Migraine and brain changes

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Chapter 3

Iron accumulation in migraine

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IRON HOMEOSTASIS

Iron plays an important role in many biochemical processes. In general, iron is essential for proper functioning of the body due to its involvement in oxygen transport, oxygen storage, transportation of electrons, glucose metabolism, synthesis of neurotransmitters and myelin, and DNA replication [Connor and Benkovic, 1992;Kell, 2009;Rouault and Cooperman, 2006]. The body needs to maintain iron concentrations stable, because iron shortage as well as iron excess lead to dysfunction. Excess of iron is harmful because of its role in the formation of highly reactive hydroxyl radicals, which cause damage to all components of a cell, including proteins, lipids, and DNA. The imbalance between reactive oxygen species and the ability of the body to detoxify the reactive intermediates, or to repair the resulting damage, is called oxidative stress. Oxidative stress is involved in many diseases, including neurological diseases. To prevent an excess of iron, the body regulates the amount of it by changes in uptake, storage and release in relation to its need. Recently, the protein hepcidin was found to play an important role in this process of iron homeostasis by regulating intestinal iron absorption [Ganz and Nemeth, 2011]. Ferritin is the protein that serves to store iron in a soluble and non-toxic form, to deposit it in a safe form, and to transport it to areas where it is required [Maguire et al., 1982]. Ferritin is also involved as a delivery protein in the brain [Hulet et al., 1999] and is especially present in larger concentration in the basal ganglia [Aquino et al., 2009]. Iron is important for the brain, as the brain requires relative much energy and iron is an essential component of ATP synthesis [Gordon, 2003]. In addition, iron is essential for the production of lipids and cholesterol and is therefore important in the synthesis and metabolism of myelin and neurotransmitters [Levenson and Tassabehji, 2004;Thomas and Jankovic, 2004]. Brain iron homeostasis is different from other organs because of several brain specific characteristics. First, brain tissue is protected from free influx of iron from the plasma by the blood brain barrier [Burdo et al., 2003;Burdo and Connor, 2003]. This barrier, together with the ventricular system, actively regulates iron transportation by transferring receptors on capillary endothelial cells[Connor, 1994] as well as on endothelial cells of the choroid plexus [Moos, 1996]. Second, the concentration of iron varies between different parts of the brain. Brain regions with motor function (extrapyramidal regions) contain more iron than non-motor parts [Koeppen et al., 1995].

IRON AND THE BRAIN

In 1922, Spatz already recorded the distribution of iron in the different areas of the brain by immersion of brain slices in a staining solution (Perl's stain or the Prussian Blue stain). Today, iron in the brain can be detected by using magnetic resonance imaging (MRI) and is visible on T2-weighted and T2*-weighted images as hypointensity caused

by field heterogeneity and magnetic susceptibility effects [Drayer et al., 1986a;Haacke et al., 2005]. A higher load of iron is associated with more hypointensity on the MR image [Haacke et al., 2005;Schenck, 1995]. Recent evidence shows a good correlation between conclusions on iron distribution in brain areas from post-mortem data and MR imaging [Peran et al., 2009a]. In adults, the largest concentration of iron is found in the globus pallidus, red nucleus, substantia nigra (including pars reticularis), followed by caudate nucleus and putamen. By staining of brain slices as well as by MR imaging, infants have demonstrated to have only minimal concentrations of iron in the brain [Diezel PD, 1955;Drayer et al., 1986b]. The increase in iron concentration in the brain is speculated to be associated with a change in vascularisation [Faucheux et al., 1999]. Age-specific iron accumulation in the human brain has been described as early as in 1958, by Hallgren [Hallgren and Sourander, 1958]. He already demonstrated, by staining of brain slices, an increase of especially ferritin in specific brain structures, including the globus pallidus and putamen as preferred sites during the first three decades of human life [Hallgren and Sourander, 1958]. More recent post-mortem studies have shown higher ferritin levels at older age in several basal ganglia, including caudate nucleus, putamen, substantia nigra, and globus pallidus [Connor et al., 1995;Zecca et al., 2001]. These findings have been confirmed by MR imaging results, demonstrating age-related iron increase among these basal ganglia [Bartzokis et al., 1997]. Two recent MRI studies on changes in brain iron concentration related to aging show an increase of iron in all basal ganglia with increasing age, with specific age-related iron deposition patterns for the different structures[Cherubini et al., 2009;Peran et al., 2009b]. For instance, the globus pallidus shows a clear increase of iron concentration from childhood into adulthood. Substantia nigra already contains more iron than the globus palidus at younger age and increase follows a steeper curve, whereas both putamen and caudate nucleus show a much slower rate of iron increase with aging [Aquino et al., 2009]. Furthermore, iron increase follows a precise accumulation direction from posterior to anterior and from medial to lateral parts of the basal ganglia [Aquino et al., 2009]. Below the age of 15 years, iron accumulation is largest in the medial part of the internal globus pallidus, whereas it is largest in the lateral part between the ages of 15-30 years of age [Aquino et al., 2009]. Mechanisms responsible for early accumulation in the substantia nigra and globus pallidus are not clear, but it could be the result of preferential or abnormal local neuronal uptake of iron [Bartzokis et al., 1997], abnormal transportation of iron along white matter pathways connecting these nuclei [Drayer et al., 1986a;Aoki et al., 1989] or it is based on a decreased efficiency of the usual iron transport from the basal ganglia to areas elsewhere due to age-related loss of neurons [Dietrich and Bradley, Jr., 1988;Cross et al., 1990]. After the age of 50 years, all basal ganglia show a large variability between subjects for hypointensity on MRI, because the T2 values of deep nuclei are significantly influenced by non-iron-related tissue changes, such as myelin loss or an increase in water content associated with microvascular changes [Aquino et al., 2009;Bartzokis et al., 1997;Schenker et al., 1993]. Despite the large variability of brain

