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Review Article

Iron Deposition in the Brain during the Aging Process and in Neurodegenerative Diseases: A Post-Mortem Review Study

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Received: November 20, 2019; **Published:** December 30, 2019

Abstract

Background and Purpose: The role of iron (Fe) accumulation in the brain is still a matter of debate. The present review examines all the available post-mortem data in the aging brain and in those with neurodegenerative diseases.

Results: During normal aging there is a progressive increase of Fe, mainly in the basal ganglia. Most neurodegenerative diseases display Fe accumulation during the progression of their disorder. This is the most severe in frontotemporal lobar degeneration and to a lesser degree in amyotrophic lateral sclerosis and Parkinson's disease.

Conclusion: In all neurodegenerative diseases and during aging there is evidence that Fe accumulation contributes to further neuronal degeneration and promotes disease progression.

Keywords: *Post-Mortem Brain Iron; Normal Aging; Alzheimer's Disease; Frontotemporal Lobar Degeneration; Lewy Body Disease; Parkinson's Disease; Progressive Supranuclear Palsy; Amyotrophic Lateral Sclerosis; Multiple System Atrophy*

Introduction

Ferroptosis is a unique form of programmed cell death, characterized by cytosolic accumulation of iron, lipid hydroperoxides and their metabolites, and affected by the fatal peroxidation of polyunsaturated fatty acids in the plasma membrane [1]. There are many histological techniques to demonstrate iron (Fe) deposits in post-mortem brains [2].

Particle induced X-ray emission (PIXE) analysis can be used to quantify not only Fe but also other trace elements in fresh samples of different brain regions [3] (Figure 1). The accuracy of the method has been previously shown by comparison of animal brain matter examined with PIXE analysis and with instrumental neutron activation analysis in the Institute of Nuclear Sciences of the Ghent University [4].

Semi-quantitative assessment and distribution of Fe in the different brain regions and structures can also be made with 7.0-tesla magnetic resonance imaging (MRI), using the gradual echo T2*(GRE T2*) weighted sequence [5]. Although the technique is mainly used for the detection of micro-bleeds in our research centre, it can also be applied to determine the degree of mineralization in the basal ganglia and brainstem nuclei [6]. However, Fe deposition cannot be quantified in the cerebral cortex with this method. Susceptibility- weighed MRI or quantitative susceptibility mapping have to be used [7,8].

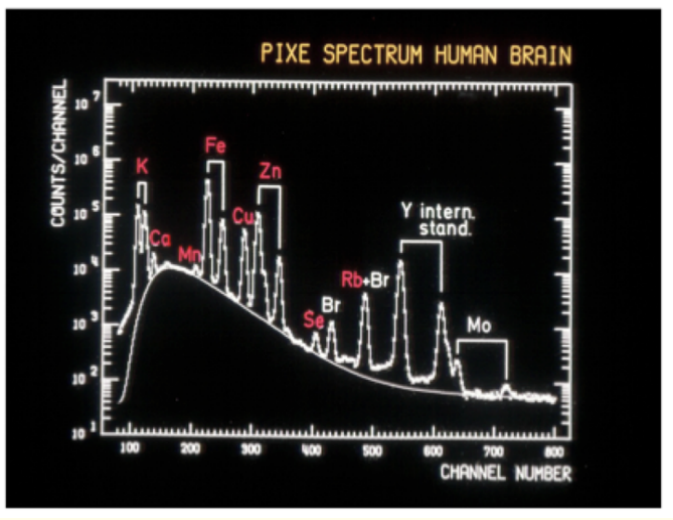

Figure 1: *Spectrum of potassium, calcium and six trace elements, including iron on particle induced X-ray examination (Institute for Nuclear Sciences, Ghent University).*

Iron deposition during normal brain aging

Astrocytes are largely responsible for the distribution of Fe in the normal brain. As capillary endothelial cells are separated from the neuropil by the end-feet of astrocytes, they are ideally positioned to transport Fe to other brain cells [9] (Figure 2).

