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EC NEUROLOGY
Research Article

Cerebrovascular Lesions During Normal Aging: A Neuropathological Study with 7.0-Tesla Magnetic Resonance Imaging

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Received: January 12, 2018; **Published:** February 26, 2018

Abstract

Introduction and Purpose: Successful aging is associated with regional brain shrinkage and an increased cerebrovascular risk. The present post-mortem study investigates whether the increase of small cerebrovascular lesions is more frequent in normal elderly persons compared to adult ones.

Patients and Methods: 34 persons with normal cognition and without a stroke history underwent an autopsy. The incidence and the severity of cerebrovascular lesions in post-mortem brains of 20 adult (average age: 43 ± 12 years) and 14 elderly (average age: 75 ± 8 years) brains were examined. The neuropathological examination included a microscopic evaluation of the small lesions on a whole coronal section of a cerebral hemisphere at the level of the mamillary body. In addition T2 and T2* 7.0-tesla magnetic resonance imaging (MRI) on three coronal sections was performed.

Results: The neuropathological examination revealed more severe white matter changes (WMCs) and an increase of cortical micro-bleeds (CoMBs) in the elderly compared to the adult brains. No differences were observed concerning cortical micro-infarcts (CoMIs). Similar findings were observed on MRI examination: increased severity of WMCs and incidence of CoMBs were found to the same extend in the frontal, the central and the occipital section of the elderly brains. CoMIs were on the other hand rare and similarly distributed in the three sections of the adult and the elderly brains.

Discussion: During the aging process only increased severity of WMCs and of the incidence of CoMBs are observed. CoMIs, which are the most specific cerebrovascular lesions, are not amplified by getting older. In neurodegenerative diseases WMCs and CoMBs are mainly related to the regions with most severe changes.

Conclusion: The brain changes during normal aging are not due to the increased impact of cerebrovascular disease but rather the consequence of the age-related neuronal degeneration.

Keywords: *Brain Aging; Post-Mortem Examination; 7.0-Tesla MRI; White Matter Changes; Cortical Micro-Bleeds; Cortical Micro-Infarcts*

Abbreviations

WMCs: White Matter Changes; CoMBs: Cortical Micro-Bleeds; CoMIs: Cortical Micro-Infarcts; MRI: Magnetic Resonance Imaging; AD: Alzheimer's Dementia; LBD: Lewy Body Dementia; FTLD: Frontotemporal Degeneration; VaD: Vascular Dementia; ALS: Amyotrophic Lateral Sclerosis; CAA: Cerebral Amyloid Angiopathy; PSP: Progressive Supranuclear Palsy

Introduction

Successful aging is associated with regional brain shrinkage and an increase in vascular risk [1]. The coexistence of lacunes and large infarcts results in higher likelihood of clinical diagnosis of dementia [2]. Mixed or a load of CoMBs, with some specificity for location, is associated with accelerated cognitive decline of older people [3]. WMCs in the temporal and occipital areas are associated with increasing age [4]. Lacunar infarcts rather than WMCs are associated with further risk of decline in higher functional capacity level [5]. WMCs during the aging process are generally considered to be due to chronic ischaemia [6].

The incidence of CoMIs is significantly low in normal persons compared to those with AD, LBD and with VaD [7]. CoMIs are rare FTLD and in ALS [8]. CoMBs are frequent in AD, mainly when associated to CAA [9] and in LBD [10]. On the other hand CoMBs are rare in FTLD [11] and in PSP [12]. WMCs are most frequently observed in VaD brains but also to some extend in AD-CAA and FTLD cases with a different topographic distribution [13].

As the incidence of small cerebrovascular lesions varies in different specific neurodegenerative diseases, it is important to know their impact on the normal aging process.

The present study compares the frequency of CoMIs and CoMBs as well as the severity of WMCs on neuropathological examination and 7.0-tesla magnetic resonance imaging (MRI) of post-mortem brains between adult and elderly persons without a history of stroke or cognitive decline.

Material and Methods

Thirty-four patients, who had been admitted for a non-cerebral disease at the Lille University Hospital, underwent a general autopsy including the brain. None of them had a stroke history or known cognitive disturbances. A previously obtained informed consent 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, federated to the "Centre des Resources Biologiques" that acted as an institutional review board.

The patients consisted of 20 adults (43 ± 12 years) and 14 elderly ones (75 ± 8 years). One fresh cerebral hemisphere was deeply frozen for biochemical examination. The remaining hemisphere, the brainstem and most of the cerebellum were fixed in formalin for 3 weeks.

Neuropathological examination

The standard procedure consisted of examining samples 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 stained with haematoxylin–eosin, luxol fast blue and Perl. When necessarily immune-staining for protein tau, β-amyloid, α-synuclein, prion protein, TDP-43 and ubiquitin was performed.

