Frequency and topography of small cerebrovascular lesions in vascular and in mixed dementia: a post-mortem 7-tesla magnetic resonance imaging study with neuropathological correlates

Jacques De Reuck, Florent Auger, Nicolas Durieux, Vincent Deramecourt, Claude-Alain Maurage, Charlotte Cordonnier, Florence Pasquier, Didier Leys, Regis Bordet

Centre Hospitalier Régional Universitaire de Lille (CHRU), Lille, France

Abstract

Introduction: Mixed dementia (MixD) refers to a combination of definite Alzheimer's disease (AD) and vascular encephalopathy. The existence of a "pure" type of vascular dementia (VaD) is controversial. There is a need to find magnetic resonance imaging (MRI) characteristics allowing the distinction between VaD and MixD. The present post-mortem 7.0-tesla MRI compares the frequency or severity and the topography of the small cerebrovascular lesions in brains of patients with VaD and with MixD.

Material and methods: Based on neuropathological criteria, 14 brains were classified as VaD, 24 as MixD and 11 as controls. Three coronal sections of a cerebral hemisphere and a horizontal section of a cerebellar hemisphere underwent T2 and T2* 7.0-tesla MRI examination. The mean values and topographic distribution of white matter changes (WMCs), lacunar infarcts (LIs), cortical microbleeds (CoMBs) and cortical microinfarcts (CoMIs) were determined and compared between the different groups.

Results: Compared to the controls, both VaD and MixD brains had significantly more severe WMCs and increased numbers of CoMBs and CoMIs. Lacunar infarcts predominated only in the VaD cases. On mutual comparison of VaD and MixD brains, CoMBs and CoMIs predominated in the frontal lobe and the cerebellum of VaD, while were mainly present in the occipital lobe of MixD. White matter changes predominated in the temporal lobe of MixD cases. Lacunar infarcts were significantly increased in the corona radiata and putamen of VaD patients.

Conclusions: The present post-mortem MRI study shows clear differences in the distribution and the types of cerebrovascular lesions on high-field MRI, confirming that VaD and MixD are different diseases.

Key words: post-mortem 7.0-tesla MRI, vascular dementia, mixed dementia, topographic distribution of small cerebrovascular lesions, cortical microbleeds, cortical microinfarcts, white matter changes, lacunar infarcts.

Communicating author:
Prof. Jacques De Reuck, CHRU Lille, EA 1046, Leopold II Laan 96, 9000 Ghent, Belgium, phone: 32 9 2218844, 32 9 2215668,
e-mail: dereuck.j@gmail.com

Introduction

Mixed dementia (MixD) refers to a combination of definite Alzheimer's disease (AD) and vascular encephalopathy. The distinction between MixD and "pure" vascular dementia is controversial [15,23]. In demented patients vascular lesions on structural magnetic resonance imaging (MRI) are often misdiagnosed as probable vascular dementia (VaD) as compared to autopsy-confirmed diagnosis [20]. Also the utility of their detection for the individual diagnosis of VaD or MixD is limited [28]. Major vascular lesions differ between VaD and MixD [17].

An important obstacle in the standardization of diagnosis is the fact that vascular brain lesions are a large group comprising heterogeneous changes that have different pathogenesis [14]. Our previous post-mortem study showed that the lesion pattern in VaD and MixD is different: while the global severity of the white matter changes is more or less similar, lacunes in the corona radiata predominate in the former and cerebral amyloid angiopathy-related lesions in the latter [9].

So there is a need to quantify and determine the topography of the different types of cerebrovascular lesions in VaD and MixD. Post-mortem MRI is an additional complement of the neuropathological assessment of these lesions [21]. 7-tesla MRI is the most suitable technique to detect small cerebrovascular lesions in post-mortem brains [26].

The present post-mortem 7.0-tesla MRI study with neuropathological correlates investigates whether there are differences in severity and topography of small cerebrovascular lesions between VaD and MixD brains in order to find neuroimaging criteria that allow the distinction between both disease entities.

Material and methods

Out of a series of 162 consecutive autopsied patients, followed up at the Lille University Hospital, who underwent a MRI examination, according to the neuropathological criteria [2,4], 14 with a diagnosis of VaD, 24 of MixD and 11 control brains, without a history of dementia or stroke, were selected.

They all underwent a post-mortem 7.0-tesla MRI examination of 3 coronal sections of a cerebral hemisphere and one horizontal section of a cerebellar hemisphere, followed by an extensive histological examination of the brain samples.

Previously obtained informed consent of the patients or from the nearest family allowed an autopsy for diagnostic and scientific purposes. The brain tissue samples were acquired from the Lille Neuro-Bank of the Lille University that is a part of the "Centres des Resources Biologiques" and acts as an institutional review board.

