Iron Mapping in Multiple Sclerosis

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KEYWORDS

• Iron • Ferritin • Multiple sclerosis • MR imaging • Magnetic susceptibility • Neurodegeneration • Biomarker

KEY POINTS

- Most nonheme brain iron is stored in the globular storage protein ferritin, which can be assessed by MR imaging through relaxation enhancement and susceptibility effects.
- R_2^* mapping and quantitative susceptibility mapping represent the currently most relevant approaches for assessing iron levels in vivo.
- Cerebral iron levels are highest in deep gray matter and are associated with age, and disease duration and disability in multiple sclerosis.
- Iron mapping in multiple sclerosis lesions and white matter remains an unmet need.

INTRODUCTION

Owing to the existence of the blood–brain barrier, the iron content of the brain is largely decoupled from the iron stores of the remaining body. This inaccessibility makes brain iron more difficult to study and also explains why less is known about iron metabolism in the brain compared with other organs.

Consequently, extrapolation of iron levels in the brain from those measured in serum or other organs is misleading. So far, MR imaging thus represents the only noninvasive tool on hand for this purpose, because it can use several mechanisms affected by the presence of iron, including relaxation enhancement and susceptibility effects.

Improvements in MR imaging methodology over recent years have already allowed gaining important insights into multiple sclerosis (MS)-related alterations of brain iron metabolism. This review, therefore, gives an overview on current MR imaging techniques for brain iron mapping and their application to MS. In addition, possible limitations and future directions that promise advances in this field are discussed briefly.

IRON DISTRIBUTION AND METABOLISM IN THE NORMAL BRAIN

The normal adult brain contains approximately 60 mg of nonheme iron, which corresponds with 1% of the total iron content of the human body.[1] Iron in the brain is needed for oxygen transport, myelination, electron transport, storage and activation, and many other relevant metabolic processes.[2]

Most of the iron is tightly complexed in proteins, but iron may also be present in a soluble 'pool' of low-molecular-weight complexes such as Fe(III) ATP and ferric citrate. The concentration of free iron is very low and is estimated to be less than 10^{-18} M Fe^{3+} and 10^{-8} M Fe^{2+}.[3] Most of the nonheme iron is stored in ferritin that keeps iron in a soluble and nontoxic state. Ferritin consists of a spherical protein shell, 12 nm in diameter, that encapsulates up to 4500 iron ions as hydrated iron oxide (Fe^{3+}) nanocrystal with a diameter of up to 8 nm.[4] Ferritin is composed of 24 subunits of varying composition, a heavy (H) polypeptide chain and a light (L) polypeptide. These peptides have different physiologic roles, including the uptake and oxidation of ferrous iron, growth of the

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iron oxide nanocrystal, and reduction and release. The H-subunit has a specific ferroxidase activity for rapid iron uptake, whereas the L-subunit facilitates mineralization.[4,5] The relative abundance of H- and L-ferritin varies between cell types[6] and between brain regions.[7] Although oligodendrocytes express similar amounts of L- and H-subunits, neurons express mostly H-ferritin. Ferritin is not distributed uniformly across the brain, but most of the iron is intracellular and in lysosomes and mitochondria. The highest ferritin concentrations are found in oligodendrocytes and their processes, in motor neurons, and in myelinated axons close to the inner shell of the myelin sheet.[8–10] Ferritin found at the surface of myelin is associated with the ferritin in the processes of the oligodendrocytes.[10]

It is commonly accepted that iron accumulates in the brain as a function of age, with almost no iron present at birth.[1] The accumulation can be best described by an exponential saturation function, reaching a ceiling effect after the fourth decade of life.[11,12] In the adult brain, iron concentration varies greatly across different brain regions. Concentrations of up to 200 mg/kg wet weight can be found in the globus pallidus whereas cerebral white matter usually has iron levels around 40 mg/kg.[1,13] Interestingly, the reason for this iron accumulation is still unclear because, in the adult brain, only a few percent of all stored iron is really needed for iron-dependent processes. A possible explanation for this implies that iron transport to the brain mostly represents a 1-way traffic.

As indicated, transferrin or other iron transporters cannot simply cross the blood–brain barrier, which is also why brain iron levels are independent from serum iron levels.[14] Iron transport into the brain over the blood–brain barrier is an active process that is regulated through transferrin receptors on capillary endothelial cells in the parenchyma and the choroid plexus.[15] In contrast, iron leaves the brain with the bulk outflow of cerebrospinal fluid (CSF) through the arachnoid villi and other channels.[16]

Brain maturation and other developmental processes can cause a delay or shift between inflow and outflow. A recent study has elucidated an unbalanced import and outflow of brain iron using a staggered design, where rats were fed with 3 stable iron isotope tracers.[17] The turnover rate of iron entering the brain resulted in a half-life of approximately 9 months. The observed tracer accumulation in brain iron over the study period was extrapolated to an increase of brain iron in the rat brain by approximately 30% from early adulthood to the end of life, which corresponds well with observations in the human brain.[1]

ALTERED IRON HOMEOSTASIS IN THE BRAIN WITH MULTIPLE SCLEROSIS

Perturbation of iron homeostasis in MS seems to occur at several metabolic levels and, because an excess of iron may induce oxidative stress, it has been speculated that iron may be involved in the pathophysiology and pathogenesis of MS.[18]

So far, histology has detected iron within microglia at the edge of MS lesions,[19,20] corresponding with the dark rings observed on susceptibility weighted MR imaging in vivo.[21] The iron in the microglia has been assumed to originate from extracellular space, where it had presumably been released by myelin and oligodendrocytes upon their destruction. It was speculated consequently that iron in microglia cells might propagate chronic, low-grade inflammation unlinked to demyelination per se, that might in turn promote neurodegeneration and disease progression.[20]

In contrast, the center of most MS lesions is characterized by a loss of iron while only very few chronic active lesions demonstrate increased iron levels. In normal-appearing white matter (NAWM), a loss of iron has been found to be paralleled by a loss of myelin and oligodendrocytes with disease progression, and these processes in turn could be related to chronic inflammation.[20]

MS-related iron accumulation in deep gray matter (GM), its relation to iron levels in and around MS lesions, and the cellular distribution have not been studied by histology so far. In CSF, transferrin and ferritin levels in MS patients are within normal ranges. Elevated ferritin levels in CSF have been reported only in progressive MS so far.[22]

MAGNETIC PROPERTIES OF IRON COMPOUNDS

MR imaging can assess most iron compounds in the brain owing to their distinct magnetic properties. The magnetic susceptibility, that is, the response of a material or atom to an external magnetic field, is determined largely by unpaired electrons in unfilled shells. Because of its 4 unpaired electrons in the *d*-shell, iron has great potential for a high paramagnetism (ie, positive magnetic susceptibility, which allows a material to become magnetized), but the effective susceptibility largely depends on the binding and spin state. The 4 iron atoms in an oxygenated hemoglobin molecule, for instance, have a spin number of zero and are therefore diamagnetic, that is, they cannot be magnetized.[23] In contrast, Fe^{3+} in some sulfur proteins can reach a maximum spin of 5/2,[24] which corresponds with a magnetic moment of 5.92 Bohr magnetons.[25]