A whole coronal section of a cerebral hemisphere, at the level of the mamillary body, was taken for the semi-quantitative evaluation of WMCs, CoMBs and 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 [14].

MRI examination

A 7.0-tesla MRI Bruker BioSpin SA was used with an issuer-receiver cylinder coil of 72 mm inner diameter (Ettlingen, Germany), according to a previously described method [15]. Three coronal sections of a cerebral hemisphere were submitted to T2 and T2* MRI sequences: a frontal one, a central one and one at the level of the occipital lobe. The brain sections, previously cleaned from formalin, were placed in a plastic box filled with salt-free water, of which the size did not allow significant tissue movements.

The ranking scores of severity of the WMCs were evaluated separately in the different brain sections in the same way as done on the neuropathological section. The number of the small cerebrovascular lesions was also determined by consensus evaluation. The inter-rater reliability resulted in an interclass correlation coefficient of 0.90.

Statistical analyses

Comparison was done between the adult and the elderly groups. 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.

Results

The gender distribution is not statistically different with 50% males in the adult and 78% in the elderly group. The vascular risk factors are also similar (Table 1).

Items	Adult n = 20	Elderly n = 14	p value
Average age (years with SD)	43 (±12)	75 (±8)	< 0.0001
Male gender (%)	50	78	N.S.
Arterial hypertension (%)	10	18	N.S.
Diabetes (%)	0	0	N.S.
Hypercholesterolemia (%)	15	28	N.S.
Smoking (%)	15	18	N.S.
Antithrombotic use (%)	15	25	N.S.

Table 1: *Comparison of the epidemiological data (standard deviations) between the adult and the elderly persons without a stroke history or cognitive dysfunction.*

On the neuropathological examination a statistically significant increase of the WMCs (p = 0.007) and of CoMBs (p = 0.007) in the elderly patients is observed compared to adult ones, while the other cerebrovascular lesions are absent or very low in both groups (Table 2). None of the brains display neurofibrillary degeneration or Lewy bodies in the neurons. As incidental finding one brain of a 51-year old woman has a small cerebellar infarct.

Items	Adult n = 20	Elderly n = 14	p value
White matter changes	0.0 (0.0)	1.0 (0.9)	0.007
Cerebral amyloid angiopathy	0.0 (0.0)	0.0 (0.0)	N.S.
Lacunar infarcts	0.0 (0.0)	0.0 (0.0)	N.S.
Territorial infarcts	0.1 (0.3)	0.0 (0.0)	N.S.
Cerebral haematomas	0.0 (0.0)	0.0 (0.0)	N.S.
Cortical micro-infarcts	0.0 (0.0)	0.0 (0.0)	N.S.
Cortical micro-bleeds	0.0 (0.0)	0.8 (0.7)	0.007

Table 2: *Comparison of the semi-quantitative severity scores (standard deviation) of the cerebrovascular lesions on neuropathological examination between adult and elderly brains.*

On MRI evaluation WMCs are significantly increased to the same degree in all the hemispheric sections of the elderly compared to adult brains (p ≤ 0.03) (Figure 1). CoMIs are absent or scarce without statistical differences between the three brain sections of both groups (Figure 2). CoMBs are significantly increased to the same extend in the frontal, the central and the occipital section of the elderly group (p ≤ 0.04) (Figure 3) (Table 3).