One fresh cerebral hemisphere was frozen for biochemical examination. The remaining hemisphere, the brainstem, and most of the cerebellum were fixed in formalin for three weeks.

Neuropathological examination

The disease diagnosis was made according a standard procedure and examination of a large number of samples. In addition to the detection of macroscopic visible lesions such as haematomas, territorial and lacunar infarcts (LIs), a whole coronal section of a cerebral hemisphere, at the level of the mammillary body and a horizontal section of a cerebellar hemisphere were taken for the semi-quantitative evaluation of the small cerebrovascular lesions such as white matter changes (WMCs), cortical microbleeds (CoMBs), and cortical microinfarcts (CoMIs).

The mean values for WMCs were the average of the ranking scores: no change (R0), a few isolated (R1), frequent 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 percentage number [6].

The diagnosis of cerebral angiopathy (CAA) was made when a majority of β-amyloid stained vessels were present in at least three of the four examined samples and as not-CAA, β when absent or scarce, in case of a few stained vessels in one or two slides [13].

Magnetic resonance imaging examination

Three coronal sections of a cerebral hemisphere were submitted to T2 and T2* MRI: a frontal one at the level of the head of the caudate nucleus, a central one at the level of the mammillary body and one at the level of the parietal and occipital lobes. In addition, one horizontal section of a cerebellar hemisphere was also examined.

A 7.0-tesla MRI Bruker BioSpin SA with an issuer-receiver cylinder coil of 72 mm inner diameter

(Ettlingen, Germany) was used, according to a previous described method [7].

The ranking scores of severity of the WMCs were evaluated separately in the different brain sections as done on the neuropathological section. Lacunar infarcts were defined as small-rounded lesions with a diameter between 3 and 15 mm in the corona radiata, internal capsule, caudate nucleus, putamen, globus pallidus, thalamus and cerebellar white matter [27]. The number and the location of the small cerebrovascular lesions were determined by consensus evaluation of three observers (JDR, FA, ND), blinded to the neuropathological diagnosis. The inter-rater reliability resulted in an interclass correlation coefficient of 0.82.

Statistical analysis

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 ≤ 0.01 for significant and ≤ 0.001 for highly significant. Values set at ≤ 0.05 but more than > 0.01 were considered as marginal significant and not included as relevant due to the relative small sample sizes.

Results

The average age at death was not significantly different between the groups: 75 ($\pm$ 10) years in the VaD patients, 76 ($\pm$ 11) in the MixD and 71 ($\pm$ 9) in the control group ($p = 0.16$). Also the gender distribution was similar with 80% males in VaD, 54% in MixD and 73% in the control groups, respectively ($p = 0.62$).

Arterial hypertension and the use of antithrombotic agents were the only more frequently found clinical vascular risk factors in the VaD and MixD patients compared to the controls (Table I).

On neuropathological examination, the semi-quantitative evaluation of the degree of severity showed a significant increase in WMCs and higher incidence of CoMIs and CoMBs in VaD as MixD compared to controls. On the other hand, LIs and territorial infarcts were only more frequent in the VaD group, while CAA related lesions were more observed in the MixD group (Table II).

Table I. Comparison of vascular risk factors between normal controls (C) and patients with vascular dementia (VaD) and mixed dementia (MixD)

Vascular risk factors	C	VaD	MixD
	($n = 11$)	($n = 14$)	($n = 24$)
Arterial hypertension	18%	86%**	75%*
Diabetes	0%	43%	33%
Hypercholesterolemia	27%	50%	46%
Smoking	18%	21%	13%
Antithrombotic use	18%	93%**	83%**

*$p \leq 0.01$; **$p \leq 0.001$

Table II. Mean values (standard deviations) of the neuropathological lesions in normal controls (C) compared to those in vascular dementia (VaD) and mixed dementia (MixD) brains

Cerebrovascular lesions	C	VaD	MixD
	($n = 11$)	($n = 14$)	($n = 24$)
White matter changes	0.4 (0.7)	1.7 (1.3)*	1.4 (1.2)*
Cerebral amyloid angiopathy	0.0 (0.0)	0.5 (0.8)	2.7 (0.5)**
Lacunar infarct	0.0 (0.0)	2.5 (0.9)**	0.2 (0.5)
Territorial infarct	0.0 (0.0)	2.0 (1.4)**	0.1 (0.4)
Haematoma	0.0 (0.0)	0.9 (1.2)	0.4 (0.7)
Cortical microinfarcts	0.2 (0.4)	2.2 (1.3)**	3.4 (1.0)**
Cortical microbleeds	0.3 (0.5)	1.7 (0.9)**	2.0 (1.3)**

*$p \leq 0.01$; **$p \leq 0.001$

The same findings were observed on the postmortem MRI, concerning WMCs, LIs, CoMBs and CoMIs (Table III).

