IRON AND GGT - BRAIN: OXIDATIVE STRESS, NEURODEGENERATION, PARKINSON'S, ALZHEIMER'S, HUNTINGTON'S DISEASES

As on other Science Library pages, we do not present a lengthy narrative on each neurodegenerative disease, but rather will briefly summarize or quote the most relevant take-home points and/or research conclusions from each study. Article titles are linked to abstracts archived at the U.S. National Library of Science. Several articles on GGT and the brain are included. Many articles also have Full free text PDF links. Our Iron Science Library pages include:

- IRON: Your Heart, Cardiovascular System, Oxidative Stress and Mortality
  - IRON: Cancer, Oxidative Stress and Mortality
- IRON: Diabetes, Metabolic Syndrome, Liver Diseases, Oxidative Stress and Mortality
- IRON: Bacterial, Fungal, Viral, Protozoan Infections and infectious Processes
- (see also) Iron Reduction Therapy
- Insulin Resistance: Iron, GGT & Oxidative Stress
- Hereditary Hemochromatosis
- GGT Science Library

Towards a unifying, systems biology understanding of large-scale cellular death and destruction caused by poorly liganded iron: Parkinson's, Huntington's, Alzheimer's, prions, bactericides, chemical toxicology and others as examples (1) Full free text

In this comprehensive 2010 review, the author "highlights the literature evidence suggesting that the degenerative effects of many diseases and toxicological insults converge on **iron dysregulation**." Based on the literature, the author also suggests, "...**despite the many kinds of agent involved, there may be at least some unifying mechanisms of such cell death and destruction**." *[Health-e-Iron note: **Figures 4**, **1** and **3** from this review appear below]*

IRON Science Library
IRON - Cancer
IRON -Diabetes
IRON - BRAIN
IRON - INFECTION
Hereditary Hemochromatosis
Iron Reduction Therapy

Check out our monthly specials and comprehensive selection of other tests

RESOURCES & Page Links

Who should be Tested?

Women's Health - IRON, GGT & Oxidative Stress

FeGGT LifePro™ HEALTH RISK Calculator

IRON Science Library

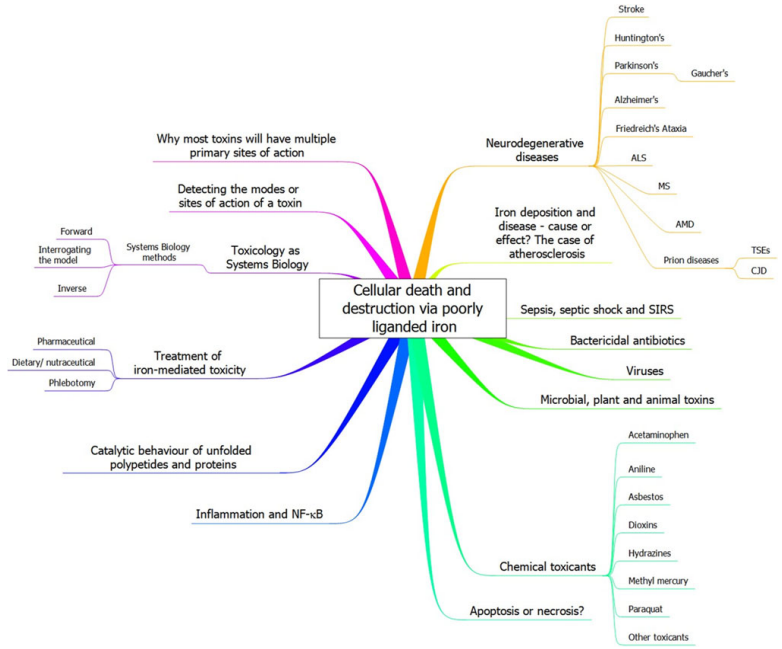

Fig. 4 A mind map (Buzan 2002) setting out the structure of this review. To read this start at ‘‘1 o’clock’’ and move outwards and clockwise

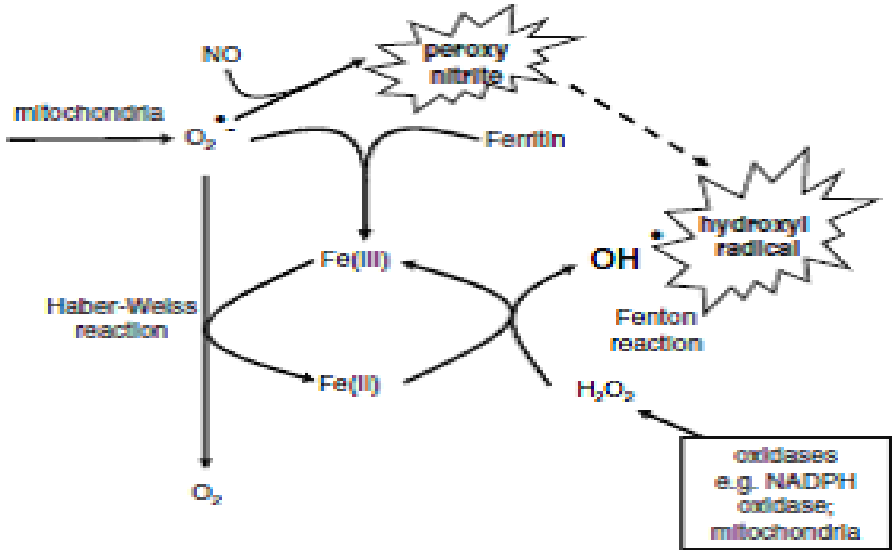

Fig. 1 The Haber-Weiss and Fenton reactions combine using poorly liganded iron in a **catalytic cycle** to produce the very damaging hydroxyl radical. Poorly liganded iron can also be liberated via the destruction of haem and other iron-containing substances. Peroxynitrite anion (ONOO-) is produced by the reaction of superoxide and nitric oxide (NO•) which when protonated (pH ca 6.5–6.8) decomposes to OH• and NO2

- IRON - Heart
- IRON - Cancer
- IRON - Diabetes
- IRON - Brain
- IRON - Infection

GGT Science Library

- GGT - Heart
- GGT - Cancer
- GGT - Diabetes
- GGT/IRON - Brain

Hereditary Hemochromatosis

- **Iron Reduction Therapy**
- **GGT & Healthy Food**
- **More Healthy Foods** & Antioxidants
  - IRON Food Content
  - Calculate BMI

Washington University School of Medicine Disease Risk Calculator: Your Disease Risk

- **Iron Disorders Institute**
- **Hemochromatosis Foundation**

IRON DEFICIENCY:

Iron Disorders Institute Pages

- **IRON Deficiency**
- **IRON and Diet**
- **IRON Deficiency Blog**

VIDEO LINKS

[Health-e-Iron note: Reminder, when GGT is elevated, glutathione and most other antioxidants are insufficient!]

