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Comparison of iron deposition in subcortical structures of brains with Parkinsonian syndromes: A post-mortem 7.0-tesla magnetic resonance study

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Abstract
It is not known whether iron (Fe) accumulation is a secondary event in the cascade of the neuronal degeneration rather than the primary cause in different Parkinsonian diseases. The purpose of the present post-mortem study is to evaluate and compare the Fe content in brains of different parkinsonian syndromes with normal control brains. Twenty-six normal brains were compared to 7 with idiopathic Parkinson's disease (PD), 18 with progressive supranuclear palsy (PSP), 18 with Lewy body dementia (LBD), 6 with corticobasal degeneration (CBD) and 5 with multiple system atrophy (MSA). The hippocampus and 11 subcortical structures were submitted to a 7.0-tesla magnetic resonance imaging (MRI). T2 and T2* sequences were performed: the degree of T2* hypo-intensity, representing the degree of Fe content in the different brain regions, was determined semi-quantitatively. No significant differences in Fe content were observed in all examined structures between normal brains and those with PD, PSP, LBD and CBD. In MSA there was a selective hypo-intensity on T2* sequence in the putamen, reflecting Fe increase, with on the other hand a significant Fe decrease at the level of the dentate nucleus of the cerebellum. The present post-mortem MRI study confirms that the increased hypo-intensity in the putamen is a diagnostic hallmark of MSA, but that also the low Fe content at the level of the dentate nucleus has also to be considered as a valuable indicator of this disease.

Keywords: Neuropathology, 7.0-tesla MRI, brain iron deposition, Idiopathic Parkinson's disease, progressive supranuclear palsy, Lewy body dementia, corticobasal degeneration, multiple system atrophy

1. Introduction
In the substantia nigra the main iron (Fe) compound in dopamine and norepinephrine neurons is the neuromelanin-iron complex that serves to trap Fe and to provide neuronal protection for oxidative stress [1].

In normal brains Fe concentrations are high in striatum, red nucleus and substantia nigra [2] but also around the dentate nucleus of the cerebellum [3]. The highest Fe concentrations in the basal ganglia are found in the globus pallidus, followed by the putamen, caudate nucleus, thalamus and white matter [4].

Ferroptosis is a unique form of programmed cell death, characterised by cytosolic accumulation of Fe, lipid peroxides and their metabolites, affecting the plasma membrane [5].

In patients with atypical Parkinsonian syndromes brain Fe accumulation has been extensive investigated with magnetic resonance imaging (MRI) [6]. However, "in vivo" MRI observations have to be validated by post-mortem examination [7]. T2 and T2*- weighted MRI images are currently the preferred methods to visualize and quantify the amount of Fe in the deep brain structures [8, 9].

The present post-mortem 7.0-tesla MRI study investigates and semi-quantifies the amount of Fe in different structures of the brains of patients with Parkinson's disease and atypical parkinsonian syndromes compared to normal controls.

2. Material and methods
Fifty-four patients with a Parkinsonian syndrome, who had been followed up at the Lille University Hospital, and 26 without a neurological disease 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.

On post-mortem examination 7 brains were diagnosed with idiopathic Parkinson's disease (PD), 18 with progressive supranuclear palsy (PSP), 18 with Lewy body dementia (LBD), 6 with corticobasal degeneration (CBD) and 5 with multiple system atrophy (MSA).

The refined published neuropathological criteria were used for the assessment of idiopathic PD [10]. The post-mortem diagnosis of PSP was made according to the NINDS neuropathological criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy) [11]. LBD was diagnosed according to the report of the consortium on DLB international workshop [12]. The diagnostic criteria of CBD were those proposed by the international consortium of behavioral neurology [13]. The neuropathological diagnosis of MSA was made according to the second consensus statement on the diagnosis of multiple system atrophy [14].

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 parietal lobe.

Also a horizontal section through brainstem and a cerebellar hemisphere was examined. The severity of the Fe deposition was semi-quantitative rating on the T2*-weighted images: no hypo-intensity (R0), small scattered hypo-intensity signals (R1), confluent zones of hypo-intensity (R2) and homogeneous dens hypo-intensity of the whole structure (R3).

