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Prevalence of cerebrovascular lesions in patients with Lewy body dementia: A neuropathological study

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ABSTRACT

Background: The co-existence of vascular pathology in patients with Lewy body dementia (LBD) is still a matter of debate. This study analyses the prevalence and the severity of cerebrovascular lesions in post-mortem brains of patients with LBD.
Patients and methods: Twenty brains of demented patients with autopsy-proven Lewy body disease were compared to 14 brains of age-matched controls.
Results: Associated Alzheimer disease (AD) features, stages I–IV, were present in 70% of the LBD brains and in 7% of the controls ($P < 0.001$). Cerebral amyloid angiopathy (CAA) was only present in 30% and lipohyalinosis in 10%. A semi-quantitative analysis, performed on a coronal section of a whole cerebral hemisphere and on a horizontal section through the pons and the cerebellum, revealed significantly more mini-bleeds in the LBD brains ($P = 0.007$), predominantly in the cerebral cortex ($P = 0.03$). Other cerebrovascular lesions were only rarely observed. Comparison of the LDB brains, with and without moderate AD features and CAA, showed no difference in the severity of the cerebrovascular lesions including mini-bleeds.
Conclusions: The prevalence of mini-bleeds in LBD brains appears to be independent from the co-existence of moderate AD pathology and CAA. It is more probably due to disturbances of the blood–brain barrier, related to the neurodegenerative process itself.

1. Introduction

Alzheimer's disease (AD) is by far the most common degenerative dementia, followed by vascular dementia (VaD), Lewy body dementia (LBD), and frontotemporal dementia. These dementia subtypes have more overlapping signs and symptoms than defining ones [1,2]. Multiple and different associated pathological features may contribute to a clinical symptom constellation in LBD [3]. Alzheimer-related lesions have an influence on the progression of the neurodegenerative process and on the cognitive decline of LBD patients as well as of Parkinson patients with dementia. On the other hand, the progression of the disease and the cognitive decline are considered as largely independent from co-existent vascular pathology [4,5]. Lewy body pathology is considered inversely correlated to the severity of atherosclerosis, infarcts and small-vessel disease. On the other hand cerebral amyloid angiopathy (CAA), associated to AD features, is frequent in patients with LBD [6,7].

The present post-mortem study compares the prevalence and the severity of cerebrovascular lesions and their responsible factors in a series of brains from patients with LBD to controls. In addition LDB brains with and without coexisting AD features and CAA are mutually compared.

2. Materials and methods

2.1. Dementia and control population

From 2000 up to 2010, 158 consecutive patients with a clinical history of a neurodegenerative dementia came to autopsy: in 20 (13%) of them the neuropathological diagnosis of LBD was made.

During the same period of time, 14 post-mortem brains of age-matched controls were obtained. The controls consisted of brains of elderly patients who died from an illness not related to a brain disease.

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2.2. Clinical data and vascular risk factors

Thirteen (65%) patients had been followed-up in the Memory Clinic of the Lille University Hospital. Seven (35%) patients were issued from a general hospital. Detailed clinical data, including vascular risk factors were available in 18 patients (90%).

The pre-mortem diagnosis of LBD had been retained in 9 of the 20 patients. The presumed clinical diagnosis was AD in 5, Parkinson disease in 4 and Creutzfeldt–Jacob disease in 2 patients.

2.3. Neuropathological analyses

The brain tissue samples were first used for diagnosis and afterward integrated in the Lille Neuro-Bank, dependant from the Lille University and co-federated by the "Centre des Resources Biologiques", acting as institutional review board. The neuropathological evaluation was performed blinded to history and clinical data.

2.3.1. Neurodegenerative lesions

Several small samples of the cerebral cortex and of the hippocampus of one fresh cerebral hemisphere were taken for histochemical examination. The remaining brain was fixed in formalin and, after 3 weeks, samples were taken from the primary motor cortex, the associated frontal, temporal and parietal cortex, the primary and secondary visual cortex, the cingulate gyrus, the basal nucleus of Meynert, the amygdaloid body, the hippocampus, basal ganglia, mesencephalon, pons, medulla and cerebellum. Slides from paraffin-embedded sections were immuno-stained for protein tau, β-amyloid, α-synuclein, prion protein, TDP-43 and ubiquitin.

The post-mortem diagnosis of DLB was made according to the Kosaka and McKeith criteria [8]. Additional AD features were staged according to the classification of Braak and Braak [9]. CAA was evaluated, according to the CERAD criteria [10].

