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The Impact of Cerebral Amyloid Angiopathy in Progressive Supranuclear Palsy: A Neuropathological Study with Magnetic Resonance Imaging Correlations

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Abstract

Introduction and Purpose: Cerebral amyloid angiopathy (CAA) is frequently found in Alzheimer's disease but can also be associated to other neurodegenerative diseases. The present post-mortem study investigates the impact of CAA in progressive supranuclear palsy (PSP).

Materials and Methods: Sixteen PSP brains without CAA were compared to 9 ones with CAA. In addition to the gross and histological examination of the brain a large coronal section of a cerebral hemisphere was used to quantify small cerebrovascular lesions such as white matter changes (WMCs), cortical micro-infarcts (CoMIs) and cortical micro-bleeds (CoMBs). In addition, 7.0-tesla magnetic resonance imaging (MRI) was performed on three coronal sections of a cerebral hemisphere to investigate whether there were topographic differences of the small cerebrovascular lesions between PSP brain without and with CAA. Also, the presence of cortical superficial siderosis (CoSS) was investigated on MRI.

Results: No quantitative differences in WMCs, CoMIs and CoMBs could be detected between both groups. Also no regional differences were observed on MRI. CoSS was, however, significantly present in the PSP group with CAA while completely absent in the non-CAA group.

Discussion: The only impact of CAA on PSP brains was the frequent occurrence of CoSS that has recently been recognized as an additional Boston criterion for CAA. As in other neurodegenerative diseases the effects of CAA seem to be less severe than in those without these associations

Keywords: *Neuropathology; 7.0-Tesla Magnetic Resonance Imaging; Progressive Supranuclear Palsy; Cerebral Amyloid Angiopathy; White Matter Changes; Cortical Micro-Infarcts; Cortical Micro-Bleeds; Cortical Superficial Siderosis*

Abbreviations

PSP: Progressive Supranuclear Palsy; CAA: Cerebral Amyloid Angiopathy; AD: Alzheimer's Disease; LBD: Lewy Body Disease; MRI: Magnetic Resonance Imaging; CoSS: Cortical Superficial Siderosis; WMCs: White Matter Changes; CoMIs: Cortical Micro-Infarcts; CoMBs: Cortical Micro-Bleeds

Introduction

PSP appears to be a more heterogeneous disease than initially suspected, as it is frequently associated to other neurodegenerative disorders [1]. The relation between parkinsonian syndromes and stroke is conflicting [2]. Multi-infarct state is observed in 32.8% patients with PSP while only in 5.9% of those with Parkinson's disease [3].

Small cerebral bleeds mainly occur in the dentate nucleus of the cerebellum and in the tegmentum pontis of PSP brains while rare in the cerebral hemispheres [4]. Also, micro-infarcts are rare in this disease [5].

The Boston criteria for CAA are mainly based on clinical and neuroimaging criteria. However, a definitive diagnosis of CAA requires a neuropathological confirmation, demonstrating lobar cortical or subcortical haemorrhage, severe CAA with vasculopathy and the absence of any other diagnostic lesion [6]. CAA is frequently associated to AD [7]. However, in a large clinical-neuropathological study CAA is also found to be associated in 25% of the PSP cases [8]. CAA can also sometimes mimic the clinical symptoms of PSP [9]. So, it is worthwhile to study the impact of cerebrovascular lesions due to CAA in PSP brains.

This post-mortem study compares the incidence of these lesions in post-mortem brains with 7-tesla MRI correlates between "pure" PSP brains to those associated with CAA (PSP-CAA).

Materials and Methods

Twenty-five patients with PSP, who had been followed up at the Lille University Hospital, 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.

Sixteen PSP brains without CAA were compared to 9 with CAA (PSP-CAA).

The post-mortem diagnosis of PSP was made according to the NINDS neuropathological criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy) [10]. The post-mortem diagnosis of CAA was made according to a recent consensus protocol [11]. The degree of CAA was evaluated semi-quantitatively in 4 cortical samples and graded from 0 to 3 [12]. Only grade 2 was reached in our series of PSP-CAA brains.