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.

3. Results

The patients with normal post-mortem brains had an average age of 66 (SD: 12) years, which was statistically not different from the 72 (SD: 5) years of the CBD and the 69 (SD: 8) years of the MSA brains. In the other groups the average age at death was older: 76 (SD: 8) years in PD ($p \leq 0.05$), 79 (SD: 7) years in PSP ($p \leq 0.01$) and 82 (SD:8) years in LBD ($p \leq 0.01$). Gender distribution was different with a male predominance of 85% in the LBD group, compared to the normal and other parkinsonian groups, ranging from 43 until 60% ($p \leq 0.05$).

Mild additional Alzheimer features were present in 12 % of PSP and in 24% of LBD brains. Moderate cerebral amyloid angiopathy was only present in 18% of the LBD group.

Semi-quantitative evaluation of the Fe content in the hippocampus and the main subcortical structures did not show any differences between the normal brains and those with PD, LBD, PSP and CBD. In the MSA brains a significant increase of Fe was only observed in the putamen ($p \leq 0.01$), while a moderate decrease of Fe was observed at the level of the dentate nucleus ($p \leq 0.05$) (table 1) (Fig 1-2).

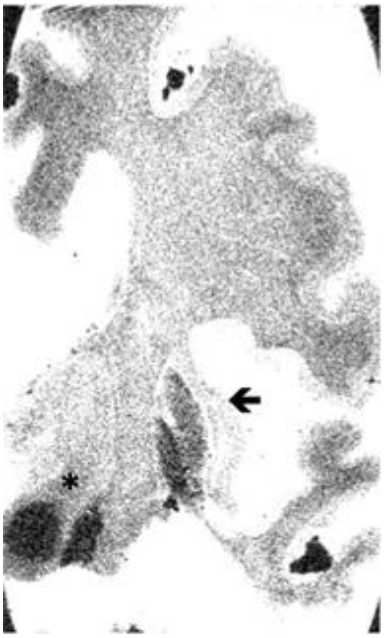

Fig 1: T2* MRI sequence of a coronal section of a cerebral hemisphere of a brain with multiple system atrophy. There is a selective hypo-intensity of the putamen (black arrow). The hypointensity in the globus pallidus is within normal range. Note the preserved Fe content in the substantia nigra and the red nucleus (*).

Fig 2: T2* MRI sequence of a horizontal section of a cerebellar hemisphere of a brain with multiple system atrophy. No hypo-intensity is observed at the level of the dentate nucleus (white arrow).

Table 1: Semi-quantitative Fe content evaluation (standard deviation) of normal brains and of brains of patients with idiopathic Parkinson disease (PD), progressive supranuclear palsy (PSP), Lewy body dementia (LBD), corticobasal degeneration (CBD) and multiple system atrophy (MSA).

Items Normal PD PSP LBD CBD MSA
(n = 26) (n = 7) (n = 18) (n = 18) (n= 6) (n = 5)
Hippocampus 0.3(0.7) 0.0(0.0) 0.2(0.5) 0.0(0.0) 0.0(0.0) 0.0(0.0)
Claustrum 0.3(0.6) 0.0(0.0) 0.4(0.9) 0.4(0.5) 0.0(0.0) 0.0(0.0)
Caudate nucleus 0.7(0.8) 1.0(1.0) 1.4(1.0) 1.4(1.1) 0.6(0.9) 0.6(0.5)
Putamen 1.4(1.1) 1.8(0.4) 1.7(1.1) 1.9(1.1) 1.2(0.4) 3.0(0.0)**
Globus Pallidus 2.0(1.2) 1.8((0.4) 1.7(1.5) 1.9(1.3) 1.6(0.5) 3.0(0.0)
Thalamus 0.6(1.0) 0.4(0.6) 0.5(0.6) 0.4(0.5) 1.0(0.0) 0.2(0.4)
Mamillary body 0.9(1.1) 1.0(0.7) 1.6(1.2) 0.7(1.0) 0.8(0.4) 0.6(0.5)
Geniculate body 1.3(1.2) 1.0(0.7) 1.2(1.1) 1.7(1.4) 0.8(0.4) 1.2(0.8)
Subthalamic nucleus 1.0(1.3) 1.6(0.6) 1.1(1.1) 0.8(0.9) 0.8(0.5) 1.6(0.9)
Red nucleus 2.5(0.7) 2.2(0.8) 1.8(1.2) 3.0(0.0) 2.0(0.0) 3.0(0.0)
Substantia Nigra 2.6(0.5) 2.2(0.8) 2.3(1.0) 3.0(0.0) 2.0(0.0) 3.0(0.0)
Dentate nucleus 2.0(1.2) 1.4(0.9) 1.5(1.2) 1.4(1.3) 1.4(0.5) 0.6(0.5)*

