indicate a higher incidence of cerebrovascular lesions and greater susceptibility to death from stroke in AD in the population studied, but further prospective clinico-pathological studies are warranted.

Key words Alzheimer disease · cerebrovascular lesions · cerebral amyloid angiopathy · Braak stageing · clinico-pathological correlations

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Introduction

Cerebrovascular pathology frequently coexists with Alzheimer disease (AD) and may show synergistic effects on cognitive decline [1–8, 14, 28–30], but the results of epidemiological and clinico-pathological studies on the relations between the two types of lesion are controversial [3, 4, 6–8, 11, 26, 32–34]. While the impact of small concomitant cerebrovascular lesions (CVLs) was considered to be unimportant for cognitive decline in severe AD [13, 20], others showed that the presence of CVLs may play an important role in determining the presence and severity of the clinical symptoms of AD, lowering the threshold of AD pathology required for the clinical expression of dementia [6, 8, 25, 32–34], and that patients with concomitant infarcts are older, more severely demented, but have less severe AD pathology than patients without CVLs [3, 8, 32, 34]. In a consecutive autopsy series of elderly demented patients (Mini-Mental State Examination [9] (MMSE) > 20), 81.9 % revealed AD-related pathology, but only 34.9 % were "pure" AD

(CERAD [24] positive, Braak stages [2] 5–6), while 26.7 % macroscopically showed accompanying CVLs (lacunes, hippocampal sclerosis, leukoencephalopathy, old or fresh infarcts, hemorrhages associated with cerebral amyloid angiopathy/CAA/, or mixed AD + vascular encephalopathy), the rest presenting with other additional pathologies [14]. In another series of 424 autopsy-confirmed AD cases, comparison was made between those without (67.4 %) and with vascular pathology (32.6 %) [15]. In both series, AD patients without vascular pathology were older than those with CVLs (79.8 vs 84.6 years). While their Braak stages were comparable (5.1 AD vs 4.7–4.9), the severity of cognitive decline in AD without additional vascular pathology was higher than in those with CVLs (mean MMSE 1.7 vs 5.0 to 8.0). No comparison was made with age-matched controls [15]. Much higher frequency of vascular pathology (82.1 %) was reported in a retrospective study of the Einstein Aging Study of 67 patients with autopsy-proven AD, 44.8 % with minimal to modest degree of CVLs (CAA and/or 1–2 lacunar infarcts or mild LE), 38.3 % with severe cerebrovascular pathology (at least > 2 lacunes, medium to large vessel strokes, multiple microinfarcts, hippocampal sclerosis or severe LE) and only 17.9 % without additional vascular pathology [3]. The group with modest vascular pathology was slightly younger at death than the other two groups (78 ± 11 years vs 84 ± 11/no vascular pathology) and 86 ± 8 years (severe vascular pathology); otherwise the three groups did not differ significantly in cognitive scores, gender ratio, ApoE ε4 frequency, brain weight, or Braak stage. Unlike the findings in other studies, the extent of vascular pathology did not influence clinical expression or severity of AD pathology [3]. In a preliminary study of 173 autopsy-proven AD and 130 age-matched control brains, we observed a higher incidence of vascular pathology than in controls (56.5 % vs 42.4 %), but the results for minor to moderate CVLs (43.8 % vs 33.9 %) and for severe CVLs (12.7 vs 8.5 %) were not significant ($p < 0.03$) [16]. In all these studies, Braak score and brain weight, but not the severity of vascular pathology, contributed to the production of cognitive impairment.

We retrospectively compared the frequency of additional cerebrovascular pathology in two large consecutive groups of autopsy-proven AD and age-matched control subjects.