The standard diagnostic procedure was the same as in our previous study [13]. In addition to the detection of the macroscopic visible lesions such as haematomas, territorial and lacunar infarcts a whole coronal section of a cerebral hemisphere at the level of the mamillary body was taken for the semi-quantitative microscopic evaluation of the small cerebrovascular lesions: WMCs, CoMIs and CoMBs. The mean values of 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 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 [14]. Three coronal sections of a cerebral hemisphere were submitted to SPIN ECHO T2 and T2* MRI sequences: frontal, central and parieto-occipital one. 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 incidence of focal areas of isolated CoSS, not associated to a visible underlying lesion, was evaluated on the T2* sequence [15]. The inter-rater reliability resulted in an interclass correlation coefficient of 0.74.

Statistical analysis consisted in univariate comparisons of unpaired groups, 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 for moderately significant, at ≤ 0.01 for significant and at ≤ 0.001 for highly significant.

Results

The average age at death was similar in the PSP patients without and with CAA: 75 (SD: 8) years in the former and 75 (SD: 17) years in the latter group. Also, gender distribution was not significantly different with 44% males in the former and 56% ones in the latter.

The incidence of the cerebrovascular lesions on the neuropathological examination was low and not significantly different between PSP brain without and with CAA (Table 1).

Items	PSP (n = 16)	PSP-CAA (n = 9)	p value
Cerebral lobar haematoma	0.1 (0.3)	0.0 (0.0)	N.S.
Territorial infarct	0.2 (0.5)	0.2 (0.4)	N.S.
Lacunar infarct	0.1 (0.3)	0.6 (1.3)	N.S.
White matter changes	0.9 (1.0)	1.2 (1.1)	N.S.
Cortical micro-infarct	0.2 (0.5)	0.8 (1.3)	N.S.
Cortical micro-bleed	0.0 (0.0)	0.0 (0.0)	N.S.

Table 1: *Comparison of the severity of the cerebrovascular lesions (standard deviation) in progressive supranuclear palsy without (PSP) and with cerebral amyloid angiopathy (PSP-CAA).*

On MRI examination also no differences in the incidence of WMCs, CoMIs and CoMBs were observed between both groups in the frontal, central and parieto-occipital sections. On the other hand focal areas of CoSS were significantly present in the PSP-CAA group (Figure 1 and 2) en absent in the group without CAA ($p < 0.001$) (Table 2).

Discussion

Although the numbers of patients of the two groups of PSP patients were small, a highly significant predominance of multifocal CoSS was observed in the PSP group with CAA. MRI is the best technique to detect these lesions [16]. However, CAA had no direct impact on the incidence of the other more common cerebrovascular lesions, as their incidence remained as low as in PSP brains without CAA. CoSS

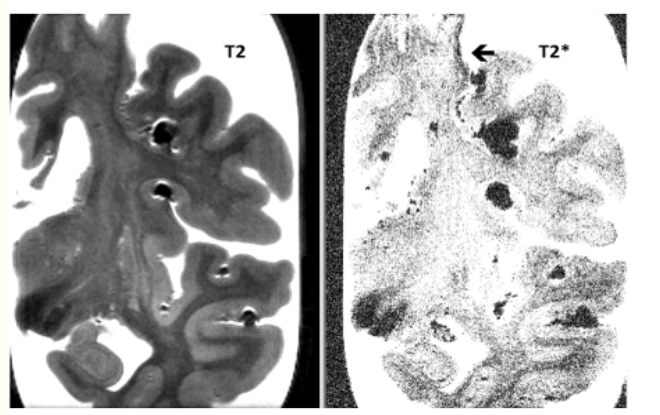

Figure 1: *Spin-Echo T2 (A) and T2* (B) magnetic resonance imaging of a parietal coronal section of a cerebral hemisphere in a brain with progressive supranuclear palsy associated to cerebral amyloid angiopathy. Mild diffuse hyper-intensity of the corona radiata is observed on the T2 sequence and focal cortical superficial siderosis on the T2* one (arrow).*