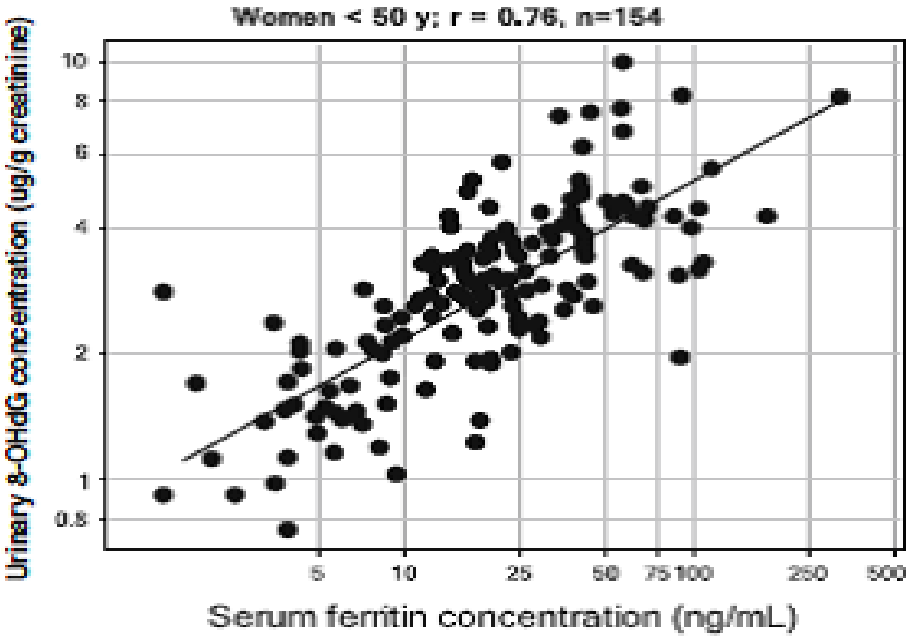

Fig. 3 Very strong relationship between serum ferritin concentrations and urinary concentrations of the DNA damage/oxidative stress marker 8-hydroxy-20-deoxyguanosine. Data are replotted from Fig. 1 of Hori et al. (2010)
Arch Toxicol (2010) 84:825–889 827 123

Iron toxicity in neurodegeneration (2) Free full text

In this 2012 review the authors suggest, "Iron is an essential element for life on earth, participating in a plethora of cellular processes where one-electron transfer reactions are required. Its essentiality, coupled to its scarcity in aqueous oxidative environments, has compelled living organisms to develop mechanisms that ensure an adequate iron supply, **at times with disregard to long-term deleterious effects derived from iron accumulation**. **However, iron is an intrinsic producer of reactive oxygen species, and increased levels of iron promote neurotoxicity because of hydroxyl radical formation, which results in glutathione consumption, protein aggregation, lipid peroxidation and nucleic acid modification**."

Serum elevated gamma glutamyl transferase levels may be a marker for oxidative stress in Alzheimer's disease (3) Free full text

The authors noted, "...(GGT) plays a role in cellular glutathione uptake, which is an important element of antioxidant mechanisms. An increase in serum GGT is thought to be an early and sensitive marker of oxidative stress. Oxidative stress has a role in the pathogenesis of Alzheimer's disease (AD). The aim of this study was to investigate the GGT levels in AD." "In this cross-sectional study, 132 patients with AD (mean age: 74.1 +/- 7.4, female 62.9%) and 158 age- and gender-matched normal controls (mean age: 74.5 +/- 6.3, female 67.1%) were evaluated. ... Serum GGT, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase concentrations were determined." "Median (min-max) GGT levels were 18 (**9-70) in AD group** and 17 (**5-32**) in normal controls. Mann-Whitney U test showed that **GGT levels were significantly higher in AD patients** (**p = 0.012**). Linear regression analysis revealed **AD was an independent correlate of elevated GGT levels**. **Hypertension**, **diabetes mellitus**, total **cholesterol**, and **low density lipoprotein cholesterol** were **not associated with GGT levels**." The researchers concluded, "**GGT levels were increased significantly in AD patients**..."

Iron accumulation in Alzheimer disease is a source of redox-generated free radicals (4) Free full text

This 1997 laboratory research completed in the U.S., the researchers noted, " Damage from free radicals has been demonstrated in susceptible neuronal populations in cases of Alzheimer disease. In this study, **we investigated whether iron, a potent source of the highly reactive hydroxyl radical that is generated by the Fenton reaction with H2O2, might contribute to the source of radicals in Alzheimer disease**. The researchers conclude, "**Taken together, these findings indicate that iron**

"*Understanding Antioxidants*" (2:31)

"Antioxidants vs. free radicals" (3:10)

Dr. Mercola on "Is iron helping or slowly killing you?"

Dr. Mercola on iron as "anti-antioxidant?" (8:44)

To learn more about the antioxidant protection afforded by various fruits, you can read more on this site:

Fruitsinfo.com

Check out our monthly specials and comprehensive selection of other tests

RESOURCES & Page Links

Who should be Tested?

Women's Health - IRON, GGT & Oxidative Stress

FeGGT LifePro™ HEALTH RISK Calculator

IRON Science Library

- IRON - Heart
- IRON - Cancer
- IRON - Diabetes
- IRON - Brain

accumulation could be an important contributor toward the oxidative damage of Alzheimer disease." *[Health-e-Iron note: Figure 1 from this review appears below]*

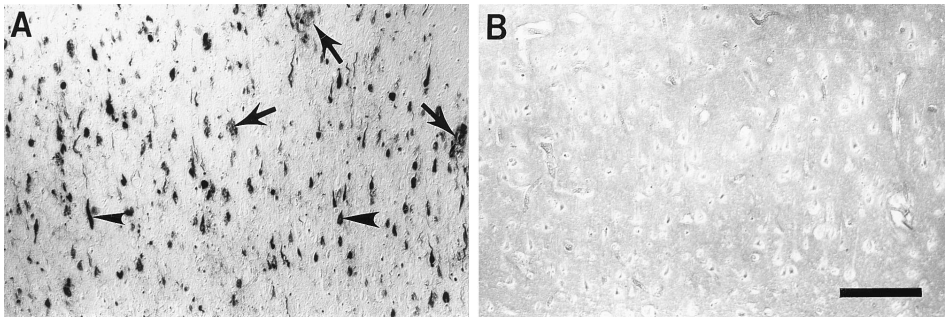

FIG. 1. Histochemical detection of iron in AD (A) compared with control cases (B) show striking association of iron with neurofibrillary tangles (arrowheads) and senile plaques (arrows) characteristic of the AD brain. (Scale bar = 200 mm.)

High ferritin levels have major effects on the morphology of erythrocytes in Alzheimer's disease (5) Free full text

The authors noted, "Unliganded **iron both contributes to the pathology of Alzheimer's disease** (AD) **and also changes the morphology of erythrocytes** (**RBCs**). We tested the hypothesis that these two facts might be linked, i.e., that the RBCs of AD individuals have a variant morphology, that might have diagnostic or prognostic value." The researchers reviewed the literature and test four different microscopy techniques to compare and analyze trend between different levels of serum ferritin in individuals affected by AD. Based of their analyses, the authors stated, "**We argue that high ferritin levels may contribute to an accelerated pathology in AD**. Our findings **reinforce the importance of** (**unliganded**) iron in **AD**, and **suggest the possibility both of an early diagnosis and some means of treating or slowing down the progress of this disease**.

Alzheimer disease: evidence for a central pathogenic role of iron-mediated reactive oxygen species (6)

In this 2004 review the researchers suggest, "**Since oxidative damage represents one of the earliest pathological changes in Alzheimer disease, it is likely that aberrant redox activity is among the earliest changes in the transition to the disease state. In this review, we consider the wealth of evidence implicating a central role for metals in Alzheimer disease**."