Subjects and methods

Consecutive cases (n = 730, 252 men and 478 women, aged at death between 57 and 103, mean 82.4 ± 4.4 (SD) years) from the research files of the Institute of Clinical Neurobiology, Vienna, Austria, derived from three large general hospitals in Vienna (two acute and one chronic hospital) between 1 Jan. 1992–31 Dec. 2001, which clinically fulfilled the NINDCS-ADRDA [22] and the Consortion to Establish a Registry for Alzheimer Disease (CERAD) criteria of probable AD [24] and were confirmed at autopsy as definite AD using the NIA criteria [19], the CERAD criteria [24], neuritic Braak & Braak staging [2], and the National Institute for Aging and Reagan Institute (NIA-RI) criteria for AD [12] were included. Some of the patients had been in the Vienna Prospective Dementia Study [1], with regular clinical and neuropsychological examination, including MMSE evaluation [9], no later than 6 months prior to death. All brains were sectioned according to a well-established protocol in the Institute of Clinical Neurobiology [1, 14, 15]. Coronal slices of around 1 cm in thickness were cut through the cerebral hemispheres and transverse slices through the brainstem and cerebellum. The presence of recent and old ischemic lesions, lacunes, and cerebral hemorrhages was documented at both naked eye and histological sections. Fresh brain weight was reported in most of the cases. Multiple formalin-fixed brain sections from isocortex, limbic areas, basal ganglia, brainstem, and cerebellum were examined using routine stains, modified Bielschowsky silver impregnation, and immunohistochemistry for tau protein (antibody AT-8), amyloid β peptide (antibody 4G8), and a-synuclein (monoclonal and polyclonal antibodies) [see 2, 14–16]. All autopsy-proven AD cases had been clinically demented (MMSE < 20), were NIA-Khachaturian positive, CERAD B, B/C or C, and revealed neuritic Braak stages 5 and 6. As in another recent autopsy study of AD brains [3], cases corresponding to the autopsy criteria of Lewy body dementia [22] and/or Lewy body variant of AD/LBV/AD/[10] were excluded.

At variance with the study by Crystal et al. [3], subjects were divided into 5 groups of vascular pathology: 1. AD brain without concomitant vascular pathology (n = 380); 2. AD brains with additional minimal (1 +) CVLs (1–2 small lacunes, mild to moderate degrees of CAA with or without mild CVLs, moderate LE; n = 160); 3. AD brain with moderate (2 +) vascular pathology (> 2 lacunes or severe lacunar state in basal ganglia and/or white matter, hippocampal sclerosis, severe CAA with moderate CVLs; n = 70), 4. AD brain with severe (3 +) vascular pathology (old or recent large or small vessel infarcts, multiple microinfarcts, old or recent cerebral hemorrhages; n = 120). (this last group was divided into two subgroups: 3 + a with old infarcts or hemorrhages (n = 68), and 3 + b with acute infarcts or hemorrhages less than 1–2 days old (n = 50)); 5. AD brain with additional non-vascular pathology (old concussions, chronic subdural hematoma; n = 2). The severity of CAA was globally subdivided into 5 degrees (0 to 4) [see 15, 16], but it was not correlated with the severity of amyloid β brain load.

The *control group* consisted of 535 consecutive autopsy cases from the same sources in the years 1991 to 2001 (229 men and 306 women aged at death between 60 and 100; mean 83.0 ± 9.1 years) without known neurological or psychiatric disease who had died unexpectedly, from myocardial infarction, pulmonary embolism, cardiac insufficiency, shock or cancer. Postmortem examination had been made to evaluate the cause of death, and neuropathological study was the same as in AD cases. None of them had been clinically demented (MMSE > 25), around 25 % were Khachaturian questionable or positive, all were CERAD 0 or A (23 %), most showed Braak scores 0 to 2, and only 29 % were Braak stages 3 or 3–4. The ApoE allele was determined only in part of the brains, using a semi-nested PCR method for autopsy tissues from formalin-fixed blocks followed by a two enzyme restriction analysis employing AfIII and HaeII [31]. The examination of brains was unblinded. Chi square tests were used for statistical analysis, $p < 0.01$ was considered as statistically significant.