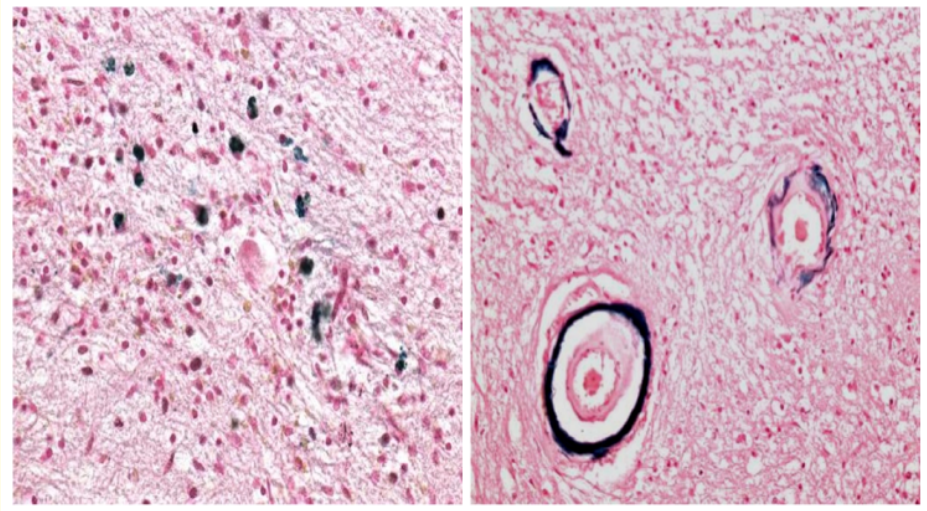

Figure 2: *Perl staining of the basal ganglia in an aging brain. Iron deposits are present in astrocytes (A) and around blood vessels at the level of the blood-brain barriere (B) (Laboratory of Neuropathology, Centre Hospitalier Universitaire de Lille).*

The highest concentrations of Fe in the cerebral hemispheres are found in the globus pallidus, followed by the putamen, the caudate nucleus and the thalamus on the transverse relaxation rates R2 and R2* MRI [10]. On PIXE analysis the Fe concentration, expressed in µg/g dry weight, is significantly higher in grey than in the white matter areas. The highest concentrations are found in the cerebral cortex, basal ganglia and brainstem nuclei [3]. The Fe concentration increases during the aging process in different human brain regions, but most strongly in the basal ganglia [11,12]. The Fe content is lower in infant brains compared to adults [13]. Also, the Fe concentration decreases after the age of 80 years [14]. This is probably due to progressive age-related neurodegenerative changes [15].

Iron deposition in neurodegenerative diseases

Neurodegeneration with brain Fe accumulation has initially been described in a heterogeneous group of inherited rare clinical and genetic entities with cognitive decline and behavioral abnormalities [16]. However, different other neurodegenerative diseases also display various degrees of Fe accumulation.

The main debate concerns the possible role of Fe accumulation in Alzheimer dementia (AD) [17,18]. There are many single reports showing an increase of Fe around senile plaques and neurofibrillary tangles [19- 22]. A meta-analysis reported that several articles from one laboratory showed a large increase of Fe in AD cortex, while seven other articles failed to reproduce the hypothesis that transition metal overload accounts for oxidative injury in this disease [23]. Severe cerebral amyloid angiopathy (CAA) contributes to Fe increase in the cerebral cortex of AD brains due to their more frequent association and presence of micro-bleeds [24]. In our post-mortem 7.0-tesla MRI study of AD brains only a moderate Fe increase in the caudate nucleus was observed [25].

Frontotemporal lobar degeneration (FTLD) comprises a spectrum of clinical syndromes and is pathologically and genetically heterogeneous [26]. In FTLD a selective and highly significant increase of Fe in the neo-striatum and to a lesser degree in the paleo-striatum, thalamus and the sub-thalamic nucleus is observed on MRI examination (Figure 3). The Fused in Sarcoma (FUS) and the TAR domain binding Protein 43kDa (TDP) sub-groups have overall a higher Fe content than the Tau sub-group [25]. However, an old previous post-mortem study had also showed global increase of Fe in the brain of two patients with Pick's disease, which is now considered as a Tau type of FTLD [27].