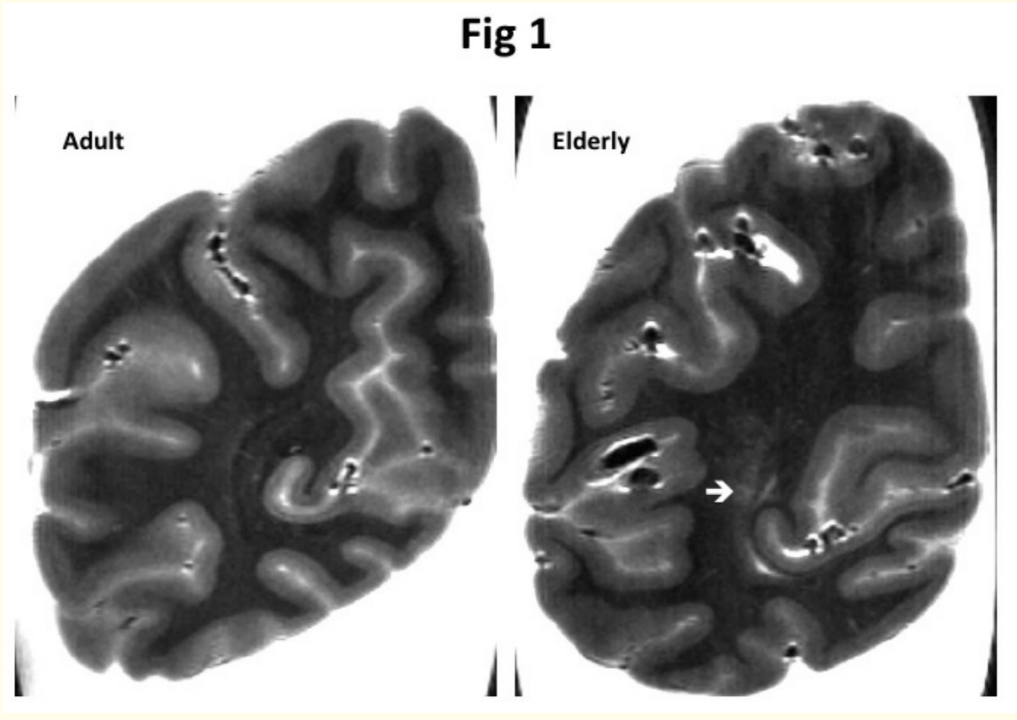

Figure 1: *Spin Echo T2 7.0-tesla MRI of occipital coronal sections of a cerebral hemisphere of an adult and an elderly brain. Periventricular hyperintensities, representing white matter changes, are only observed in the elderly brain (arrow) and absent in the adult one.*

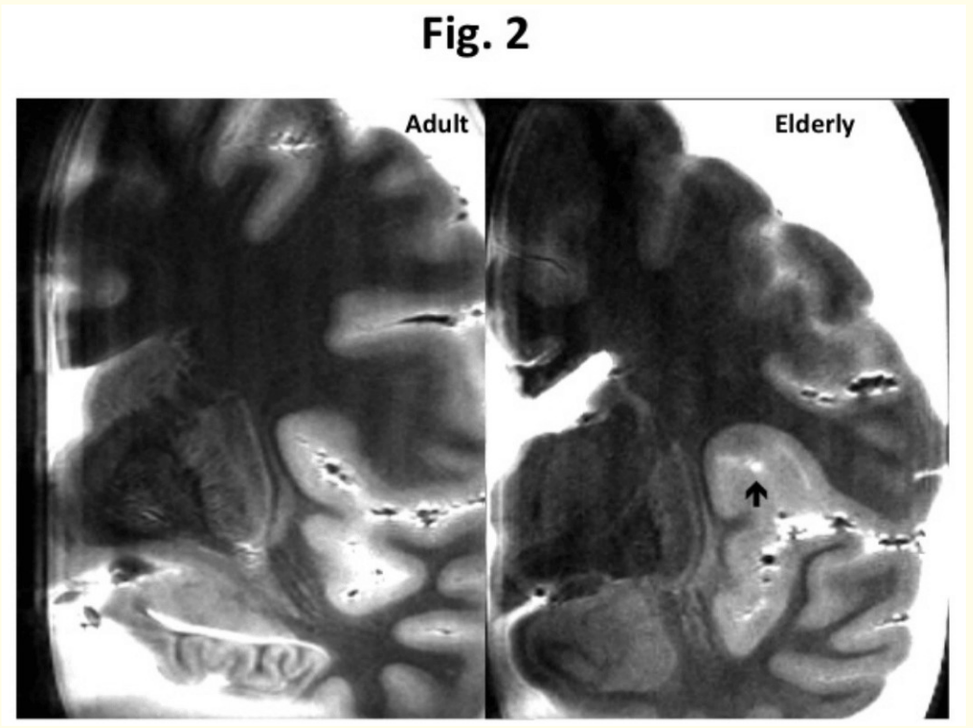

Figure 2: *Spin Echo T2 7.0-tesla MRI of central coronal sections of a cerebral hemisphere of an adult and an elderly brain. A single cortical hyperintensity, representing a small insular infarct, is observed in the elderly brain (arrow). No infarct is present in the adult brain.*