Detection and localization of markers of oxidative stress by in situ methods: application in the study of Alzheimer disease (7)

This 2010 review describes the chemistry relevant to oxidative stress and the proteins generated in the process. The authors' relate the following in the concluding remarks of their abstract: "In neurodegenerative diseases, heme oxygenase-1 (HO-1) induction is coincident with the formation of neurofibrillary tangles. This enzyme that converts **heme, a prooxidant, to biliverdin/bilirubin (antioxidants) and free iron has been considered an antioxidant enzyme.** But seen in the context of arresting apoptosis, HO-1 and tau may play a role in maintaining the neurons free from the apoptotic signal (cytochrome c), **since tau has strong iron-binding sites. Given the importance of iron as a catalyst for the generation of reactive oxygen species, changes in proteins associated with iron homeostasis can be used as an index of cellular responses.** One such class of proteins is the **iron regulatory proteins (IRPs) that respond to cellular iron concentrations by regulating the translation of proteins involved in iron uptake, storage, and utilization. Therefore, IRPs are considered to be the central control components of cellular iron concentration**."

Causes of oxidative stress in Alzheimer disease (8) Free full text

The abstract of this 2007 review states, "**Oxidative stress is one of the earliest events of Alzheimer disease (AD)**, with implications as an important mediator in the onset, progression and pathogenesis of

- IRON - Infection

GGT Science Library

- GGT - Heart
- GGT - Cancer
- GGT - Diabetes
- GGT/IRON - Brain

Hereditary Hemochromatosis

- **Iron Reduction Therapy**
- **GGT & Healthy Food**
- **More Healthy Foods** & Antioxidants
- IRON Food Content
- Calculate BMI

Washington University School of Medicine Disease Risk Calculator: Your Disease Risk

- **Iron Disorders Institute**
- **Hemochromatosis Foundation**

IRON DEFICIENCY:

Iron Disorders Institute Pages

- **IRON Deficiency**
- **IRON and Diet**
- **IRON Deficiency Blog**

VIDEO LINKS

[Health-e-Iron note: Reminder, when GGT is elevated, glutathione and most other antioxidants are insufficient!]

"*Understanding Antioxidants*" (2:31)

"Antioxidants vs. free radicals" (3:10)

Dr. Mercola on "Is iron helping or slowly killing

the disease. **The generation of reactive oxygen species (ROS) and its consequent cellular damage/response contributes to much of the hallmark AD pathology seen in susceptible neurons**. The sources of ROS-mediated damage appear to be multi-faceted in AD, with interactions between abnormal mitochondria, **redox transition metals**, and other factors. In this review, we provide an overview of these potential causes of oxidative stress in AD."

Therapeutics for Alzheimer's disease based on the metal hypothesis (9) Free full text

In this 2008 paper,the authors pospose, "The excessive accumulation of Abeta oligomers in the synaptic cleft would then be predicted to adversely affect synaptic neurotransmission. Based on these findings, we have proposed the "**Metal Hypothesis of Alzheimer's Disease**," which stipulates that the neuropathogenic effects of Abeta in Alzheimer's disease are promoted by (and possibly even dependent on) **Abeta-metal interactions**."

Increased iron and free radical generation in preclinical Alzheimer disease and mild cognitive impairment (10) Free full text

In this 2010 report based on previously reported findings the researchers state, "It is now established that oxidative stress is one of the earliest, if not the earliest, change that occurs in the pathogenesis of Alzheimer's disease (AD). Consistent with this, mild cognitive impairment (MCI), the clinical precursor of AD, is also characterized by elevations in oxidative stress." They further indicate, **"Increased iron was found at the highest levels both in the cortex and cerebellum from the pre-clinical AD/MCI cases. Interestingly**, **glial accumulations of redox-active iron in the cerebellum were also evident in preclinical AD patients and tended to increase as patients became progressively cognitively impaired**. Our findings suggests that an **imbalance in iron homeostasis is a precursor to the neurodegenerative processes leading to AD and that iron imbalance is not necessarily unique to affected regions**."

Frontiers in Alzheimer's disease therapeutics (11) Free full text

In 2011, this research team discusses the therapeutics available for the treatment of Alzheimer's disease and the status of promising research throughout the world. "**Current therapeutics** on the market, including cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, **provide symptomatic relief but do not alter progression of the disease.** Therefore, **progress in the areas of prevention and disease modification may be of critical interest.** In this review, we summarize novel AD therapeutics that are currently being explored, and also mechanisms of action of specific drugs within the context of current knowledge of AD pathologic pathways. In the full paper they refer to redox metals (iron and copper) as follows: "In this regard, nanoparticle metal chelators present an exciting future avenue to accomplish anti-aggregation of Aβ. **Redox metals iron and copper** are shown to be elevated in AD brain ...and appear to induce Aβ oxidation and self-assembly ... Consequently, **metal chelators attempt to obstruct the interaction of Aβ and redox metals to prevent aggregation in AD vulnerable neurons**."

HFE gene variants affect iron in the brain (12) Free full text

In this 2011 review, the authors describe how one of the common **hemochromatosis gene variants, H63D**, (**approximately 74 million people in the U.S. have at least one H63D mutation**) "...is associated with **iron** dyshomeostasis, **increased oxidative stress**, **glutamate release**, **tau phosphorylation**, **and alteration in inflammatory response**, **each of which is under investigation as a contributing factor to neurodegenerative diseases**." This review discusses, "the current knowledge of the association of the HFE gene variants with neurodegenerative diseases: amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and ischemic stroke."

Oxidative Stress and the Aging Brain: From Theory to Prevention (13) Free full text

The authors this 2007 review discuss the "**free radical theory of aging**," which postulates "**that aging and its related diseases are the consequence of free radical-induced damage to cellular macromolecules and the inability to counterbalance these changes by endogenous anti-oxidant**

defenses." **They further discuss effective dietary interventions that include whole food sources of antioxidants such as fruits**, **vegetables**, **nuts and grains**.

Metals, oxidative stress and neurodegeneration: a focus on iron, manganese and mercury (14) Free full text

In this 2013-published paper the authors review and note: "Essential metals are crucial for the maintenance of cell homeostasis. Among the 23 elements that have known physiological functions in humans, **12 are metals**, **including iron (Fe)** and manganese (Mn). **Nevertheless**, **excessive exposure to these metals may lead to pathological conditions**, **including neurodegeneration**. Similarly, exposure to metals that do not have known biological functions, such as mercury (Hg), also present great health concerns. **This review focuses on the neurodegenerative mechanisms and effects of Fe**, Mn and Hg. **Oxidative stress (OS)**, **particularly in mitochondria**, **is a common feature of Fe**, Mn and Hg **toxicity**. However, the primary molecular targets triggering OS are distinct. **Free cationic iron is a potent pro-oxidant and can initiate a set of reactions that form extremely reactive products**, such as OH. Mn can oxidize dopamine (DA), generating reactive species and also affect mitochondrial function, leading to accumulation of metabolites and culminating with OS. Cationic Hg forms have strong affinity for nucleophiles, such as -SH and -SeH. Therefore, they target critical thiol- and selenol-molecules with antioxidant properties. **Finally**, **we address the main sources of exposure to these metals, their transport mechanisms into the brain**, **and therapeutic modalities to mitigate their neurotoxic effects**." *[Health-e-Iron note: **Figure 1** from this paper is below]*