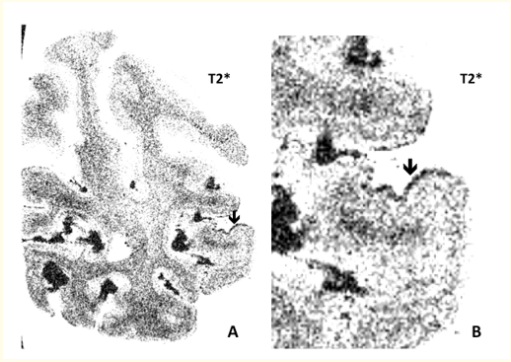

Figure 2: *T2* magnetic resonance imaging of an occipital coronal section of a cerebral hemisphere as a whole (A) with detail view (B) in a brain with progressive supranuclear palsy associated to cerebral amyloid angiopathy. The focal cortical area of superficial siderosis is indicated by the arrows.*

Items	PSP n = 16	PSP-CAA n = 9	p value
White matter changes			
Frontal	0.6 (0.7)	0.6 (0.8)	N.S.
Central	0.6 (0.8)	0.8 (0.9)	N.S.
Parieto-occipital	0.9 (1.0)	1.2 (1.1)	N.S.
Cortical micro-infarcts			
Frontal	0.2 (0.5)	0.2 (0.4)	N.S.
Central	0.4 (0.6)	0.5 (0.7)	N.S.
Parieto-occipital	0.6 (0.8)	0.4 (0.5)	N.S.
Cortical micro-bleeds			
Frontal	0.9 (1.2)	0.7 (0.5)	N.S.
Central	1.1 (1.3)	1.2 (0.8)	N.S.
Parieto-occipital	1.3 (1.2)	1.0 (1.0)	N.S.
Cortical superficial siderosis	0.0 (0.0)	1.5 (0.8)	< 0.001

Table 2: *Magnetic resonance imaging comparison of the distribution and the severity of the small cerebrovascular lesions (standard deviation) in progressive supranuclear palsy (PSP) without and with cerebral amyloid angiopathy (LBD-CAA).*

was recently considered as an additional Boston criterion for CAA [17,18]. Overall, multifocal CoSS is found in 29,8% of patients with clinically probable CAA [19].

One possible bias of this study could be due to the fact that the CAA grading only reached stage 2 instead of stage 3 of severity. The WMCs in the PSP brains with and without CAA have also to be considered as due to Wallerian degeneration rather than of vascular origin [20].

It is unclear why the global impact of CAA in PSP is restricted. Perhaps vascular amyloid derives from a different source can explain why CAA has less cerebrovascular impact in PSP [21]. As seen in the present series, CAA and amyloid plaques are frequently not associ-

ated [22]. Vascular amyloid could be a product of smooth muscle cells in the vascular wall, resulting from the release of amyloid precursor protein from degenerating smooth muscle cells [23]. Also, AbetaPP mRNA is increased in the cerebral cortex of CAA brains associated to AD and LBD but not in PSP [23]. PSP is part of the PIck complex diseases and share a favorable vascular risk profile, with a low incidence of cerebrovascular lesions [24]. An inverted region on chromosome 17 is linked to many of the Pick complex diseases [25].

Also, the impact of additional AD pathology in CAA brains is reduced compared to those without these neurodegenerative lesions [26]. In LBD the association with CAA only leads to a minor increase of CoMIs [27].

All these factors can probably explain why CAA is only responsible for the presence of CoSS in PSP brains compared to those with the brains fulfilling all the classical clinical Boston criteria. As the risk and the impact of CAA is reduced in PSP no special additional treatment has to be proposed. The use of anticoagulant or antithrombotic drugs has to be avoided, if possible.

Conclusion

The present study shows that the impact of CAA in PSP brains is only limited to the presence of CoSS.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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