Results

Among 730 consecutive cases of autopsy-proven AD, 52 % were free of essential cerebrovascular pathology except for minor to moderate CAA without CVLs as compared with 67.2 % in age-matched controls ($p < 0.01$; Fig. 1). The Braak stages of these patients were 5 and/or 6 (mean 5.2) indicating progressed AD (Fig. 2). Neu-

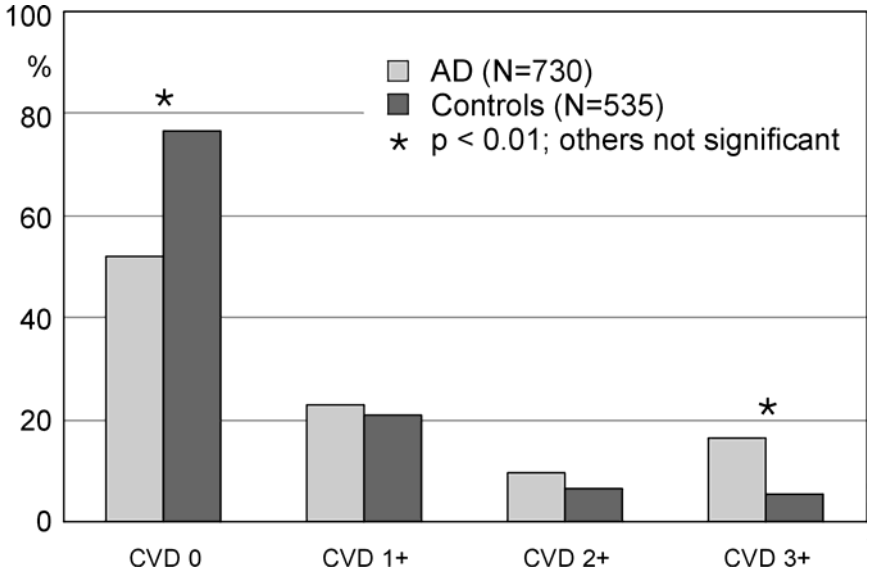

Fig. 1 Frequency of vascular pathology in AD brains and control cases

ropsychological testing performed in 46 of these patients revealed severe dementia (mean MMSE 1.1/30). Brain weight in AD without CVLs was significantly lower than in age-matched controls (mean 1014 vs 1196 g, $p < 0.001$) (Fig. 2). The incidence of severe CAA (grade 3 and 4) in brains without essential CVD was around 35 %, that of minor to moderate CAA 64 %, while only in 1 % was no definite CAA detected.

Minor vascular pathology, mainly single lacunes and moderate to severe CAA without CVLs, was seen in 22 % of severely demented AD patients; their mean MMSE (1.2/30) and their mean Braak score of 5.0 (range 4–6) were practically identical with that of "pure" AD cases (Fig. 2). The incidence of CAA in AD brains was 97.7 %, 24 % of which showing severe grades of CAA, half of them with additional CVLs (mainly hemorrhages, less frequent infarcts or lacunes) and half without as compared with 97.6 % CAA in a previous autopsy series of AD [14]. There was no correlation between the severity of CAA and both minor and multiple subcortical lacunes. Minor lacunes and mild leukoencephalopathy were accompanied with severe CAA in 31 % and with mild CAA in 66 %, while in 2 % no CAA was detected. Hippocampal sclerosis had a similar prevalence of CAA (30:70 %). There were no severe degrees of CAA or accompanying hemorrhages seen in the control series showing mild CVLs in 20.9 %.