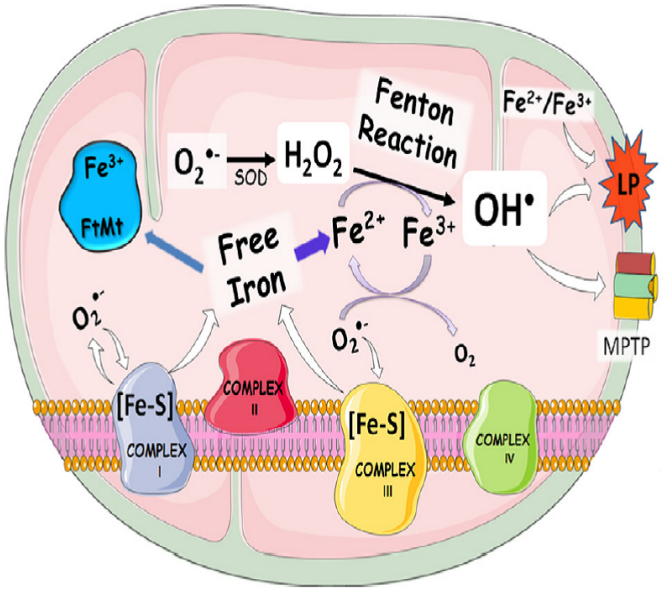

Fig. 1. Fe and mitochondria oxidative stress: Fenton reaction and hydroxyl radical formation are critical factors in Fe-induced mitochondrial toxicity; this type of reaction is thought to be central in neurodegeneration. Fe can start mitochondrial oxidative stress via interaction with different reactive oxygen species (ROS). Free Fe can be released from mitonchondrial Fe–sulfur clusters in complexes I and III upon interaction with ROS (in the figure it is shown the release of superoxide anion by these complexes and the potential oxidation of Fe–S cluster by $O_2^{\bullet-}$; the oxidation of the Fe–sulfur clusters can increase the free Fe in the mitochondrial matrix. This can facilitate the operation of the toxic Haber–Weiss and Fenton reactions, feeding a general pro-oxidant cycle). The redox pair Fe^{2+}–Fe^{3+} can also directly stimulate lipid peroxidation, which can intensify the oxidative stress and contribute to mitochondrial and cellular demise via mPTP formation. Free cationic Fe (regardless of the redox state) is the critical element for neurotoxicity and it can be buffered by intramitochondrial ferritin (FtMt), which acts as an antioxidant protein in the mitochondrial matrix.

Serum elevated gamma glutamyltransferase levels may be a marker for oxidative stress in Alzheimer's disease (15)

[Health-e-Iron note: although this section is primarily focused on iron in the brain, GGT has been shown to play a central role in the oxidative damage process that is evident in many neurodegenerative disorders.] This research was published in 2008. The researchers first noted, "Gamma glutamyltransferase (**GGT**) plays a role in cellular glutathione uptake, which is an important element of antioxidant mechanisms. **An increase in serum GGT is thought to be an early and sensitive marker of oxidative stress**. **Oxidative stress has a role in the pathogenesis of Alzheimer's disease** (**AD**). **The aim of this study was to investigate the GGT levels in AD**." "In this cross-sectional study, 132 patients with AD (mean age: 74.1 +/- 7.4, female 62.9%) and 158 age- and gender-matched normal controls (mean age: 74.5 +/- 6.3, female 67.1%) were evaluated. For cognitive assessment, MMSE and clock drawing tests were performed; DSM-IV and NINCDS-ADRDA criteria were used. Serum GGT,

aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase concentrations were determined." "**Median** (min-max) **GGT levels were 18** (9-70) **in AD group and 17** (5-32) **in normal controls**. **Mann-Whitney U test showed that GGT levels were significantly higher in AD patients** (**p = 0.012**). **Linear regression analysis revealed AD was an independent correlate of elevated GGT levels**. **Hypertension**, **diabetes mellitus**, **total cholesterol**, **and low density lipoprotein cholesterol were not associated with GGT levels**. The researchers concluded, "**GGT levels were increased significantly in AD patients**. To evaluate the role of GGT as a marker of oxidative stress in AD, further studies are needed."

Relationship between carbohydrate-deficient transferrin, gamma-glutamyl transferase, and mean corpuscular volume levels and alcohol-related brain volume decreases in male drinkers (16)

This 2012-reported study was undertaken in the Netherlands. The objective of the investigation was to evaluate "the association between **mean corpuscular volume** (**MCV**), **carbohydrate-deficient transferrin** (**CDT**), **and gamma-glutamyl transferase** (**GGT**) **levels and gray and white brain matter in male drinkers to find out which if any of these biomarkers of alcohol consumption is indicative for alcohol-related differences in brain volume**." "Plasma levels of CDT, GGT, and MCV and magnetic resonance imaging-determined brain gray and white matter volumes were assessed in 55 male drinkers. Current alcohol intake and lifetime alcohol intake were determined by self-report measures. The relationship between MCV, CDT, and GGT and brain volumes was explored using multiple linear regression analyses." "**There was a significant negative relationship between plasma GGT and MCV levels and gray matter volumes**. **Middle-aged male drinkers with highly elevated GGT and MCV levels** (**twice the standard deviation above the mean**) **have 4-12% less parietal and occipital gray matter than males with average GGT and MCV levels**. **There was no association between CDT levels and brain gray or white matter**." The researchers concluded, "**Elevated GGT and MCV levels may be indicative of alcohol-related gray-matter decline in male drinkers**. **The link with GGT may reflect that elevated GGT levels are a sign of increased oxidative stress**. **The link with MCV levels may reflect a decreased oxygen transport to the brain**."

Relationship between liver function and brain shrinkage in patients with alcohol dependence (17) Free full text Slide with charts

This study was reported in 2012. The investigators noted, "**Oxidative stress has been proposed as one of the mechanisms of alcohol-induced brain shrinkage and alcohol-induced hepatotoxicity**. The aim of this study was to assess the correlations between liver function and **brain volume** (**BV**) measurements in patients with alcohol dependence." "**We recruited 124 patients with alcohol dependence and 111 healthy control subjects from National Institute of Health**, **National Institute on Alcohol Abuse and Alcoholism inpatient alcohol treatment program. Gamma-glutamyl transferase** (**GGT**), **aspartate aminotransferase** (**AST**), **alanine aminotransferase** (**ALT**), as well as hematocrit (Hct) and albumin were assayed shortly after admission. Magnetic resonance imaging examination was conducted in both groups (after 3-week abstinence in the patient group). We used stepwise linear regression analyses to determine the variables most strongly correlated with brain shrinkage." "**Patients with alcohol dependence had lower BV**, **and greater brain shrinkage as measured by gray matter ratio** (**GMR**), **white matter ratio** (**WMR**), **brain ratio** (**BR**), **and higher cerebrospinal fluid ratio ratio** (**CSFR**) **compared with their healthy counterparts**. **Age and sex were significantly correlated with some BV measurements in both patient and control groups**. Body mass index (BMI) was significantly correlated with CSFR, BR, GMR, and WMR; Hct with CSFR and BR; **serum GGT level with BV**, **CSFR**, **BR**, **GMR**, **and WMF in the patient group**. **No biological variables were correlated with BV indices in the control group**. **In gender-stratified analysis**, **age was significantly correlated with brain shrinkage in male patients but not in female patients**. **Serum GGT level in male and female patients**, **Hct in male patients**, **and AST levels in female patients were significantly correlated with brain shrinkage**." The investigators concluded, "**Our results showed that the higher levels of liver function indices**, **especially GGT**, **correlated with BV shrinkage as measured using CSFR**, **BR**, **GMR**, **and WMR in patients with alcohol dependence but not in controls**. **Serum GGT level outweighed aging effect on brain shrinkage in female patients**."