On mutual comparison of the VaD and the MixD brain CoMBs, predominated in the frontal lobe and in the cerebellum of the former, while increased in the temporal and the occipital lobes in the latter group (Fig. 1). Cortical microinfarcts predominated in the frontal lobe and the cerebellum of the VaD group, while increased in the occipital lobe of the MixD group (Fig. 2). White matter changes predominated only in the temporal lobe of the MixD group (Fig. 3). As to LIs they were significantly increased in the corona radiata and the putamen in the VaD group (Fig. 4, Table IV).

Discussion

The present study shows a difference in the distribution and types of the small cerebrovascular lesions in patients with VaD compared to those with MixD. Their heterogeneity was already previously suspected [16,22,25]. Our previous neuropathological study demonstrated that LIs due to arteriosclerotic angiopathy are the most common lesions in VaD, while CAA related lesions are more frequent in MixD, suggesting that the latter represent the natural end-stage evolution of Alzheimer's disease [9]. There is a strong correlation between CAA and age [17,19]. However, in contrast to a previous neuropathological study [1], more territorial infarcts are observed in VaD than in MixD brains. This is probably due to more additional large-vessel disease in the former group [18].

Cortical microinfarcts predominate in the frontal lobe and in the cerebellum of VaD as cerebral arteriosclerosis is their main cause [8,18], while according to the validated Boston criteria for CAA, they predominate in the occipital lobe in MixD [10]. The same is also observed for CoMBs, although also

Table III. Mean values (standard deviations) of the MRI lesions in normal controls (C) compared to those in vascular dementia (VaD) and mixed dementia (MixD) brains.

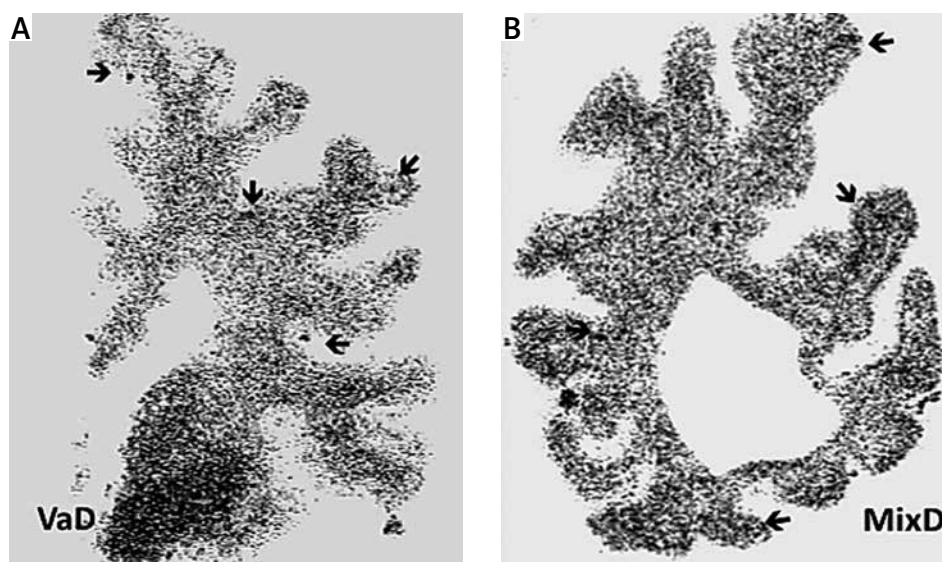| MRI lesions	C	VaD	MixD
	(n = 11)	(n = 14)	(n = 24)
White matter changes	0.2 (0.4)	1.4 (0.6)**	1.5 (0.6)**
Lacunar infarct	2.8 (1.0)	14.4 (1.9)**	3.3 (2.2)
Cortical microinfarcts	0.2 (0.4)	5.2 (1.4)**	4.9 (0.8)**
Cortical microbleeds	3.3 (1.1)	10.4 (1.6)**	9.8 (2.0)**