Moderate vascular pathology (> 2 lacunes or severe lacunar state, hippocampal sclerosis or LE) was seen in 9.6 % of demented AD patients, their mean MMSE 2.1/30

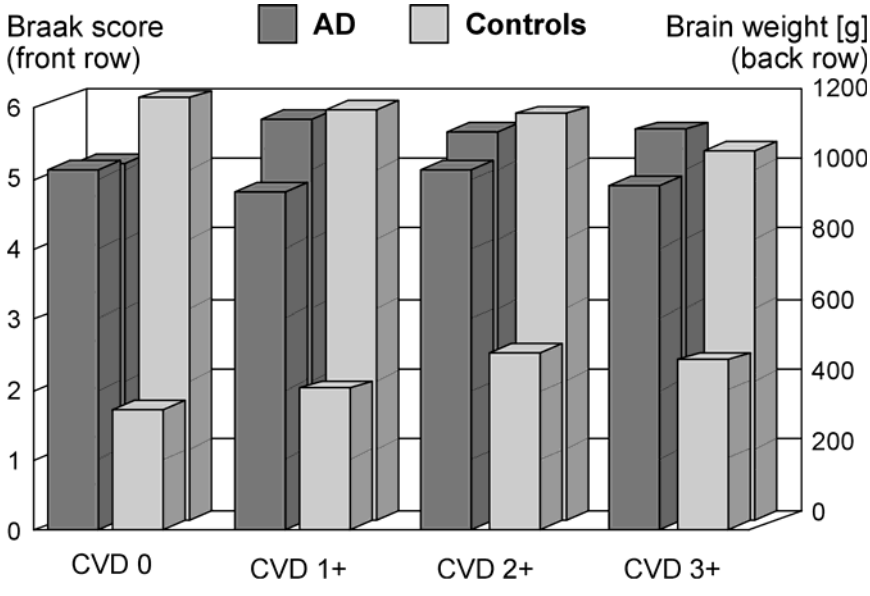

Fig. 2 Braak scores and mean brain weight in AD brains without and with vascular pathology of various degrees and controls

and their mean Braak stage of 5.0 (range 4–6) were the same as in both "pure" AD and that with mild vascular pathology. The mean age of AD cases with severe vascular pathology was not significantly higher than that in "pure" AD patients and those with mild CVLs (84.6 vs 80.2 and 81.97 years, respectively).

The incidence of *moderate vascular pathology* in controls was lower than that in AD patients (6.5 vs 9.6 %), with a mean age at death comparable to AD cases with similar vascular pathology (85.7 vs 84.6 years). It was slightly higher than in both "pure" AD cases and controls without vascular pathology (80.2 vs. 79.5 years), while their mean Braak stage of 2.5 (range 0–4) was significantly lower than in all AD cases with comparable vascular pathology (Fig. 2).

Combined mild to moderate vascular pathology present in 31.6 % of AD brains (MMSE 0–10; mean 2.3; $n = 24$) was insignificantly higher than in controls (27.4 %) ($p > 0.05$), with significant differences in the Braak score (5.0 vs 2.4), but similar mean age at death (AD 83.27 vs 94.49 years controls). The mean brain weight in AD brains with mild to moderate vascular pathology did not differ significantly from that of controls with comparable cerebrovascular pathology (mean 1138 vs 1119 g), while it was significantly lower in "pure" AD (mean 1014 g) than in AD with mild to moderate CVL (mean 1139 and 1110 g, respectively) ($p > 0.05$) (Fig. 2).