Premenopausal hysterectomy is associated with increased brain ferritin iron (18) Free full text

This 2012 reported study was undertaken at the the David Geffen School of Medicine at UCLA in Los Angeles. The researcher's stated: "**Iron is essential for triggering oligodendrocytes to myelinate**, **however**, **in gray matter (GM) iron increases with age and is associated with age-related**

degenerative brain diseases. **Women have lower iron levels than men**, **both in the periphery and in the brain**, **particularly in white matter (WM)**, **possibly due to iron loss through menstruation**. We tested the hypothesis that hysterectomy could increase WM iron levels. We assessed 3 WM and 5 gray matter regions in 39 postmenopausal women, of whom 15 had premenopausal hysterectomy, utilizing a validated magnetic resonance imaging technique called field-dependent R2 increase (FDRI) that quantifies ferritin iron. A group of 54 matched male subjects was included for comparison. **Amongst women**, **hysterectomy was associated with significantly higher frontal lobe WM iron**. **Men had higher iron levels than women without hysterectomy in 3 brain regions but did not differ from women with hysterectomy in any region**. **The results suggest that menstruation-associated blood loss is a source of gender differences in brain iron**." The researcher's concluded that, "**It is possible that brain iron can be influenced by peripheral iron levels and may thus be a modifiable risk factor for age-related degenerative diseases**."

Oxidative damage and mutation to mitochondrial DNA and age-dependent decline of mitochondrial respiratory function (19)

In this review 1998 the authors discuss, "the production of the reactive oxygen species (ROS) and free radicals in the mitochondria." and **the role of increased ROS generation**, **which increases oxidative stress and oxidative damage**, **in the pathogenesis of degenerative diseases**. They suggested, "**This vicious cycle operates in different tissue cells at different rates and thereby leads to the differential accumulation of mutation and oxidative damage to** mtDNA **in human aging**."

Alterations in Brain Transition Metals in Huntington Disease: An Evolving and Intricate Story (20)

This study 2012 examined **transition metal (including iron)** deposition in the brains of 34 patients with symptomatic Huntington's disease. The subjects were compared to 56 matched healthy controls and 28 Huntington's disease gene carriers. **Transmission metal deposits increased from onset and through disease progression**. The researchers concluded, "**An important and early role of altered metal homeostasis is suggested in the pathogenesis of Huntington's disease**."

Brain iron deposition fingerprints in Parkinson's disease and progressive supranuclear palsy (21)

This 2012 study reviewed and compared the anatomical distribution of brain iron accumulations in classical Parkinson's disease patients with that in cases of progressive supranuclear palsy. "**We report that an abnormal brain iron accumulation is a marker for ongoing neurodegeneration in both conditions**, **but the conditions differ with respect to the anatomical distribution of these accumulations**."

Iron dysregulation in movement disorders (22)

In this 2012 review, the authors state, "Neurodegeneration with brain iron accumulation (NBIA) involves several genetic disorders, two of which, aceruloplasminemia and neuroferritinopathy, are caused by mutations in genes directly involved in **iron metabolic pathway**..." "Increased cellular iron uptake in these diseases may be caused by impaired recycling of iron which normally involves lysosomes. Abnormal iron utilization by mitochondria, as has been proposed in Friedreich's ataxia, is another possible mechanism of iron accumulation. **Other**, **more common degenerative movement disorders**, **such as Parkinson's disease**, **Huntington's disease**, **multiple system atrophy and progressive supranuclear palsy also exhibit increased brain iron content**."

Brain structure in healthy adults is related to serum transferrin and the H63D polymorphism in the HFE gene (23) Free full text

This 2012 research report was published by a team of investigators fro UCLA. They examined common variants in genes associated with transferrin levels. They "...**found that a commonly carried polymorphism (H63D at rs1799945) in the hemochromatotic HFE gene was associated with white matter fiber integrity. This gene has a well documented association with iron overload. Our statistical maps reveal previously unknown influences of the same gene on brain microstructure and transferrin levels. This discovery may shed light on the neural mechanisms by which iron affects cognition, neurodevelopment, and neurodegeneration**."

Iron and neurodegeneration in multiple sclerosis (24) Full free text

This Austrian research group used recently developed MRI technology to quantify brain iron levels in multiple sclerosis patients. The summary of this 2011 report suggests, "**increased iron deposition has been consistently reported to occur in multiple sclerosis, but its role in pathogenetic processes of this disease has not yet been completely clarified. Whether increased brain iron levels are also the cause or only the consequence of tissue destruction is still a matter of debate**." *[Health-e-Iron note: **Figure 2** from this review appears below]*

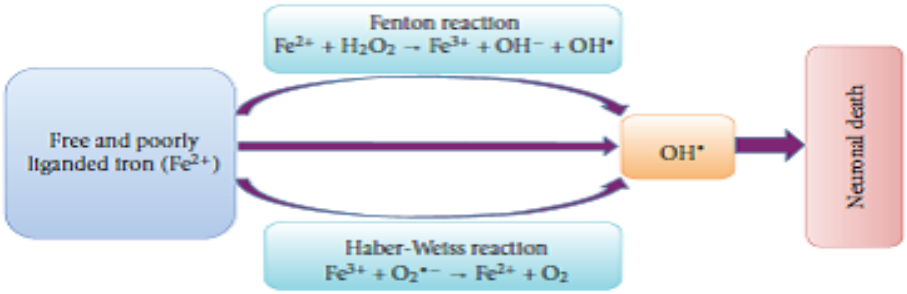

Figure 2: Generation of reactive and damaging hydroxyl radicals (OH•). Free Iron (Fe2+) reacts trough the Fenton reaction with hydrogen peroxide, leading to the generation of very reactive and damaging hydroxyl radicals (OH•). Superoxide can also react with ferric iron in the Haber-Weiss reaction leading to the production of Fe2+, which then again affects redox cycling. The highly reactive hydroxyl radicals lead to oxidative stress-induced lipid peroxidation, mitochondrial dysfunction, and increase in intracellular free-calcium concentration, and finally causing neuronal death

Iron deposition and inflammation in multiple sclerosis. Which one comes first? (25) Full free text

This is a 2011 commentary reviews some of the recent literature covering the role of iron and the pathogenesis of multiple sclerosis. There is nothing in this article that settles the issue of the relative importance and **juxtaposition of iron and inflammation in the development of multiple sclerosis**.

Iron deposition is independent of cellular inflammation in a cerebral model of multiple sclerosis (26) Full free text

This 2011 research was an underlying mouse model study that was referred to in the above commentary. The researcher concluded, "**The findings indicate that iron deposition around vessels can occur independently of inflammation providing evidence against the hypothesis that iron deposits account for inflammatory cell infiltrates observed in MS**."