*p ≤ 0.01; **p ≤ 0.001*

Fig. 1. T2* MRI demonstrating the presence of cortical microbleeds (arrows) on a coronal section of the frontal lobe in a patient with vascular dementia **(A)** and of the occipital lobe in a patient with mixed dementia **(B)**.
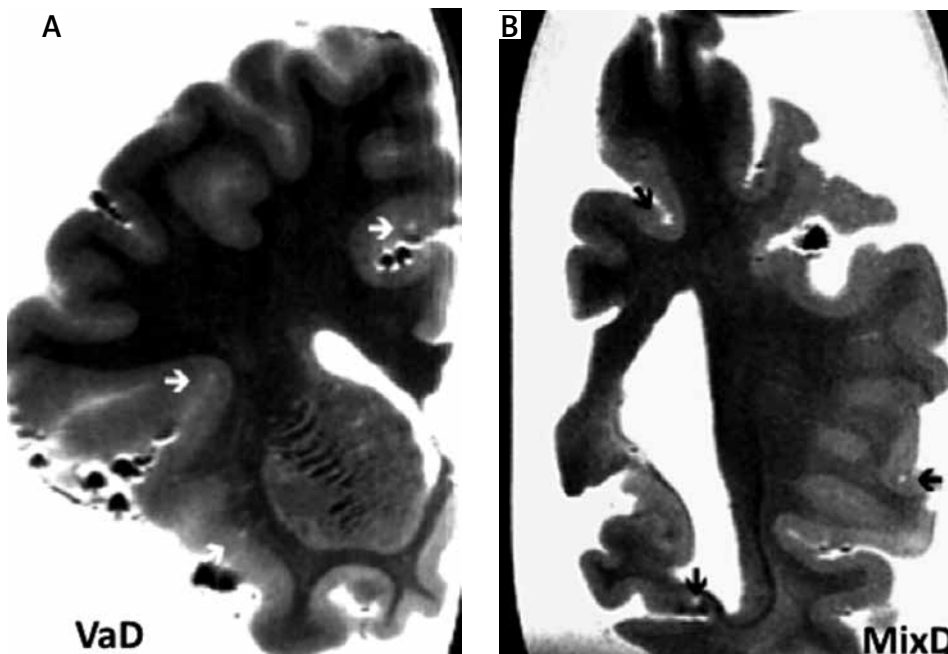
Fig. 2. T2 MRI demonstrating the presence of cortical microinfarcts (arrows) on a coronal section of the frontal lobe in a patient with vascular dementia **(A)** and of the occipital lobe in a patient with mixed dementia **(B)**.
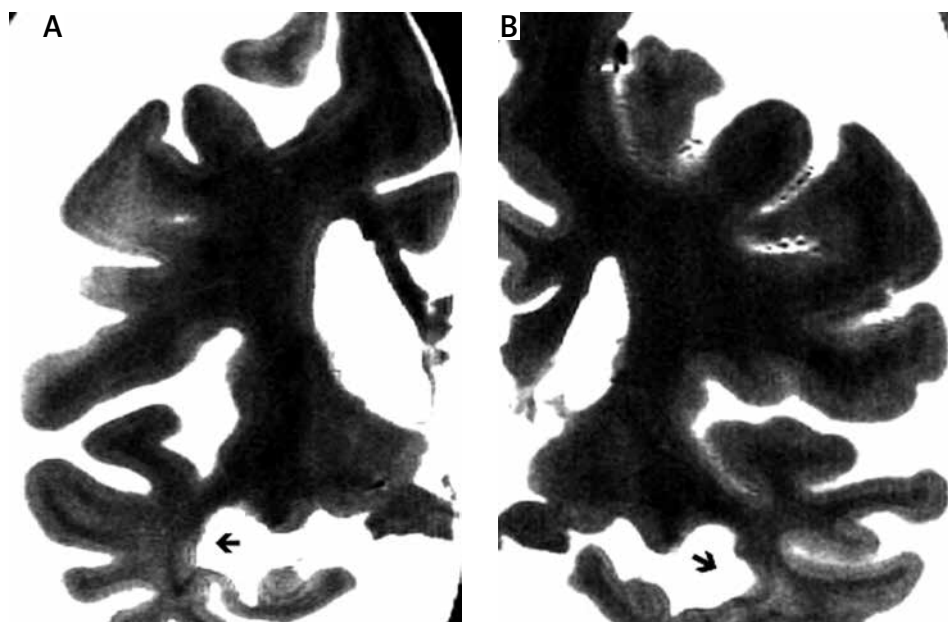

Fig. 3. T2 MRI of a central coronal section of a mixed dementia brain showing, in addition to the enlargement of the temporal horn, more selective temporal white matter changes.

highly present in the temporal lobe of MixD brains. The latter can be explained by the fact that CoMBs are not only due to micro-vascular lesions, but also to the severity of the neurodegenerative changes themselves in AD [6].

White matter changes are, as a whole, as severe in VaD as in MixD [9]. The present study shows a predominance in the temporal lobe of MixD brains associated to the temporal lobe atrophy, due to the underlying severity of the Alzheimer lesions [3].