iron accumulation among elderly subjects, it has been suggested that if hypointensity is found in the caudate nucleus, this could be a sign of central nervous system disease instead of being part of a normal aging process [Milton et al., 1991]. This was confirmed by a recent MRI study among elderly subjects which described presence of hypointensity of the caudate nucleus to be associated with the presence of a higher load of age-related cerebral changes, like more atrophy and a higher load of white matter hyperintensities [van Es et al., 2008]. Iron excess in the basal ganglia is damaging, because it increases the tissue's susceptibility for apoptosis and inflammation, it could lead to basal ganglia dysfunction due to decreased protein synthesis, and the tissue becomes more vulnerable for the damaging effect of reactive oxygen species. This destructive process is being summarized by Zecca as iron accumulation, invasion and increased reactivity [Zecca et al., 2004].

IRON AND NEUROLOGICAL DISORDERS

Increased iron levels in pathological relevant brain structures and iron-mediated oxidative stress are associated with several neurological disorders, including Parkinson disease, Alzheimer disease, Huntington disease, Friedreich ataxia, Amyotrophic Lateral Sclerosis, Neurodegeneration with Brain Iron Accumulation (formerly Hallervorden-Spatz syndrome), and also migraine. Every disorder has its specific mechanisms and locations of brain iron accumulation.

In Parkinson disease, iron excess has been demonstrated in the substantia nigra [Sian-Hulsmann et al., 2010;Kell, 2010;Bartzokis et al., 1997;Sian-Hulsmann et al., 2010;Kell, 2010;Gotz et al., 1990;Gorell et al., 1995;Ryvlin et al., 1995] and was found to be associated with local oxidative stress, as indicated by protein disruption [Goodwin et al., 2000] and oxidative DNA damage [Sanchez-Ramos et al., 1987;Alam et al., 1997;Poon et al., 2004a;Poon et al., 2004b].

In the brains of patients suffering from Alzheimer disease, iron accumulation occurs without the normal age-related increase in ferritin, thereby increasing the risk of oxidative stress [Zecca et al., 2004]. Iron excess is found early in the disease process in several brain structures, including the basal ganglia [Connor and Benkovic, 1992;Bartzokis et al., 1997;Bartzokis and Tishler, 2000;Bartzokis et al., 2000]. Although the origin of elevated brain iron levels is unclear, the role of iron is apparent: both senile plaques and neurofibrillary tangles, characteristic for the disease, have been shown to accumulate iron [Good et al., 1992;Levine, 1997;Sayre et al., 2000;Rottkamp et al., 2000]

In Huntington disease, iron accumulation has been demonstrated in the putamen, caudate nucleus, and globus pallidus by post-mortem studies and MRI studies [Bartzokis and Tishler, 2000;Chen et al., 1993;Dexter et al., 1992;Rutledge et al., 1987]. The iron excess contributes to oxidative stress, as indicated by protein disruption [Marnett,

2000;Stadtman, 2001] and oxidative DNA damage[Alam et al., 1997;Marnett, 2000; Poon et al., 2004a;Sanchez-Ramos et al., 1987].

Friedreich ataxia was first described by the German physician Nikolaus Friedreich in 1860 [Friedreich, 1863] and is marked by a genetic mutation causing the mitochondrial protein frataxin to be lacking, leading to impaired iron export from the mitochondria, cytoplasmic depletion, induction of plasma membrane proteins involved in iron uptake, and consequent iron overload [Berg and Youdim, 2006], including excess of iron in the dentate nucleus [Koeppen et al., 2007;Waldvogel et al., 1999].

In Amyotrophic Lateral Sclerosis (ALS), increased serum levels of ferritin have been reported [Goodall et al., 2008] and MR images of the brains of ALS patients show iron accumulation in the dentate nucleus [Langkammer et al., 2010]. Although origin of iron excess in ALS is not yet clear, increased oxidative damage to DNA, lipids, and proteins can be seen early in the disease process, which makes it plausible that iron is at least partly involved [Berg and Youdim, 2006].