Iron and neurodegeneration in the multiple sclerosis brain (27)

This was a 2013-reported study from Austria. "**Iron may contribute to the pathogenesis and progression of multiple sclerosis (MS) due to its accumulation in the human brain with age**. Our study focused on non-heme iron distribution and the **expression of the iron-related proteins ferritin, hephaestin and ceruloplasmin in relation to oxidative damage in the brain tissue of 33 MS and 30 control cases**. **"We found an age-related increase of iron in the white matter of controls as well as in patients with short disease duration**. In chronic MS, however, there was a significant decrease of iron in the normal appearing white matter (NAWM) with disease duration, when corrected for age. This decrease of iron in oligodendrocytes and myelin was associated with an up-regulation of iron-exporting ferroxidases. **In active MS lesions, iron was apparently released from dying oligodendrocytes, resulting in extracellular accumulation of iron and uptake into microglia and macrophages. Iron-containing microglia showed signs of cell degeneration. At lesion edges and within centers of lesions, iron accumulated in astrocytes and axons. Interpretation: Iron decreases in the NAWM of MS patients with increasing disease duration**." The researchrs concluded, "**cellular degeneration in MS lesions leads to waves of iron liberation, which may propagate neurodegeneration together with inflammatory oxidative burst**."

Mechanisms of neurodegeneration shared between multiple sclerosis and Alzheimer's

disease (28)

In this 2011 review the author compares the disease mechanisms and commonality between Alzheimer's and multiple sclerosis. Among other things, the author concludes, "**liberation of toxic iron from intracellular stores may augment radical formation**. **Finally reactive oxygen species are also produced in the course of mitochondrial injury itself**. **Anti-oxidant and mitochondria protective therapeutic strategies may be beneficial both in multiple sclerosis and Alzheimer's disease in particular in early stages of the disease**."

Iron overload triggers redox-sensitive signals in human IMR-32 neuroblastoma cells (29)

In this 2011 laboratory study of the pathology of several neurodegenerative diseases, the investigators determined that **ferric** ammonium sulfate introduced to human neuroblastoma **cells caused increased oxidative cell levels and cell death**.

Iron overload in diabetic retinopathy: a cause or a consequence of impaired mechanisms? (30) Full free text

This 2010 review article describes the process in which the impairment of **iron homeostasis in the eye might mediate the disease process in diabetic retinopathy through destruction of heme molecules induced by hyperglycemia**. "In the diabetic eye there is an impairment of iron homeostasis, thus leading to iron overload. The mechanisms involved in this process include: **(1) Destruction of heme molecules induced by hyperglycemia (2) Intraretinal and vitreal hemorrhages (3) Overexpression of the renin-angiotensin system**. **The main consequences of iron overload are the following: (1) Retinal neurodegeneration due to the increase of oxidative stress (2) Increase of AGE-RAGE binding (3) Defective phagocytosis of retinal pigment epithelium**, **which generates the accumulation of autoantigens and the synthesis of proinflammatory cytokines**."*[Health-e-Iron note: **Figure #1** from this review appears below]*

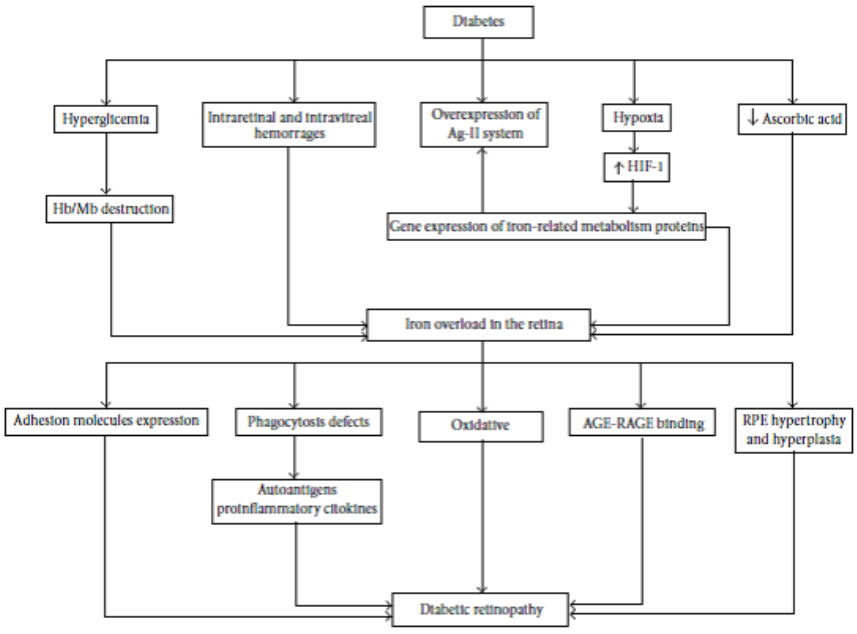

Figure 1: Scheme illustrating how diabetes influences iron metabolism in the retina and the pathogenic consequences

Increased iron levels correlate with the selective nigral dopaminergic neuron degeneration in Parkinson's disease (31)

This 2011 study of mice describes the molecular process in which **increased iron levels may lead to degeneration of dopamine neurons in the region of the brain associated with Parkinson's disease**.

Brain ferritin iron may influence age- and gender-related risks of neurodegeneration (32)

This 2007 study using MRI technology assessed brain iron in 165 healthy adults age 19-82. They observed a significant positive relationship between brain iron and age and that women had significantly lower ferritin iron than men in five regions. The researched prefaced this study with earlier findings that, "**Men are more likely to develop such diseases at earlier ages than women but brain iron levels increase with age in both genders**." The researchers concluded, "This is the first demonstration of gender differences in brain ferritin iron levels. **It is possible that brain iron accumulation is a risk factor that can be modified**. **MRI provides the opportunity to assess brain iron levels in vivo and may be useful in targeting individuals or groups for preventive therapeutic interventions**."

Brain ferritin iron as a risk factor for age at onset in neurodegenerative diseases (33)

This 2004 study explores the association of brain iron and the hemochromatosis genotypes, male gender in both Parkinson's disease and Alzheimer's disease and younger age onset in Parkinson's disease. The authors suggest, "**The results support the suggestion that elevated ferritin iron and its associated toxicity is a risk factor for age at onset of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease**."

Prevalent iron metabolism gene variants associated with increased brain ferritin iron in healthy older men (34) Full free text

In 2010 the UCLA researchers who published the above two papers studied brain iron in eight brain regions in 35 men and 31 women and determined which subjects had any of the common hemochromatosis related genotypes. The researchers stated, "**Brain iron increases with age, is higher in men, and is abnormally elevated in several neurodegenerative diseases, including AD** (Alzheimer's disease) **and Parkinson's disease, where it has been reported to contribute to younger age at onset in men. Men with the common hemochromatosis genotypes had significant higher brain iron content that the other men. The same genotype effect was observed among and women; and women had lower brain iron than men**."

Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity (35) Full free text

This 2003 research reviews data from 588 incident cases of Parkinson's disease and describes age, gender and ethnic variations.