4. Discussion

The present study only shows an increased level of Fe in the putamen and a decrease at the level of the dentate nuclei in brains with MSA. No significant differences in Fe content are observed in the dentate nuclei and the different subcortical structures between the normal and PD, PSP, LBD and CBD brains. One prejudice of this study can be due to the relative low number of patients in some of the disease groups.

Previous studies have already demonstrated Fe accumulation in the substantia nigra of PD brains, mainly in the severe forms of the disease [16]. However this does not influence the increased signal intensity on T1-weighted MRI sequence [17]. In the early stages of PD it is found to be restricted to the pars compacta of the substantia nigra [18]. In advanced stages Fe deposition extends to the pars reticularis of the sustantia nigra, the red nucleus and the globus pallidus [19]. As we did not compare early and late stages of PD in this limited series, this can explain why no differences in Fe content could be observed compared to the other groups.

In LBD, similar to other studies, we did not observe an increase of Fe in the basal ganglia and in the substantia nigra [7, 20]. Only one study reported a selective Fe increase in the substantia nigra [21].

There are some controversial results concerning the Fe

accumulation in PSP brains. A post-mortem study without MRI showed a higher Fe burden in the cerebral peduncles and substantia nigra [22]. An "in vivo" MRI study showed higher R2* values in basal ganglia, substantia nigra, and subthalamic and dentate nuclei [23]. These difference in findings can perhaps be explained by the frequent observed micro-bleeds in brainstem and cerebellum, who can be confounded with Fe deposition on T2* MRI sequences [24].

There are only sporadic case reports concerning Fe accumulation in brains with CBD, one of them showing putaminal signal hypo-intensity on T2 weighted MRI [25]. In another neuropathological study without MRI correlates widespread Fe accumulation was observed [26].

In the parkinsonian variant of MSA (MSA-P) many MRI studies show selective Fe accumulation in the putamen, contributing to the clinical diagnosis and allowing to distinct this disease from PSP [27, 32]. The loss of Fe at the level of the dentate nucleus of the cerebellum, observed in the present study, has not previously been reported. When additional cerebellar features are present in the parkinsonian variant of MSA pontine and cerebellar atrophy is seen corresponding to the distribution of the degenerative changes. The dentate nuclei and surrounding white matter are overall more or less preserved in both the parkinsonian as in the olivo-ponto-cerebellar types of MSA [33].

Brain Fe can be selective decreased in the dentate nucleus and the thalamus of patients with idiopathic restless legs syndrome, which is considered as a brain Fe deficiency disease [34]. The only progressive cerebellar disease with absence of MRI T2* hypointensity due to Fe loss in the dentate nucleus is the ataxia with oculomotor apraxia type 2 [35, 38]. Although this is a slowly progressing disease starting at young age it has similar clinical features as MSA. Even additional nigrostriatal involvement can be present [39].

There is no clear explanation why there is Fe loss in the dentate nucleus, while increased in the atrophic putamen of MSA brains.

5. Conclusion

Although the exact cause of the low Fe content in the dentate nucleus is not known it can be considered as an additional MRI diagnostic marker of MSA.

6. Disclosure

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