Table IV. Comparison of the mean values (standard deviations) of the topography of the small cerebrovascular lesions on magnetic resonance imaging between brains with vascular dementia (VaD) and mixed dementia (MixD)

Cerebrovascular lesions	VaD (n = 14)	MixD (n = 24)
Cortical microbleeds		
Frontal lobe	4.1 (0.8)**	2.1 (1.0)
Temporal lobe	1.5 (0.9)	2.6 (1.0)**
Parietal lobe	1.4 (0.6)	1.6 (1.1)
Occipital lobe	1.5 (0.9)	3.4 (1.0)**
Cerebellum	2.7 (1.1)**	0.8 (1.1)
Cortical microinfarcts		
Frontal lobe	1.6 (0.8)*	0.8 (0.8)
Temporal lobe	0.4 (0.6)	0.9 (0.8)
Parietal lobe	1.3 (1.1)	1.6 (0.6)
Occipital lobe	0.5 (0.3)	1.4 (0.8)**
Cerebellum	1.9 (0.7)**	0.4 (0.6)
White matter changes		
Frontal lobe	1.6 (0.6)	1.1 (0.8)
Temporal lobe	0.3 (0.6)	1.3 (0.9)**
Parietal lobe	0.9 (0.8)	1.7 (0.9)
Occipital lobe	0.9 (0.9)	1.3 (0.9)
Cerebellum	0.8 (0.8)	0.3 (0.7)
Lacunar infarcts		
Corona radiata	7.0 (0.5)**	0.6 (0.8)
Caudate nucleus	1.1 (0.8)	0.4 (0.7)
Internal capsule	1.1 (0.6)	0.6 (0.8)
Putamen	3.2 (0.8)**	0.9 (0.9)
Globus pallidus	1.3 (0.9)	0.3 (0.4)
Thalamus	0.7 (0.7)	0.3 (0.4)
Cerebellum	0.2 (0.4)	0.0 (0.0)

$*p \leq 0.01$; $**p \leq 0.001$

Although in our previous study, only LIs in the corona radiata were found in VaD compared to MixD [12], our present study also shows an additional increase in the putamen. Their topography corresponds to the vascular territory of the lenticulostriate arteries [5]. These findings correlate well with "in vivo" measurements of lenticulostriate arteries using 7-tesla MRI that show fewer side-branches in VaD [24].

The present post-mortem MRI study shows clear differences in the distribution and the types of cerebrovascular lesions, confirming that VaD and MixD are different diseases.
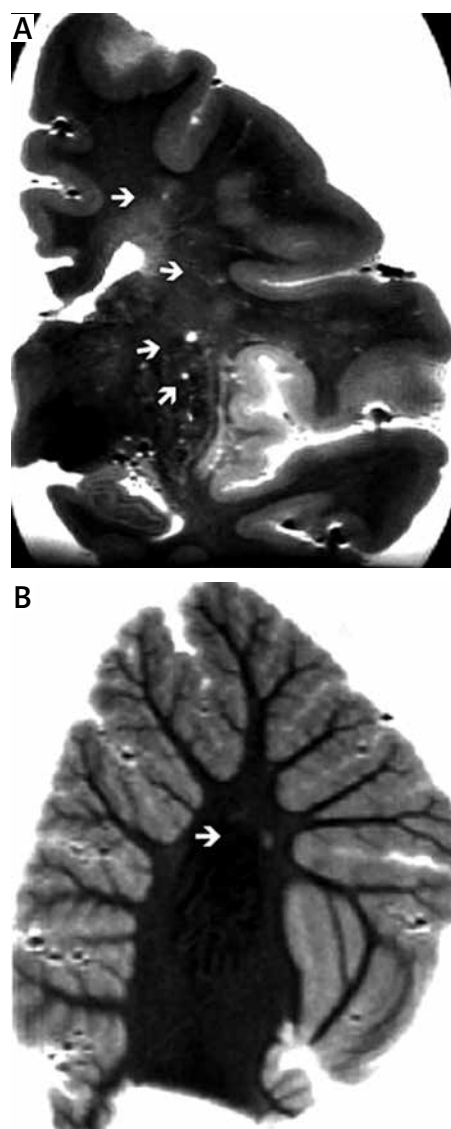

Fig. 4. T2 MRI showing on a central coronal section in addition to diffuse white matter changes also several lacunar infarcts in the corona radiata and putamen (arrows) in a patient with vascular dementia **(A)**. A lacunar infarct is also observed in the cerebellar white matter of the same patient **(B)**.

Disclosure

Authors report no conflict of interest.

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