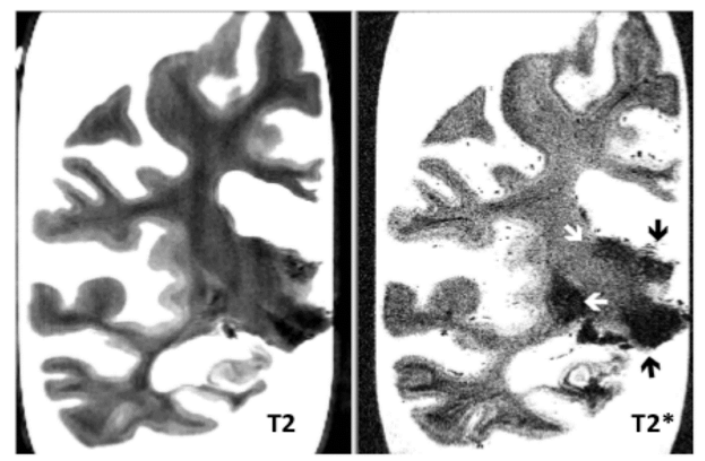

Figure 3: *7.0-tesla MRI of a post-mortem section of a brain hemisphere with frontotemporal lobar degeneration. There is extensive frontal and temporal atrophy on T2 and T2*. Iron accumulation in the basal ganglia (white arrows) and in the thalamus and subthalamic nuclei (black arrows) is seen on the T2* sequence (INSERM 1171, France).*

Disturbance of Fe metabolism is also suspected in amyotrophic lateral sclerosis (ALS) as serum Fe and ferritin are increased in this disease [28]. In ALS Fe accumulation has been shown in the ventral cervical spinal cord [29]. There is still a matter of debate whether the hypo-intensity in the pre-central gyrus on GRE T2* MRI, considered as a biomarker for ALS, is due to Fe deposition [30,31]. Our MRI study showed Fe increase in the caudate and the sub-thalamic nuclei of ALS brains [32] (Figure 4). ALS features are found in 15% associated to FTLD brains [33]. Fe accumulation has already been previously described in a patient with the FTLD-ALS complex [34]. It is now suspected that both disease entities are linked [35]. They share both the presence of TDP-43 and FUS immune cytoplasmic inclusions in neuronal and glial cells [36].

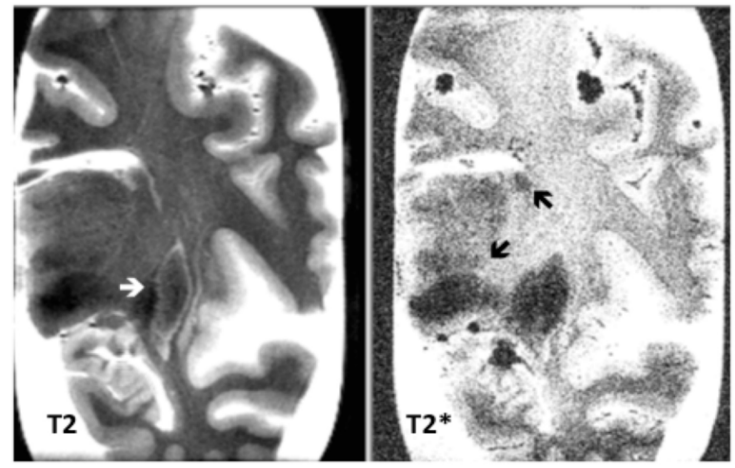

Figure 4: *7.0-tesla MRI of a hemisferic section of a brain with amyotrophic lateral sclerosis. A putaminal infarct is present on the T2 sequence (white arrow) with iron load on the T2* sequence. Iron accumulation is present in the caudate and subthalamic nuclei on T2* sequence (black arrows) (INSERM 1171, France).*

Fe accumulation in the substantia nigra of Parkinson's disease (PD) patients is mainly observed in the severe forms of the disease [37] and does not influence the increased signal intensity on MRI [38]. In the early stages it is restricted to the pars compacta of the substantia nigra [18]. As the disease progresses the Fe deposition also increases and extends to the pars reticularis of the substantia nigra, the red nucleus and the globus pallidus [39]. The increase of Fe is evident in astrocytes, macrophages, reactive microglia and non-pigmented neurons, and in damaged areas devoid of pigmented neurons [40].

