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Research Article

Comparison of the Prevalence of Cerebrovascular Lesions in Different Parkinsonian Syndromes: A Neuropathological Study with 7.0-tesla Magnetic Resonance Imaging

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Abstract

Background: In addition to idiopathic Parkinson disease (PD) atypical Parkinsonian syndromes include dementia with Lewy bodies (LBD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA). The present post-mortem study investigates whether the incidence of the various cerebrovascular lesions is different in PD compared to the atypical Parkinsonian syndromes.

Material and Methods: On post-mortem examination 5 brains were diagnosed with PD, 18 as LBD, 18 as PSP, 5 as CBD and 2 as MSA. In addition to the macroscopical examination, a 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), cortical micro-infarcts (CoMIs) and cerebral arteriosclerotic micro-infarcts (CAMIs). These lesions were also examined on three coronal sections of a cerebral hemisphere with T2 and T2* 7.0- tesla magnetic resonance imaging (MRI) sequences.

Results: On neuropathological examination CAMIs and CoMIs were significantly increased in the PD brains compared to those with CBD, LBD and PSP, while marginally increased for WMCs and CoMBs. On post-mortem MRI the severity of WMCs was not statistically different between PD, PSP, LBD and CBD brains. On the other hand, CAMIs and CoMBs were significantly increased in all sections of the PD brains compared to the atypical parkinsonian brains. CoMIs were also statistically increased in all the sections of the PD brains compared to those in the PSP and CBD, but only in the frontal and occipital sections of the LBD brains.

Discussion: Small cerebrovascular lesions are significantly more common in PD than in the different atypical parkinsonian syndromes. These differences can be explained by increased cerebrospinal fluid biomarkers of angiogenesis in PD brains while PSP and CBD have as part of the Pick's complex diseases a favorable vascular profile.

Keywords: *Post-mortem Neuropathological Examination; 7.0-Tesla Magnetic Resonance Imaging; Cerebrovascular Lesions; Parkinson's Disease; Lewy Body Dementia; Progressive Supranuclear Palsy; Corticobasal Degeneration; Multisystem Atrophy*

Abbreviations

PD: Parkinson's Disease; LBD: Lewy Body Dementia; PSP: Progressive Supranuclear Palsy; CBD: Corticobasal Degeneration; MSA: Multi-system Atrophy; AD: Alzheimer's Disease; WMCs: White Matter Changes; CoMBs: Cortical Micro-Bleeds; CoMIs: Cortical Micro-Infarcts; CAMIs: Cerebral Arteriosclerotic Micro-Infarcts; CAA: Cerebral Amyloid Angiopathy; MRI: Magnetic Resonance Imaging

Introduction

Atypical Parkinsonian syndromes include LBD, PSP, CBD and MSA [1,2]. PSP and CBD are major tauopathies while PD, LBD and MSA belong to the synucleinopathies [3]. In a large autopsy series of brains with parkinsonism 62.2% were diagnosed as PD, 19.5% as LBD, 4.2% as PSP 2.3% as MSA, 1.2% as CBD and 12.9% of other different aetiologies [4]. Overall the frequency of various cerebrovascular lesions was lower in LBD than in control brains [5]. Concomitant pathologies were found not to be infrequent among the spectrum of parkinsonian disorders [6].

In LBD CoMBs are more frequent than in control brains, independently from associated AD features and the presence of CAA [7,8]. CoMIs are also increased in LBD compared to controls [9].

In PSP CoMBs prevail in the brainstem and the cerebellum [10]. In CBD and in PSP the incidence of small cerebrovascular lesions in the cerebral hemispheres is not different from in control brains, except for a mild increase of WMCs in both and CoMBs in the former [11]. Both types of lesions can be due to the neurodegenerative process itself rather than reflecting additional cerebrovascular disease [12].

The present post-mortem study investigates whether the incidence of the various cerebrovascular lesions is different in idiopathic PD compared to the atypical Parkinsonian syndromes such as LBD, PSP and CBD. In addition to the neuropathological examination a 7.0-tesla MRI evaluation of the severity and the distribution of these lesions was performed on 3 hemispheric coronal sections.