Severe cerebrovascular pathology, including old and recent large and small vessel infarcts and hemorrhages, was seen in 16.4 % of AD patients who had a mean MMSE of 2.6 ($n = 12$), a mean Braak score of 5.0, and a brain weight which was almost identical with that of AD cases with mild or moderate vascular pathology (1106 g vs. 1100 and 1115 g), but was higher than in severe "pure" AD (Fig. 2). Severe vascular pathology comprised a) 58 cases with old infarcts and 10 cases with old hemorrhages (all with mean Braak stages 5.0 and mean MMSE between 3.1 and 4.8, and b) 38 cases with recent ischemic infarcts and 22 cases with recent hemorrhages, most of them associated with severe CAA, while only one single control case died from acute cerebral hemorrhage. In cases with acute or old ischemic infarcts, only around 30 % revealed severe CAA and 70 % showed mild to moderate degrees of CAA, while acute and old hemorrhages were associated in almost 90 % with severe degrees of CAA. Mean Braak stage of the acute group was 4–9 and mean MMSE 3/30. Recent ischemic infarcts involved the supply areas of the middle and posterior cerebral arteries (around 40 %), multiple small cortical areas mainly in the border zones (12 %), the basal ganglia and brainstem (20 % each), and the cerebellum (8 %), while old infarcts predominantly involved the ACM/ACP areas (45 %) and basal ganglia (around 30 %); less frequent were multiple small cortical, brainstem and cerebellar infarcts (10 to 15 % each). In comparison, age-matched controls showed severe vascular pathology in 5.4 % – 1.8 % old and 2.6 % recent ischemic infarcts or hemorrhages – with only minimal cognitive impairment (MMSE < 28), much lower Braak stage (mean 2.4, range 0–4), and almost the same brain weight as in "pure" AD (1048 g vs. 1014 g in AD (Fig. 2). The incidence of acute ischemic infarcts and, particularly, of acute cerebral hemorrhage was significantly higher in AD patients than in controls and may indicate a greater frequency of stroke-related deaths in the AD population, particularly related to acute cerebral hemorrhage. No significant differences of the ApoE ε3 and ε4 allele frequencies were seen between AD patients with and without vascular pathology (data not shown).

Discussion

In both a preliminary study in a small cohort [16] and the present larger consecutive series of autopsy-proven AD cases, cerebrovascular pathology of various degrees was absent in a total of 43.5 and 52 %, respectively, which was significantly more frequent than in age-matched controls (57.6 and 76.6 %, respectively) and in another small cohort of autopsy-confirmed AD brains [3]. As in the latter cohort [3], we observed no significant differences in the severity of cognitive decline between AD without and with vascular pathology, while in a previous clinico-pathological study, the latter showed a lower prevalence of severe dementia than "pure" AD patients [14]. Given the very low MMSE scores in all groups, there might be a floor effect and the lack of correlation between cognition and CVLs might be, at least in part, related to this methodological aspect. Both the degree of neuritic pathology (Braak stages) and average brain weight were similar in all groups without relation to the severity of CVLs, but brain weight was significantly higher than in non-demented age-matched controls. There were no significant differences in the frequency of ApoE ε3 and ε4 alleles. These findings correspond with those of other recent studies [3, 14, 16], but are at variance to others who reported either more severe dementia or less severe AD pathology in demented AD patients with concomitant CVLs [3, 6, 8, 25–27, 32–34]. The same applies to the fact that we observed no correlation between the severity of CAA and mild to moderate vascular pathology except for acute and old cerebral hemorrhages. These and other data suggest that the severity and distribution of neuritic AD lesions have more impact on the development of dementia, at least in progressed stages of AD, while in early stages of AD additional cerebrovascular pathology may unmask or promote the development of cognitive decline [3, 6, 14, 16, 21, 25, 27, 32–34].

In a recent comparative retrospective study of autopsy-proven Parkinson's disease (PD) of the Lewy body

type and age-matched controls the total frequency of CVLs in PD was higher than in controls (44.0 vs 32.8 %), while acute, often fatal ischemic infarcts were less frequent in PD patients (1.8 vs 2.6 %). These data neither suggest significant increase of dementia related to the prevalence of CVLs nor a greater susceptibility of stroke-related deaths in the PD population [15], while in another recent study of a large cohort of autopsy-proven PD cases, dementia was significantly related to the severity of coexistent Alzheimer pathology but not to coexistent cerebrovascular pathology [17]. These data indicate 1. similarities between AD and PD with respect to the development of cognitive impairment which appears largely independent from superimposed cerebrovascular pathology but mainly related to the degree of AD pathology, and 2. differences in the incidence of vascular pathology, which is more frequent in AD patients, many of them having a previous history of stroke, both incidences being significantly more frequent than in age-matched controls. As there are still very few data on the relations between cerebrovascular and AD pathologies, their impact on cognitive impairment and on the incidence of stroke-related death in AD, further prospective clinico-pathological studies are warranted.

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