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# Post-Mortem 7.0-Tesla Magnetic Resonance Imaging of the Hippocampus in Cortico Basal Degeneration

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## Abstract

**Introduction and Purpose: Corticobasal degeneration (CBD) is a rare neurodegenerative disease with different clinical phenotypes and characterized by deposition of abnormal tau protein in the brain. Little is known about the involvement of the hippocampus in this disease. The present post-mortem 7.0-tesla magnetic resonance imaging (MRI) investigates the degree of hippocampal atrophy (HA) and the frequency of hippocampal micro-infarcts (HMIs) and micro-bleeds (HMBs) in CBD.**

**Material and Methods: Eight brains with CBD were compared to 17 normal age-matched controls. In addition to the neuropathological examination the hippocampus was evaluated on the most representative coronal section with T2 and T2* MRI sequences. The average degree of HA was determined in both groups. The incidence of HMIs and HMIBs was also compared as well as the frequency of cortical micro-infarcts (CoMIs) and cortical micro-bleeds (CoMBs) in the hemispheric neocortex.**

**Results: Although there was global severe atrophy of the cerebral neocortex only a moderate HA was observed in the CBD brains compared to the normal controls. The incidence of HMIs and HMBs was similar between both groups. Also the frequency of CoMIIs and CoMBs in the neocortex was comparable.**

**Conclusions: In contrast to the more common neurodegenerative diseases there is only moderate HA in CBD. Also the hippocampus is not more sensitive for small cerebrovascular lesions than the hemispheric neocortex.**

**Keywords:** ***Neuropathology; Magnetic resonance imaging; Corticobasal degeneration; Hippocampus; Cerebral neocortex***

## 1. Introduction

Corticobasal degeneration (CBD) was first described by Rebeiz et al. in 1967 and was at that time called corticodentatonigral degeneration with neuronal achromasia [1]. Four clinical CBD phenotypes emerged: a corticobasal syndrome, a frontal

behavioral-spatial syndrome, a non-fluent-agrammatic variant of progressive aphasia and a progressive supranuclear palsy syndrome. The probable CBD criteria included an insidious onset and gradual progression for at least 1 year, age at onset ≥ 50 years, no similar family history or known tau mutations and at least one of the mentioned clinical phenotypes [2]. Due to the various clinical phenotypes prevalence studies are lacking, but overall CBD is considered as a rare neurodegenerative disease. The pooled incidence of frontotemporal lobar degeneration (FTLD), progressive supranuclear palsy (PSP) and CBD is reported as 10.6 per 100.000 [3]. Similar to Pick's disease and PSP, the neuropathology of CBD is characterized by severe hemispheric cerebral cortex involvement and the deposition of tau protein in the brain [4]. Beta-amyloid deposits can be present in CBD brains as additional "co-pathology" although not so intense as in Alzheimer's disease (AD) [5].

Very little is known about the hippocampal involvement in CBD. Only a moderate ß-amyloid accumulation can be observed in contrast to its severe increase in other neurodegenerative diseases such as in AD and FTLD [6]. Also, HA is prominent in AD and FTLD brains [7]. No agreements are found concerning the hippocampal size in CBD. In one study no significant HA was observed [8], while in another one some degree of HA was found due to the reduction of the cholinergic fiber network [9].

The present 7.0-tesla magnetic resonance study compares the average degree of HA and the incidence of hippocampal micro-infarcts (HMIs) and hippocampal micro-bleeds (HMBs) between post-mortem brains with CBD and age-matched normal controls. Also, the frequency of the cortical micro-infarcts (CoMIs) and cortical micro-bleeds (CoMBs) in the surrounding hemispheric neocortex of both groups is determined.

## 2. Material and Methods

The examined post-mortem brains consisted of 8 CBD ones and 17 age-matched controls. A 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 part of the "Centres des Resources Biologiques" and acts as an institutional review board.

The neuropathological diagnosis of CBD was made by the macroscopic inspection of the brain and on microscopic examination of small brain samples from the primary motor cortex, the associated frontal, temporal and parietal cortex, the primary and secondary visual cortex, the cingulated gyrus, the basal nucleus of Meynert, the amygdaloid body, and the hippocampus, basal ganglia, mesencephalon, pons, medulla, cerebellum and cervical spinal cord. Slides from paraffin-embedded sections were immune-stained for protein tau, β-amyloid, α-synuclein, prion protein, TDP-43 and ubiquitin [10].

The diagnosis of CBD was made according to the criteria proposed in 2015 and in 2017 [2,11]. Also, the Movement Disorder Society introduced diagnostic criteria in the category of "probable 4-repeat-taupathy" for the joint clinical diagnosis of progressive PSP and CBD [12].

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 [13]. Before the brain sampling, three up to six coronal sections of a cerebral hemisphere were submitted to SPIN ECHO T2 and T2* MRI sequences. The most affected cerebral hemisphere was always chosen, and the hippocampus was evaluated on the most representative section.

The degree of HA was determined on MRI according to the "in vivo" AD classification of Scheltens in 4 grades [14,15] with its application in post-mortem brains [16]. Also, the incidence of HMIs and HMBs was evaluated as previously described for cortical hemispheric CoMIs and CoMBs [17].

Unvaried 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 $\leq 0.01$ for significant and $\leq 0.001$ for highly significant. Values set at $\leq 0.05$ and more than $>0.01$ were considered as marginal significant.

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## 3. Results

The average age at death was similar between the CBD group and the control group with respectively 69 (SD: 9) and 69 (SD: 10) years. Also, the gender distribution was not statistically different with 57% males in the former and 64% in the latter group.

