

Abnormal Iron Content in Deep Grey Matter Structures of MS Patients as a Function of Age

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Introduction:

Iron is the most abundant metal in the human brain, and plays an important role in many metabolic and functional processes (1-2). For instance, iron has been shown to be necessary for the synthesis of oligodendrocytes and is a key factor in oxygen transport. Ferritin and hemosiderin are considered the two forms of iron storage elements in cells (1). Due to the importance of iron in the human body, any iron misregulation can be a major factor of neuronal death leading to neurodegenerative diseases such as MS. It has been shown that there is a strong correlation between high iron concentrations (abnormal iron presence) in the brain and neurodegeneration (3). The disturbance in iron metabolism may occur at several levels such as iron uptake and release, storage, intracellular metabolism and regulation. Moreover, in diseases such as MS, there could be multiple sources of iron buildup in lesions: a) iron could come from myelin or oligodendrocyte debris followed by concentrated iron in the macrophages, or b) iron as a product of local microhemorrhages following venous or venule wall damage. On the cellular level, new proteins (the stress protein heme oxygenase-1, for example) have been identified as key players in iron metabolism. Although their specific role in the pathogenesis of neurodegenerative diseases is not yet well-established (2), suppressing heme oxygenase-1 protein has been shown to decrease the motor deficits seen in experimental autoimmune encephalomyelitis (EAE) models. Free iron is known to cause the formation of highly reactive hydroxyl radicals that can trigger cell membrane dysfunction and chronic microglial activation (2). In neurodegenerative diseases, iron accumulates through a cyclic inflammatory process. During this mechanism, inflammation attracts iron-rich macrophages, whose presence increases the local iron content. This iron accumulation leads to further inflammation and iron deposition, causing the system to be self-sustainable (5). To emphasize iron involvement in MS, several studies suggest iron deposition in different parts of the brain, such as white matter and gray matter areas (2,5). This evidence of iron deposition has been supported by histological studies as well as by animal models. Iron deposition has been typically seen in the neurons and oligodendrocytes (2) in the thalamus and the putamen (6) as well as in macrophages and microglia. In order to classify this iron deposition as normal or abnormal, we felt that it would be necessary to follow iron load over time for MS patients and normal volunteers as a function of age.

Materials and methods:

14 MS patients were recruited for this study with mean age of 39 ranging from 19 to 66 years old. A velocity compensated 3D gradient echo sequence was used to generate susceptibility weighted images (SWI) with a high sensitivity to iron content. All SWI images were acquired at 1.5T with a resolution of 0.5x0.5x2mm³. Imaging parameters were TR=49ms, TE=40ms; FA=20°; and BW=80 Hz/pixel and 220 Hz/pixel. The SWI filtered phase images were used as a means to quantify iron content. The correlation between T2 signal intensity and phase was used to compare potential inflammation with putative iron content. We performed a region-of-interest analysis of 7 structures in the deep gray matter, including the globus pallidus (GP), the caudate nucleus (CN), the putamen (PUT), the thalamus (THA), the substantia nigra (SN), the red nucleus (RN) and the pulvinar thalamus (PT). A two region analysis concept was used where each structure is separated into two ROI: a high iron content region and a normal iron content region. These regions were differentiated using threshold values cited in previous work (7). The measured values were compared to previously established baseline iron content in these structures as a function of age. Linear regression was performed for the normal data to examine iron as a function of age.

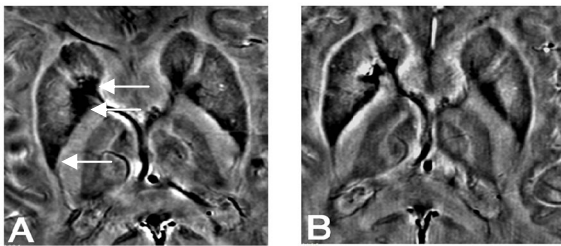


Figure 1. Visualization of the thalamic structures using SWI filtered phase images in the same patient scanned twice: once in 2006 and again in 2008, showing iron increase in the deep gray matter structures (arrows).

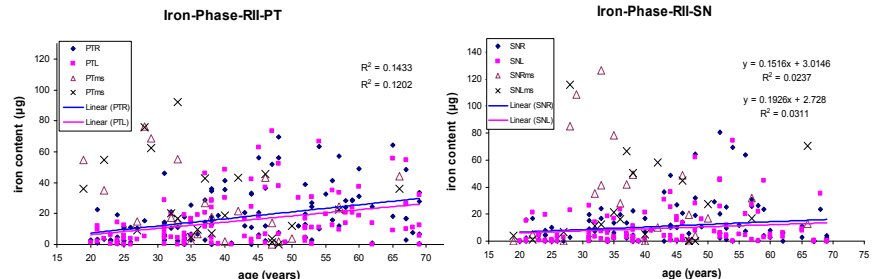


Figure 2: Region 2 iron content as a function of age in the pulvinar thalamus (left plot) and substantia nigra (right plot) using filtered phase SWI images.

Results:

Figure 1 shows a case with clear iron overload in the deep gray matter structures: CN, PUT and GP. This iron increase was also seen in the SN and slightly in the RN. In normal subjects, we found that iron showed a linear dependence on age up to the age of 40 years for most structures and after that the dependence with age became even stronger. We found that the area of the high iron content region increased with age over and above the increase of the average iron content per pixel. Overlaying the 14 MS cases on these plots reveals that MS patients have significantly higher iron content than normal subjects. The most dramatic increases in iron content were seen in MS patients under the age of 35 years in the PT (Figure 1- left) and SN (Figure 2- right). 71% of all the patients have shown abnormal iron deposition in at least one of these structures.

Discussion and Conclusion:

Our results show that there is a strong iron dependence on age in most deep gray matter structures. For instance, the thalamus, the red nucleus as well as the pulvinar thalamus showed a linear increase throughout the whole life span. Despite this natural increase in iron, for young MS patients (under the age of 40 years), there was a clear increase in local iron content in the PT and SN. A key direction to pursue will be to compare cognitive and motor scores with these increases in iron content. Further, understanding the iron increase in MS may become an important direction to better understand the etiology of MS.

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