The relevance of iron in the pathogenesis of Parkinson's disease (36) Free full text

This 2011 review covers the various ways iron could be complicit in Parkinson's disease. "**Iron-mediated cellular destruction is mediated primarily via reactive oxygen or/and nitrogen species induced oxidative stress**. **Furthermore**, **these pathogenic mechanisms appear to be closely interlinked to the cascade of events leading to cellular death. There are conflicting reports about the stage during disease progression at which nigral iron change occurs in PD**. **Some have found that there are no changes in iron content SN in asymptomatic incidental Lewy body disease, suggesting it may represent a secondary event in the cascade of neuronal degeneration**. **In contrast**, **others have found an elevation of iron in SN in pre-clinical stages**. **These discrepancies may be attributed to the occurrence of different sub-groups of the disease. This concurs with the notion that PD represents a group of related diseases with a number of potential pathogenic pathways**." *[Health-e-Iron note: **Figure 2** from this review appears below]*

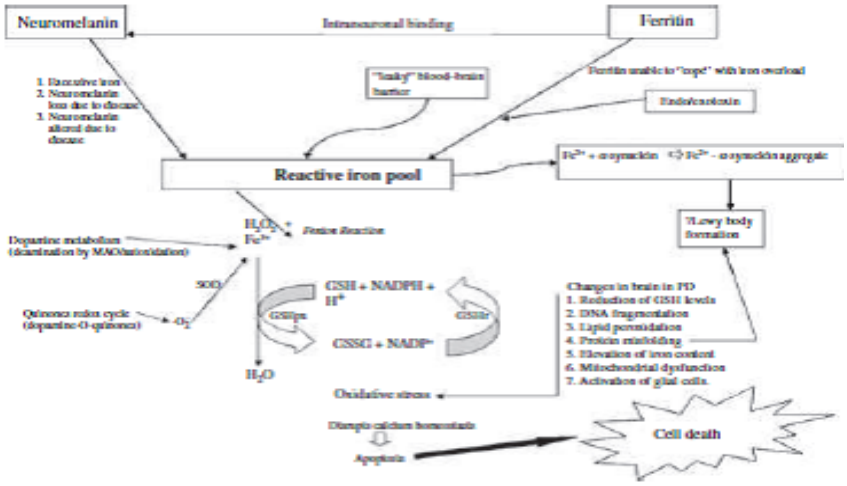

Fig. 2 Iron-mediated neuronal cell death in Parkinson's disease. Putative pathway sources for iron release, such as ferritin, neuromelanin (NM) or neurotoxins. Neurotoxins, such as MPTP, kainate, 6-hydroxydopamine (6-OHDA) can mediate release of iron. Alternatively, some malfunction in the blood–brain barrier, 'leaky', may also increase the access of iron into the brain. Subsequently, this reactive-free iron may react via the Fenton reaction with the hydrogen peroxide produced from example monoamine oxidase metabolised dopamine, to yield toxic and hydroxyl (OH·) free radical species. In addition, the reactive iron may cause a-synuclein to aggregate, which may also lead to the generation of OH· and/or Lewy body formations. These highly reactive OH· radicals may orchestrate a cascade of cellular deleterious events such as oxidative stress. Antioxidants such as GSH that comprises a major cellular defence system attempts to protect the cells from the onslaught of events elicited by oxidative stress, such as DNA damage, protein misfolding/damage, lipid peroxidation of the cell membrane, 'consumption' of cellular antioxidants. Finally, oxidative stress may disturb the cellular calcium homeostasis, thereby resulting in excitotoxicity and finally apoptoticinduced cell death. The elevated iron levels in the substantia nigra may thus play an instrumental role in the vulnerability and degeneration of this area, which is characteristic to Parkinson's disease. GSHpx, glutathione peroxidase; SOD, superoxide dismutase; GSHr, glutathione reductase.

Chelators in the treatment of iron accumulation in Parkinson's disease (37) Free full text

In this 2012 review the authors note that "Iron is an essential element in the metabolism of all cells. **Elevated levels of the metal have been found in the brains of patients of numerous neurodegenerative disorders**, **including Parkinson's disease (PD)**. The pathogenesis of PD is largely unknown, although **it is thought through studies with experimental models that oxidative stress and dysfunction of brain iron homeostasis**, **usually a tightly regulated process**, **play significant roles in the death of dopaminergic neurons**. **Accumulation of iron is present at affected neurons and associated microglia in the substantia nigra of PD patients**. **This additional free-iron has the capacity to generate reactive oxygen species**, **promote the aggregation of α-synuclein protein**, **and exacerbate or even cause neurodegeneration**. There are various treatments aimed at reversing this pathologic increase in iron content, **comprising both synthetic and natural iron chelators**. **These include established drugs**, **which have been used to treat other disorders related to iron accumulation**. **This paper will discuss how iron dysregulation occurs and the link between increased iron and oxidative stress in PD**, including the mechanism by which these processes lead to cell death, before assessing the current pharmacotherapies aimed at restoring normal iron redox and new chelation strategies undergoing research."

Iron, the substantia nigra and related neurological disorders (38)

This 2009 review "attempts to provide a critical evaluation of the many avenues of exploration into **the role of iron in one of the most iron-enriched and clinically investigated areas of the brain, the** substantia nigra."

Dietary iron, animal fats, and risk of Parkinson's disease (39)

In this 1998 research, "in a population-based, case-control study, we addressed the hypothesis that high dietary iron intake was associated with PD. We assessed dietary iron intake with a semiquantitative food-frequency questionnaire in 104 PD patients and 352 control subjects, frequency matched for age and gender. **We also studied the association of PD and dietary iron and animal fat intake in the presence of different iron stores measured by transferrin saturation**." The researchers found, "No significant differences were observed between patients' and control subjects' dietary intake of iron from food or supplements" However, they also reported, "**Among those with high transferrin saturation, risk of PD was two times higher (relative risk, 1.9**; 95% CI, 0.5-7.2) **for those who reported high intake of animal fat compared with those who reported low intake**."

MRI evaluation of brain iron in earlier- and later-onset Parkinson's disease and normal subjects (40)

The 1999 study describes the different patterns of brain iron accumulation found by comparing earlier-onset Parkinson's disease development (before age sixty) to older-onset. **In earlier-onset Parkinson's, higher ferritin iron was observed compared to the older-onset cases, and conversely, in the older-onset cases, higher free iron was observed compared to the earlier-onset cases**. The researchers suggested that, "**The FDRI** (imaging) **results suggest that disregulation of iron metabolism occurs in Parkinson's disease and that this disregulation may differ in earlier-versus later-onset Parkinson's disease**."

HFE variants, APOE and Alzheimer's disease: findings from the population-based Rotterdam study (41)

In a 2009 study of 268 incident cases of Alzheimer's disease compared to 2,079 control individuals in the Netherlands, the researchers **found there was no significant difference in the frequency of hemochromatosis genotypes in the subject compared to controls, however, age of onset was earlier in both males and females who were homozygous for the H63D mutation and was earlier by 6+ years and 2+ years respectively. In addition**, **in men both homozygous for H63D and carrying APOE epsilon 4, the mean age of Alzheimer's disease onset was 5+ years earlier than in those homozygous for H63D**, **but not having APOE epsilon 4**. The researchers concluded, "**Our results suggest that HFE variants are not strong determinants of AD in the general population but may modify the age of onset**."

The hemochromatosis gene affects the age of onset of sporadic Alzheimer's disease (42)

In a 2001 study similar to the one directly above, researchers in Italy found that **patients carrying the HFE H63D variant had a mean age of Alzheimer's disease onset approximately 5 years earlier than those without who did not have and HFE mutation.** The researchers concluded, "**that mild disturbances of iron homeostasis associated with a common genetic determinant may interact with other pathogenic mechanisms involved in Alzheimer's disease. HFE mutations may anticipate Alzheimer's disease clinical presentation in susceptible individuals**."