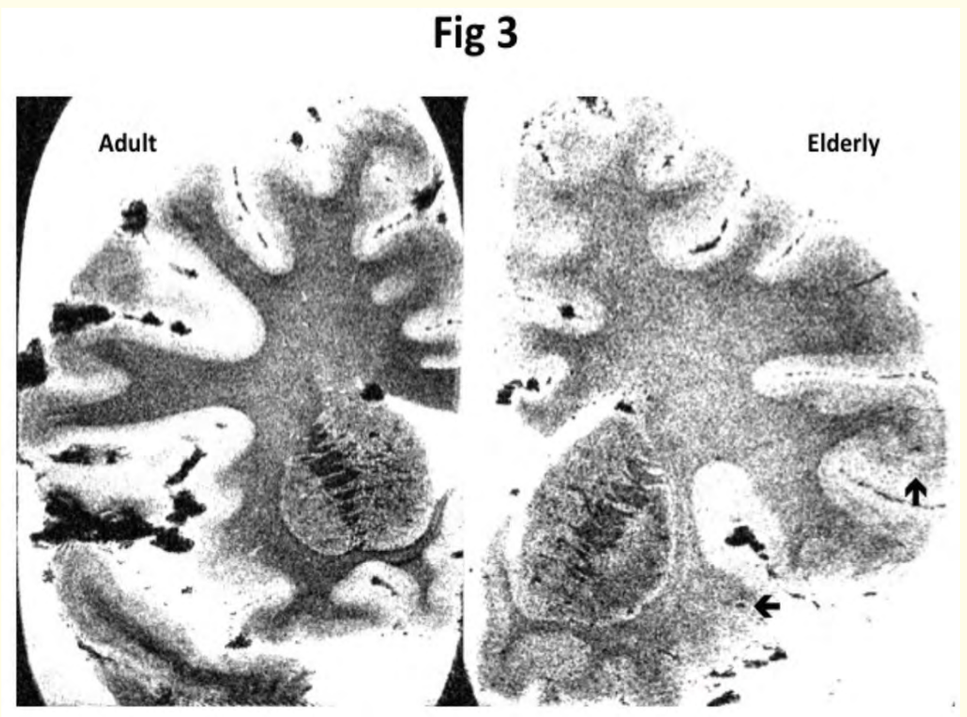

Figure 3: *T2*-weighted gradient-echo sequence 7.0-tesla MRI of frontal coronal sections of a cerebral hemisphere of an adult and an elderly brain. Two small cortical micro-bleeds are observed in the elderly brain (arrows). No micro-bleeds are seen in the adult brain.*

Items	Adult n = 20	Elderly n = 14	p value
White matter changes			
Frontal	0.0 (0.0)	0.6 (0.5)	0.02
Central	0.0 (0.0)	0.6 (0.5)	0.02
Occipital	0.1 (0.3)	0.8 (0.7)	0.03
Cortical micro-infarcts			
Frontal	0.0 (0.0)	0.4 (0.7)	N.S.
Central	0.2 (0.6)	0.3 (0.5)	N.S.
Occipital	0.1 (0.4)	0.0 (0.0)	N.S.
Cortical micro-bleeds			
Frontal	0.4 (0.6)	1.3 (1.0)	0.04
Central	0.1 (0.4)	1.1 (1.0)	0.04
Occipital	0.1 (0.4)	1.8 (1.3)	0.02

Table 3: *Comparison of the semi-quantitative severity scores (standard deviation) and distribution of the cerebrovascular lesions on magnetic resonance imaging of three coronal sections of a cerebral hemisphere between adult and elderly brains.*

Discussion

The present post-mortem study revealed an increased incidence of CoMBs and of the severity of WMCs, without a raise of the number of CoMIs, when comparing brains of elderly to adult patients without a history of a neurological disorder. None of them had mild signs of a neurodegenerative disease. Only one adult person had a small cerebellar infarct. Silent strokes occur mainly in the vertebro-basilar circulation [16].

In neurodegenerative diseases the presence of CoMBs is mainly linked to the regions with the most severe histological changes rather than to associated cerebrovascular disease [17,18]. They are considered as linked to a significantly reduced cerebral blood flow as risk for neural injury and neurodegeneration [19]. In healthy elderly persons CoMBs are found in 8% on clinical 1.5- and 3.0- tesla MRI [20]. During the aging process they are frequently associated to increasing WMCs [21,22].

The present study confirms that the WMCs are widespread without clear areas of predilection [23].

WMCs in patients with cerebrovascular diseases are mainly due to regional chronic ischaemia [24]. However, in neurodegenerative diseases other factors concerning their pathogenesis are also suspected [25]. Cortical metabolic changes are assumed to contribute to the development of WMCs [26,27]. There is also evidence that genetic risk factors can be responsible for their increase [28,29]. In a previous multi-centre autopsy study CoMIs were overall identified in 10% of cognitively normal adults, although significant differences between the different participating groups were observed [30]. This is not statistically different from the 3% incidence of normal adults observed in our study. The low incidence of CoMIs in our adult as well elderly patients without clinically important vascular risk factors make an ischaemic aetiology of the WMCs during the aging process not highly contributively.

Conclusion

The present study argues that the increase of WMCs and CoMBS is related to the aging neurodegenerative changes rather than to associated cerebrovascular disease.

Disclosure Statement

The authors have no conflict of interest to declare.

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Volume 10 Issue 3 March 2018