In Lewy body dementia (LBD) no significant Fe increase is observed in the basal ganglia and in the substantia nigra [41].

In progressive supranuclear palsy (PSP) a higher FE burden in the cerebral peduncles and substantia nigra has been described [42]. Another "*in vivo*" study showed higher R2* values in basal ganglia, substantia nigra, and sub-thalamic and dentate nuclei [43,44]. In our post-mortem 7.0-tesla MRI study of brains with confirmed diagnosis of PSP no significant increase of Fe is observed in the deep brain structures. The discrepancies between the different studies can perhaps be explained by the predominance of micro-bleeds in the brainstem and cerebellum. Also a loss of Fe signal in the substantia nigra and the red nucleus can be observed in the end-stage of the disease due to the severe neuronal loss [45].

In the parkinsonian variant of multiple system atrophy (MSA) many MRI studies have confirmed the Fe accumulation in the putamen, in which the most severe atrophy occurs. This allows differentiation of this disease from PSP, which also presents clinically mainly as a parkinsonian syndrome [46-48].

In advanced cases of Huntington's disease Fe accumulation in the globus pallidus, the putamen and the caudate nucleus is observed, dependent on the degree of severity of the disease [49,50].

Although Wilson's disease is an autosomal recessive inherited disorder of hepatic copper metabolism with accumulation in the brain, also increased Fe deposition has been described, respectively in the dentate nucleus of the cerebellum [51], in the globus pallidus [52] and in the putamen [53].

Conclusion

Fe accumulation in the brain is not restricted to the normal aging process or to neurodegenerative diseases but can also been observed in other disorders such as in those with cerebral infarcts, multiple sclerosis and traumatic brain injury [54-57].

In neurodegenerative diseases there is evidence of a consistent correlation between the severity of the cognitive dysfunction and the degree of Fe deposition [58]. Excess levels of Fe can lead to increased oxidative stress in AD and PD diseases [59]. Although there is already Fe accumulation in "pure" AD brains, it further increases in those with concomitant CAA [60]. Fe can facilitate Aß deposition and accelerate the disease process [61]. There are ongoing studies to treat AD patients with neurorestorative iron chelators [62].

In PD brains Fe interacts with dopamine and neuromelanin in dopamine and norepinephrine neurons. The main Fe compound in dopamine and norepinephrine is the neuromelanin-iron complex. Neuromelanin serves to trap iron [63]. As Fe dysfunction, including its uptake, storage and release, plays a key role in PD, there is evidence to support Fe chelation as a plausible therapeutic strategy [64].

The main surprising observation in our post-mortem study is the severe Fe accumulation in the deep brain nuclei of FTLD and to a lesser degree in ALS brains [25,32]. Pathological involvement of the basal ganglia in FTLD is common, mainly due to the interconnection between the basal ganglia and the frontal cortex [65]. TDP-43 or FUS immune cytoplasmic inclusions in neuronal and glial cells are observed in the TDP-43 and FUS types of FTLD as well as in ALS [35]. H63D polymorphism can represent the disease-modifying gen, fostering Fe deposition in the basal ganglia [66,67]. A logical therapeutic approach should be to start clinical studies with iron-selective chelators [68].

As conclusion it can be stated that in all neurodegenerative diseases and during normal aging there is evidence that Fe accumulation contributes to further neuronal degeneration and promotes disease progression.

Disclosure

The author has nothing to declare in relation to this article. No funding was received for the publication of this article.

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Volume 12 Issue 1 January 2020