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Research Article

Age-Related Iron Deposition in the Deep Brain Structures of Normal Subjects: A Post-Mortem 7.0-Tesla Magnetic Resonance Study

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Abstract

Background: There are many studies concerning the iron (Fe) content in the brain during normal aging. However most of them are magnetic resonance imaging (MRI) studies performed in volunteers during life. There is a lack of post-mortem confirmation. The present post-mortem 7.0-tesla MRI study compares the Fe content in different mainly subcortical structures between young, middle- and old-aged normal brains.

Material and Methods: Thirty- five brains, consisting of 10 from young, 15 from adult and 10 from old persons without a history of any neurological disorder were submitted to a 7.0-tesla MRI. The hippocampus and 11 subcortical structures were examined: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.

Results: The Fe content was different between brains of young adults and those of middle- and old-aged ones: it was increased in the caudate nucleus, putamen, substantia nigra and red nucleus of middle-aged, compared to young adults. No statistical differences were observed between middle-aged and elderly brains.

Discussion: The increase of Fe from young tot adult age reflects the accumulation of dopamine and neuromelanin, as part of the maturation process. The absence of a significant Fe increase in the elderly can be explained by hypertrophy of the remaining pigmented neurons compensating the atrophy of the substantia nigra.

Keywords: Post-mortem 7.0-tesla MRI; Iron content; Normal brains; Aging process

Abbreviations

Fe: Iron; MRI: Magnetic Resonance Imaging; AD: Alzheimer's Disease

Introduction

In the central nervous system, iron (Fe) in several proteins is involved in many important processes such oxygen transportation, oxidative phosphorilation, myelin production, and synthesis and metabolism of neurotransmitters [1]. The Fe concentration is highest in specific nuclei of the basal ganglia and the brainstem, increasing with age [2]. The curves for R2* versus age show an exponential increase with increasing age in all the basal ganglia of healthy subjects [3]. In 6 post-mortem brains the highest Fe concentrations are found in the globus pallidus, followed by the putamen, caudate nucleus, thalamus and white matter regions [4]. Astrocytes are largely responsible for distributing Fe in the brain [5]. In the brain stem the Fe content is high in the substantia nigra and low in the locus coeruleus [6]. Striatum and brain stem structures are found to be higher in Fe concentration in older than in younger adults, whereas cortical white matter and thalamus should have lower concentrations in elderly than in young adults [7].

Higher R2*-determined Fe in the basal ganglia correlates with cognitive impairment during normal brain aging, independently of concomitant brain abnormalities [8]. Beside age body mass index and smoking are found to be associated to increased R2* values in normally aging subjects [9].

The great majority of magnetic resonance (MRI) studies are performed during life in healthy volunteers. So there is a need for an extensive post-mortem validation study of the Fe content in several post-mortem brain structures in relation to age.

The present post-mortem 7.0-tesla MRI study compares the degree of Fe deposition in a large number of subcortical structures and in the hippocampus of post-mortem brains of young- and middle-aged individuals and elderly persons without a history of neurodegenerative and/or known cerebrovascular diseases.

Material and Methods

Thirty-five 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 10 young adults (29 ± 2 years), of 15 middle-aged adults (52 ± 6 years) and of 10 elderly ones (74 ± 8 years).

The right cerebral hemisphere was deeply frozen for biochemical examination. The left hemisphere, the brainstem and most of the cerebellum were fixed in formalin for 3 weeks. After an extensive neuropathological examination a 7.0-tesla MRI Bruker BioSpin SA was used with an issuer-receiver cylinder coil of 72 mm inner diameter (Ettlingen, Germany) to evaluate different brain sections, according to a previously described method [10]. 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 parieto-occipital lobe. In addition a horizontal section through the upper brain stem and a cerebellar hemisphere were examined in the same way. 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 mean semi-quantitative values for Fe were the average of the ranking scores of the hypo-intensity on the T2* sequences in the different examined structures of each age group: no changes (R0), a few isolated spots (R1), frequent non-homogenous signal changes (R2) and a homogenous R2* signal of the whole examined structure (R3) [11]. Because the locus coeruleus is a less homogenous nucleus than the other brain stem nuclei, it is not included in our post-mortem Fe evaluation.

Statistical analyses were performed in the individual subcortical structures and the hippocampus by comparison of the Fe values between the young-adult, the middle-adult and the elderly brains. 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.

Results

Overall there is a trend of increase of Fe in all the examined samples of the adult- and old-age groups compared to the young one. However, significant statistical significance is only reached for the putamen, substantia nigra and the red nucleus (p value ≤ 0.01). In the caudate nucleus (p value ≤ 0.05) the change is only marginally significant (Figure 1). There is no statistical difference between the Fe content in the putamen of the middle- and old-aged brains, nor for the other examined structures.