Brain MRI evaluation of patients suffering from Neurodegeneration with Brain Iron Accumulation usually show iron accumulation in the globus pallidus (typical but non-specific eye-of-the-tiger sign), the substantia nigra, and the dentate nucleus [Savoiardo et al., 1993;Hayflick et al., 2003;Swaiman, 1991;Halliday, 1995] and histopathology demonstrates iron excess accompanied by neuronal loss and gliosis [Savoiardo et al., 1993;Galvin et al., 2000]. It is proposed that accumulation of cysteine, which chelates iron, causes oxidative stress and leads to the increase or iron in the basal ganglia [Berg and Youdim, 2006;Perry et al., 1985].

IRON AND MIGRAINE

Few studies have been published describing the association between migraine and iron levels in the brain. After earlier reports describing functional blood oxygenation level-dependent MR imaging demonstrating the involvement in pain of several specific brain structures, Welch and colleagues focused their attention on the periaqueductal grey matter, red nucleus and substantia nigra in relation to migraine [Welch et al., 2001]. It was speculated that, since these brain structures in particular show high iron levels and are densely populated with neurotransmitters that can generate free radicals, repeated migraine attacks and associated repeated hypoxia could result in release of free radicals and cell damage. This mechanism could be seen in those brain areas as accumulation of iron, similar to the processes already known in other neurodegenerative diseases as mentioned above.

To test this hypothesis, a clinic-based cross-sectional brain MRI study was carried out to assess iron levels by measuring transverse relaxation rates [Welch et al., 2001]. This study included seventeen migraine patients, diagnosed using International Headache Society (IHS) criteria, seventeen patients with chronic daily headache, and seven-

teen control participants; aged 20-64 years. Compared with controls, significant higher iron levels were found in the periaqueductal grey matter of the migraine and chronic daily headache patients. No differences were found between men and women, nor between migraine with and without aura. In addition, an association between iron accumulation and illness duration was found.

Because no relation was found between increased iron levels and age in this study, authors speculated that iron accumulation must be related to repeated headache attacks. Several explanations for the high iron content of the periaqueductal grey matter among migraineurs were given by the authors. First, as a result of the migraine related pain combined with oxidative stress, this structure could be abnormal highly metabolic active in migraineurs, since transferring-receptor binding is proportional to the metabolic activity of the neuron, and in turn may be influenced by nociceptive function. Overexpression of transferrin receptors might result in iron accumulation and free radical cell damage, a process that may be aggravated by eventual hypoperfusion during migraine attacks. As a consequence, metabolism and iron uptake in the remaining neurons would be increased, leading to even more iron accumulation. Second explanation for high iron concentration is the presence of gliosis, since glial cells have high iron content, but the authors found no evidence of gliosis on MR images of these participants. From this study, it was concluded that iron accumulation in the periaquaductal grey matter among migraineurs was the result of an impaired iron homeostasis, possibly associated with neuronal dysfunction or damage [Welch et al., 2001].

To evaluate these interesting findings in a larger, population-based group of migraineurs, brain MR images of 138 migraineurs (IHS criteria) and 75 matched controls were analyzed for iron concentration in deep brain nuclei as part of the CAMERA-study (Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis) [Kruit et al., 2009]. Because measurements in older subjects are increasingly influenced by non-iron related factors, analyses were separated into subjects younger than 50 years and older than 50 years. In the younger group, compared to controls, migraineurs demonstrated higher iron concentrations in several nuclei, including putamen, globus pallidus, and red nucleus. No differences were found between men and women, nor between migraine with and without aura. Among these participants under 50 years, an association was found between longer migraine duration and higher iron concentration in putamen, caudate nucleus, and red nucleus [Kruit et al., 2009]. These structures are all known to be involved in the normal central nociceptive network [Iadarola et al., 1998].

Data from both studies suggest that repeated migraine attacks, or the accompanying pain, are associated with higher iron concentration in several brain structures involved in central pain processing and migraine pathology. It is not known whether the increase in iron is caused by repetitive activation of the pain nuclei or whether the increased iron itself inflicts damage to these structures via free radicals in oxidative stress. Furthermore, theoretically, damage of these pain-processing nuclei could lead to chronification of migraine in specific patients. As to date, studies on this subject have a cross-

sectional design, the assumption that recurring attacks lead to accumulation of iron can not be verified. A longitudinal study is needed to follow-up on migraineurs and controls to carefully evaluate their general health status, headache history, course of migraine over the years, and measurements of brain iron concentration.

SUMMARY

During aging, iron accumulates in the brain, specifically in the basal ganglia, following a certain distribution pattern. Iron accumulation could be the result of neuronal loss, followed by substitution by cells with higher iron loads, or of leakage of the blood brain barrier, allowing iron to access the brain in higher concentration. Several neurological disorders, as well as migraine, are associated with iron excess in the brain. Higher brain iron concentration generates a reactive iron overload, which invades and damages neurons and other cells. It is not clear yet whether iron accumulation in basal ganglia plays a primary or secondary role in the pathogenesis.

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