The neuropathological examination did not reveal any degree of cerebral amyloid angiopathy in the CBD and in the normal age-matched control brains. Territorial and lacunar infarcts, as well as lobar haematomas were absent in both groups.

The only statistical difference was observed for the white matter changes: the average incidence had a marginal higher significance score in the CBD group ($p < 0.05$). A low incidence of CoMIs was observed in the control group, while absent in the CBD brains. There was a somewhat high but similar occurrence of CoMBs in both groups (TABLE 1).

TABLE 1. **Neuropathological comparison of the average incidence of the cerebrovascular lesions between brains with corticobasal degeneration (CBD) and normal controls (SD).**

| Items | CBD | Control | P value |
|---|---|---|---|
| White matter changes | 1.0 (0.8) | 0.2 (0.4) | <0.05 |
| Territorial infarcts | 0.0 (0.0) | 0.0 (0.0) | NS |
| Lacunar infarcts | 0.0 (0.0) | 0.0 (0.0) | NS |
| Lobar haematomas | 0.0 (0.0) | 0.0 (0.0) | NS |
| Cortical micro-infarcts | 0.0 (0.0) | 0.1 (0.3) | NS |
| Cortical micro-bleeds | 1.1 (0.7) | 0.8 (0.7) | NS |

The MRI revealed a somewhat more severe degree of HA in the CBD compared to the control group ($p < 0.05$) (FIG. 1). The incidence of HMIs and HMBs was not statistically different between both groups. On mutual comparison between the CBD and control brains no differences were observed concerning the frequency of CoMIs and CoMBs in the cerebral neocortex (TABLE 2). However, the mean values of the CoMBs were significantly higher than those of the HMBs ($p < 0.05$).

Fig. 1

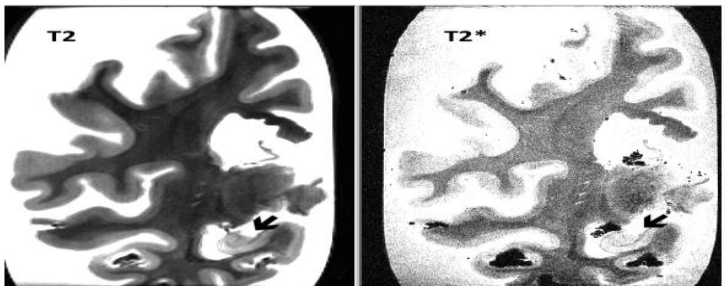


FIG. 1. **T2 and T2* magnetic resonance imaging of a coronal section of a cerebral hemisphere in a brain with corticobasal degeneration. Severe cortical atrophy of the cerebral hemisphere and moderate hippocampal atrophy with temporal horn dilation (black arrows) are observed. No micro-infarcts (T2) and micro-bleeds (T2*) in the hippocampus and in the cerebral neocortex are detected.**

TABLE 2. **Comparison of the severity of the hippocampal atrophy and the incidence of hippocampal micro-infarcts and micro-bleeds, and of cortical micro-infarcts and micro-bleeds in the neocortex between brains with corticobasal degeneration (CBD) and normal controls (SD).**

| Items | CBD | Control | P value |
|---|---|---|---|
| Hippocampal atrophy | 1.1 (0.8) | 0.2 (0.4) | <0.05 |
| Hippocampal micro-infarcts | 0.1 (0.3) | 0.3 (0.6) | NS |
| Hippocampal micro-bleeds | 0.8 (0.8) | 0.2 (0.4) | NS |
| Neocortical micro-infarcts | 0.2 (0.4) | 0.4 (0.7) | NS |
| Neocortical micro-bleeds | 1.1 (0.6) | 1.1 (0.3) | NS |

## 4. Discussion

The present study shows a moderate increased rate of HA in the CBD patients compared to normal age-matched controls. Only one small previous MRI study of six patients with CBD finds in 4 of them unilateral HA and in 2 brains mild bilateral HA [18].

Positron emission tomography (PET) is considered as a clinical useful imaging biomarker for distinction between idiopathic Parkinson disease (PD) and atypical parkinsonism associated with dementia, such as CBD [19]. Patients with “pure” CBD have the most marked bilateral hypometabolism in the basal ganglia whereas, when associated with AD, there is an additional asymmetrical involvement of the lateral parietal and temporal lobes and the posterior cingulated gyri. The association of CBD with PSP discloses a more anterior hypometabolism pattern [20]. Only one small PET study shows localized low glucose metabolism in CBD patients with unilateral HA [18].

HA is linked to memory loss in the early course of CBD. However, those cases are frequently associated to other neurodegenerative diseases such AD, PSP and PD. An increased frequency of the epilon 4 allele of apoE is observed in cases of CBD [21].

The white matter changes in CBD brains have previously been described [22,23] and are secondary and due to the severe degree of cortical degeneration, rather than to be considered as of cerebrovascular origin [24].

CBD is possibly linked to PSP and an overlap is not uncommon [25]. While CBD and PSP have been called Parkinson-plus syndromes in the past, they are now classified as FTLD-related disorders, reflecting that they pathologically differ from alpha-synucleinopathies like multiple system atrophy and PD [26]. The HA is linked to TDP-43 pathology in PSP [27].

None of our patients have associated PSP features. Also, the incidence of major cerebrovascular lesions is low and not different from the normal age-matched controls [28]. The high incidence of CoMBs and to a lesser extend of HMBs is more probably related to the age-related neurodegenerative pathology, rather than to associated cerebrovascular involvement [29-32].

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