2.3.2. Cerebrovascular lesions

The gross visible cerebrovascular lesions and the small ones, detected on microscopical examination of the small samples, were carefully noted. In addition a semi-quantitative evaluation of small microscopical lesions was performed on a whole coronal section of a cerebral hemisphere, at the level of the mamillary bodies, and a horizontal section through the mid-pons and both cerebellar hemispheres, after staining with haematoxylin–eosin, luxol fast blue (LFB) and Perl. The considered cerebrovascular lesions were bleedings, infarcts, lacunes and white matter changes. Micro-bleeds were defined as small macroscopically visible lesions of 1 mm or 3 mm diameter on gross examination. They consisted of red blood cells, when recent, and of macro- and siderophages, when older. Mini-bleeds were not visible macroscopically. They were found mainly located around small vessels on microscopical examination (Fig. 1) [11]. Isolated Perl positive deposits were not retained as mini-bleeds [12]. The term "mini-bleed" was used to avoid confusion with the term "micro-bleed", used in the MRI literature [13–15]. The degree of white matter changes was mainly evaluated on the LFB stained sections [16]. The degree of CAA was evaluated on slides from the hippocampus, the associated parietal and temporal cortex, and the visual cortex, stained with anti-β-amyloid. The brains were classified as CAA, when a majority of anti-β-amyloid stained vessels were present in at least three of the four examined samples and as not-CAA, when absent or scarce, in case of a few stained vessels in one or two slides. This classification was already made at the time of the neuropathological diagnosis and prior to the start of the present quantification study.

A semi-quantitative scale, ranking (R) 0–3, was used to evaluate the severity of the white matter changes and the frequency of micro-infarcts and of micro- and mini-bleeds, according to the previous described method [11]. The latter were also evaluated according to their location in the cerebral cortex and cortical-subcortical junction, the deep white matter, the striatum, the thalamus, the pons and the cerebellar hemispheres.

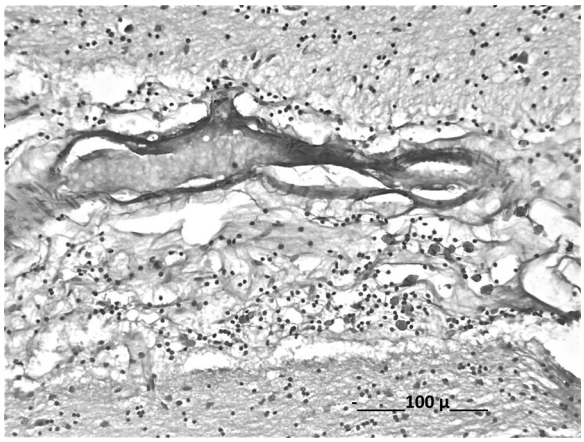

Fig. 1. Old cortico–subcortical mini-bleed composed of perivascular monocytes, macrophages and siderophages, stained by haematoxylin–eosin.

The white matter changes were restricted to the periventricular regions (R1), scattered in the centrum semiovale (R2) or forming confluent lesions (R3). For the micro-infarcts and micro- and mini-bleeds R1 corresponded to 1–2, R2 up to 5 and R3 to more than five lesions. Also the regional distribution of the mini-bleeds was determined.

The degree of amyloid angiopathy was evaluated on the four cortical slides, stained with anti-β-amyloid according to the number of affected vessels, as absent (R0), scarce (R1), moderate (R2) and severe (R3).

2.4. Classification of the comparison groups

The prevalence and the severity of cerebrovascular lesions were compared in the brains with LBD to the controls. In addition a subgroup analysis was performed comparing the severity of the cerebrovasular lesions in the LDB brains with ($n = 14$) and without AD features and CAA ($n = 6$).

2.5. Statistical analyses

The statistical analysis compared the items of the LBD group with the control group and of the LBD subgroups, with and without moderate AD features and CAA. Univariate comparisons of unpaired groups were done 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 was set at 0.05, two-tailed.

3. Results

The median age of patients with LBD was 78 (inter quartile range [IQR] 75–87) years versus 74 (IQR 73–86) years in the controls ($P = 1.0$). Male gender was 70% in the former and 37% in the latter group ($P = 0.05$). Vascular risk factors (arterial hypertension, diabetes, hypercholestolemia and smoking) and the use of antithrombotic treatment were similar in both groups (Table 1).

Moderate AD features (stages I–IV) were found in 70% of the brains with LBD and in 7% of the control brains ($P < 0.001$). CAA was observed in 30% of the LBD versus 7% in the controls brains