Materials and Methods

A total number of 48 patients, who had been followed up at the Lille University Hospital with a Parkinsonian syndrome, underwent an autopsy. 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 standard diagnostic 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, the basal ganglia, the mesencephalon, the pons, the medulla and the cerebellum. Slides from paraffin embedded sections were stained with haematoxylin-eosin, luxol fast blue and Perl. Immune-staining for protein tau, β-amyloid, α-synuclein, prion protein, TDP-43 and ubiquitin was also performed.

On post-mortem examination 5 brains were diagnosed as PD (brainstem Lewy body disease), 18 as LBD, 18 as PSP, 5 as CBD and 2 as MSA. The refined published neuropathological criteria were used for the assessment of idiopathic PD [13]. LBD was diagnosed according to the report of the consortium on DLB international workshop [14]. The post-mortem diagnosis of PSP was made according to the NINDS neuropathological criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy) [15]. The diagnostic criteria of CBD were those proposed by the international consortium of behavioral neurology [16]. The neuropathological diagnosis of MSA was made according to the second consensus statement on the diagnosis of multiple system atrophy [17]. Staging of the cerebral arteriosclerotic micro-infarcts or (CAMIs) was performed according to the recommendations of the vascular dementia group [18].

In addition to the detection of the 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 the small cerebrovascular lesions such as WMCs, CoMBs, CoMIs, and CAMIs.

The mean values of WMCs characterized by the degree of the axonal and myelin loss, 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.

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 [19]. 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 ranking scores of severity of the WMCs and the other small cerebrovascular lesions were evaluated separately in the different brain sections in the same way as was done on the neuropathological section.

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 ≤ 0.001 for highly significant, ≤ 0.01 for significant and ≤ 0.05 for marginally significant. Due to the restricted number of brains with MSA no statistical evaluation could be performed in this atypical parkinsonian syndrome.

Results

The average age of the patients with PD was not statistically different from that of the different atypical parkinsonian syndromes. Also, the gender distribution was not significantly different between all the groups (Table 1). The 2 patients with MSA were a 54 year-old woman and a 77 year-old man.

Items	PD	LBD	PSP	CBD
Number of patients	5	18	18	5
Average age (years) (Standard deviation)	73 (12)	79 (7.0)	73 (10)	71 (5)
Male gender distribution	67%	76%	50%	33%

Table 1: *Demographic features of the patients with Parkinson disease (PD), Lewy body dementia (LBD), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).*

On neuropathological examination CAMIs and CoMIs were significantly increased in the PD brains compared to those with LBD, PSP and CBD ($p \leq 0.01$), while marginally increased for WMCs and CoMBs ($p \leq 0.05$). CAA, territorial infarcts and lobar haematomas were absent or rare, without significant differences between the groups (Table 2).

Items	PD	LBD	PSP	CBD
White matter changes	1.3 (0.9)	0.7 (1.0)*	0.6 (0.9)*	0.8 (0.9)*
Cerebral amyloid angiopathy	0.0 (0.0)	0.6 (1.0)	0.2 (0.5)	0.0 (0.0)
Territorial infarcts	0.0 (0.0)	0.1 (0.2)	0.2 (0.5)	0.0 (0.0)
Arteriosclerotic micro-infarcts	3.0 (1.2)	0.1 (0.3)***	0.1 (0.2)***	0.0 (0.0)***
Lobar haematomas	0.0 (0.0)	0.1 (0.5)	0.1 (0.2)	0.0 (0.0)
Cortical micro-bleeds	2.3 (1.2)	1.2 (1.1)*	0.9 (1.0)*	1.3 (0.8)*
Cortical micro-infarcts	1.7 (0.6)	0.4 (0.2)**	0.2 (0.5)**	0.0 (0.0)***

Table 2: *Neuropathological evaluation of the severity of the cerebrovascular lesions (standard deviation) of the brains with Parkinson disease (PD) compared to those with Lewy body dementia (LBD), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).*

Marginally significant: $p \leq 0.05$; significant: $p \leq 0.01$; highly significant: $p \leq 0.001$.