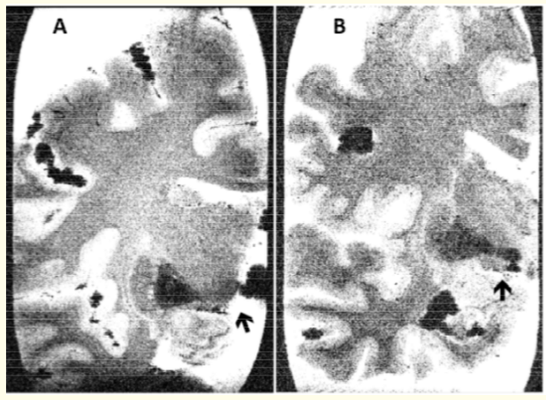

Figure 1: Comparison of coronal sections of a young-aged (A) and an adult-aged (B) normal brain on T2* sequence. Note the less hypo-intensity of the substantia nigra and the red nucleus in the former (arrow) compared to latter (latter). The globus pallidus has severe hypo-intensity in the young- and middle-aged brain section.

Only in a few brains additional neuropathological changes were present: a 51-year old female person had a small clinically silent cerebellar infarct, while in another 58-year old female a mild amount of neurofibrillary tangles (AD stage II) was present. Also in a brain of 83-year old male one cortical micro-infarct was observed.

Discussion

The present post-mortem 7.0-tesla MRI study confirms that there is a strong relation between age and regional iron content in the putamen and caudate nucleus but not in the globus pallidus and

Items	Young age (n=10)	Adult age (n=15)	Old age (n=10)
Hippocampus	0.1 (0.3)	0.3 (0.5)	0.5 (0.5)
Claustrum	0.2 (0.4)	0.5 (0.5)	0.5 (0.7)
Nucleus Caudatus	0.3 (0.5)	0.9 (0.7)*	1.1 (0.7)*
Putamen	0.4 (0.5)	1.6 (1.2)**	2.0 (1.0)**
Globus Pallidus	2.0 (1.1)	2.5 (1.1)	2.5 (1.1)
Thalamus	0.4 (0.7)	0.5 (0.7)	0.8 (0.4)
Subthalamic Nucleus	0.7 (0.7)	1.0 (0.9)	0.8 (1.0)
Corpus Geniculatum	1.4 (1.0)	1.8 (1.3)	1.7 (1.1)
Substantia Nigra	0.8 (1.0)	2.7 (0.5)**	2.5 (0.5)**
Red Nucleus	1.5 (0.5)	2.5 (0.7)**	2.5 (0.5)**
Dentate Nucleus	2.2 (0.8)	2.3 (1.3)	2.6 (1.1)

Table 1: Semi-quantitative comparison of regional iron content (standard deviation) between young-aged, adult-aged and old-aged normal brains.

P value ≤ 0.01; P value ≤ 0.05

the thalamus [12,13]. We are not able to confirm a statistical significant increase of Fe in the globus pallidus in old adults compared to young ones, as observed in some other studies [14,15]. Also no differences are found in the dentate nuclei and the hippocampi, as described in some previous studies [16,17].

There are no gender differences in our study compared to a previous one, showing that Fe increase is less in boys than in girls [18]. In an other study higher Fe content in the putamen, globus pallidus, thalamus and frontal white matter of the left cerebral hemisphere is observed, compared to the right one [19]. In our study only the left cerebral hemisphere is examined.

The main surprising findings in our study are the differences of Fe amount in the substantia nigra and red nucleus during aging: the incidence is very significantly lower in young individuals compared to middle-aged and elderly persons. No mutual differences are observed between the later two groups.

In a previous post-mortem study chemically determined Fe in the substantia nigra is 20ng/mg in the first year of life, increasing to 200ng/mg by the fourth decade and remaining stable until 90 years of age [20]. In an histological study, using cresyl violet staining, a rapid increase of pigment granule number and colouration is observed from 3 years of age until age 20, and only a further slowly increase of the pigment coloration in middle and later life [21]. All these findings have, however, not been confirmed in " in vivo" studies [22].

The increase of Fe from young tot adult age must reflect the accumulation of dopamine and neuromelanin, as part of a further maturation process during young adult life [23].

The absence of demonstration in our study of a significant Fe increase in the elderly, compared to the middle-aged group can be explained by hypertrophy of the remaining Fe pigmented neurons, compensating the atrophy of the substantia nigra during the aging process [24,25].

There is a thigh relation between Fe age-related increase and behavioural changes [26,27]. In particular Fe increase in the caudate nucleus predicts lesser improvement in working memory after repeat testing [28].

This study confirms that age has to be taken into account when evaluating the Fe content and its significance in neurodegenerative and cerebrovascular diseases.

Conclusion

The lower Fe content in the neostriatum, substantia nigra and red nucleus of young adults is the result of the progressive increase of dopamine and neuromelanin during the maturation process, while it remains stable in the elderly due to the hypertrophy of the remaining pigmented neurons, compensating the atrophy of the substantia nigra.

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Conflicts of Interest

The authors have no conflict of interest to declare.

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