On post-mortem MRI of the different coronal hemispheric sections the severity of WMCs was not statistically different between PD, PSP, LBD and CBD brains. On the other hand, CAMIs and CoMBs were significantly increased in all sections of the PD brains compared to those with an atypical parkinsonian syndrome ($p \leq 0.001$). CoMIs were also statistically increased in all the sections of the PD brains compared to those in the PSP and CBD. In LBD brains the increase was only observed in the frontal and occipital sections ($p \leq 0.01$). No significant difference was found at the level of the central section between the PD and the LBD brains (Table 3).

Items	PD	LBD	PSP	CBD
White matter changes				
Frontal section	1.0 (1.0)	1.0 (0.8)	0.8 (0.9)	1.0 (0.6)
Central section	0.7 (0.8)	1.1 (0.8)	0.9 (1.0)	1.0 (1.0)
Occipital section	0.9 (0.6)	1.1 (0.6)	1.1 (1.1)	1.0 (1.0)
Cerebral arteriosclerotic micro-infarcts				
Frontal section	2.0 (1.0)	0.2 (0.4)***	0.2 (0.5)***	0.0 (0.0)***
Central section	0.7 (0.6)	0.0 (0.0)***	0.0 (0.0)***	0.0 (0.0)***
Occipital section	1.3 (0.8)	0.2 (0.4)***	0.1 (0.3)***	0.0 (0.0)***
Cortical micro-bleeds				
Frontal section	5.3 (1.2)	1.0 (0.4)***	1.0 (1.1)***	1.3 (1.5)***
Central section	6.7 (1.3)	1.2 (0.6)***	1.5 (1.5)***	2.0 (0.9)***
Occipital section	5.7 (1.6)	1.0 (1.0)***	1.4 (1.4)***	1.7 (0.6)***
Cortical micro-infarcts				
Frontal section	2.0 (1.7)	0.7 (0.9)***	0.4 (0.6)***	0.3 (0.6)***
Central section	2.3 (1.0)	1.8 (1.0)	0.5 (0.5)***	0.0 (0.0)***
Occipital section	4.0 (1.0)	1.7 (0.9)***	0.4 (0.6)***	0.3 (0.6)***

Table 3: *NMR evaluation of the severity of the cerebrovascular lesions (standard deviation) on 3 coronal hemispheric sections of the brains with Parkinson disease (PD) compared to those with Lewy body dementia (LBD), progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD).*

Marginally significant: $p \leq 0.05$; significant: $p \leq 0.01$; highly significant: $p \leq 0.001$.

Discussion and Conclusion

The present study shows that small cerebrovascular lesions are significantly more common in PD than in the different atypical parkinsonian syndromes. The frequency of the various cerebrovascular lesions was already found to be lower in LDB and controls compared to PD brains [5]. Cerebral small-vessel disease is considered as a risk factor for the development of dementia in PD [20]. However, the minor cerebral ischaemic changes have no significant effects on the progression of the motor severity in PD [21]. Associated AD and CAA features are not the responsible causes [22]. The degree of LBD pathology is not correlated to the degree of atherosclerosis, territorial infarcts and lacunes, while AD and CAA pathologies are frequently associated [23]. In PD of very old onset the brainstem lesions are most frequently associated to AD pathology [24]. Also, Lewy body pathology in mixed neurodegenerative dementias is mainly associated with a trend of older age and arterial hypertension [25,26]. The impact of CAA in LBD is rather reduced compared to that in AD [27,28]. The fact that in LBD CoMIs are not reduced in the central section on the MRI examination, can be explained that overall they are more frequently associated to other pathologies than in the other unmixed neurodegenerative diseases [9].

Why small cerebrovascular lesions are more frequent in PD can be explained, on one hand by the increased cerebrospinal fluid biomarkers of angiogenesis leading to blood-brain dysfunction, WMCs and CoMBs [29] and on the other hand that PSP and CBD are part of the Pick complex diseases, which are known to have a favorable vascular profile [11]. An inverted region on chromosome 17 is linked to many Pick complex diseases [30].

Disclosure Statement

The author has no conflict of interest to declare.

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