Association between the HFE mutations and unsuccessful ageing: a study in Alzheimer's disease patients from Northern Italy (43)

In this second (later) 2003 study from Italy, 123 patients with sporadic Alzheimer's disease were matched with 152 controls. **The researchers found no significant differences with the prevalence of HFE mutations between subject and controls**, **and no difference in the age of disease onset**.

Gender and iron genes may modify associations between brain iron and memory in healthy aging (44)

In this 2011 study brain iron and cognitive function (verbal memory - delayed recall, working memory/attention and processing speed) were assessed in 63 healthy older individuals. "**Independent of gene status, worse verbal-memory performance was associated with higher hippocampal iron in men** (r=-0.50, p=0.003) **but not in women**." Several genetic association were also made. The researchers concluded, "The results suggest that in specific subgroups of healthy older individuals, higher accumulations of iron in vulnerable gray matter regions may adversely impact memory functions and could represent a risk factor for accelerated cognitive decline. Combining genetic and MRI

biomarkers may provide opportunities to design primary prevention clinical trials that target high-risk groups."

Tau deficiency induces parkinsonism with dementia by impairing APP-mediated iron export (45)

This 2012 study study of mice describes the accumulation of neuronal brain iron in mice and the potential of iron chelator therapy to stem the disease process in Alzheimer's disease and Parkinson's disease. The researchers suggest the following: "**These data suggest that the loss of soluble tau could contribute to toxic neuronal iron accumulation in Alzheimer's disease, Parkinson's disease and** tauopathies**, and that it can be rescued pharmacologically**."

Brain iron deposits are associated with general cognitive ability and cognitive aging (46)

In this novel 2012 study 143 nondemented subjects in the U.K., who were tested (in a very long-term study) for general cognitive ability (intelligence) at ages 11, 70 and 72 years, **the researchers found that evidence that suggested that iron deposits were related to lifetime cognitive decline**. "**Possessing more iron deposits at age 72 was significantly associated with lower general cognitive ability at age 11, 70, and 72, explaining 4% to 9% of the variance**." The researchers concluded, "**The pattern of results suggests that iron deposits are not only a biomarker of general cognitive ability in old age and age-related cognitive decline, but that they are also related to the lifelong-stable trait of intelligence**."

The link between iron, metabolic syndrome, and Alzheimer's disease (47) Free full text

This 2011 review article from Switzerland notes the following: "Both **Alzheimer's disease** (AD), the most common form of dementia, and **type-2 diabetes mellitus** (T2DM), a disease associated with metabolic syndrome (MetS), affect a great number of the world population and both have increased prevalence with age. **Recently**, **many studies demonstrated that pre-diabetes**, **MetS**, **and T2DM are risk factors in the development of AD and have many common mechanisms**. The main focus of studies is the **insulin resistance outcome found both in MetS as well as in brains of AD subjects**. However, **oxidative stress** (**OS**)**-related mechanisms**, **which are well known to be involved in AD**, **including mitochondrial dysfunction**, **elevated iron concentration**, **reactive oxygen species** (**ROS**), **and stress-related enzyme or proteins** (e.g. heme oxygenase-1, transferrin, etc.), **have not been elucidated in MetS or T2DM brains although OS and iron are involved in the degeneration of the pancreatic islet β cells**. Therefore, **this review sets to cover the current literature regarding OS and iron in MetS and T2DM and the similarities to mechanisms in AD both in human subjects as well as in animal models**."

Iron, type 2 diabetes mellitus, and Alzheimer's disease (48) Free full text

In this 2010 comment letter the authors make observations on a study that "analyzed common clinical and biochemical
features between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD)." The authors noted "**Iron is a strong pro-oxidant which catalyzes several cellular reactions that yield reactive oxygen species**. This property, while essential for its metabolic functions, makes iron potentially hazardous. Indeed, **the amount of free iron available at sites of oxidative or inflammatory injury appears to be a function of the stored iron level**." The authors further noted that, "**On the other hand**, **it is well known that neurons are not only vulnerable to impaired iron metabolism as a result of a reduced iron supply**, **but also that abnormal high cellular iron levels may lead to disordered neuronal function**." The authors conclude, "**Therefore**, **by studying the role of iron in both T2DM and AD**, **we might be able to increase our understanding of these disorders and develop new therapeutic strategies aimed at iron depletion**."

Relationships between disease progression and serum levels of lipid, urate, creatinine and ferritin in Japanese patients with amyotrophic lateral sclerosis: a cross-sectional study (49) Free full text

This is a 2012-reported study that was undertaken in Japan. The investigators noted, "**Previous studies have reported distinct serological profiles of lipid**, **urate and ferritin in Western patients with**

amyotrophic lateral sclerosis (**ALS**). We aimed to examine the levels of these serological factors and their relationship to disease progression in Japanese ALS patients." "**Ninety-two patients with definite or probable ALS** who fulfilled the revised El Escorial criteria **were analyzed for clinical and serological variables**. **Serological data at the time diagnosed with ALS were compared to those of 92 age/sex/body mass index-matched healthy controls**." "**Compared to controls**, **urate and creatinine (Cr) levels were decreased and ferritin levels were increased significantly in sera of male and female patients with ALS**. **Significant increases of serum total cholesterol** (**TC**), **low-density lipoprotein cholesterol** (**LDL-C**) **and triglyceride levels were found in female ALS patients**. **The annual decline of ALS Functional Rating** Scale-Revised (ALS-FRS) **and forced vital capacity** (FVC) **were inversely correlated with serum TC**, **LDL-C**, **Cr and urate levels**, **and were positively correlated with serum ferritin levels**. **Multivariate analysis showed that the rapid worsening of annual ALS-FRS and FVC was associated with serum levels of TC**, **LDL-C**, **Cr**, **urate and ferritin**." The investigators concluded, "**The present study indicated that serum levels of TC**, **LDL-C**, **Cr**, **urate and ferritin were correlated with clinical deterioration in ALS patients**. **These results are similar to those in Western patients**. **Metabolic and nutritional conditions of lipid**, **urate and iron could contribute to disease progression in ALS patients**. **Further studies investigating high nutrition diets and iron chelation for the treatment of ALS are warranted**."

Ischemia Modified Albumin and Plasma Oxidative Stress Markers in Alzheimer's Disease (50)

This 2013-reported research was based on a study from Turkey. "The objective of this study was to determine ischemia modified albumin (IMA) and **oxidant status in Alzheimer's disease** (**AD**). Therefore, **we evaluated the IMA and oxidant status by measuring serum uric acid**, **albumin and gamma-glutamyltransferase** (**GGT**) **in AD**. Methods: The plasma albumin, uric acid, GGT and IMA levels were measured by spectrophotometric methods in 32 AD patients and 32 healthy controls. The Mini Mental Status Examination and Clinical Dementia Rating Scale were used to evaluate the cognitive functions of AD patients. Results: AD patients had significantly higher IMA levels as compared to those of the controls respectively. **Uric acid concentrations were significantly decreased and GGT values were significantly increased in AD when compared with control group**. **Albumin levels of the patients were also compared and no significant difference was detected**. Conclusion: **Oxidative stress and IMA levels rise in AD**. **However, large prospective studies are required to understand the mechanisms leading to increased IMA levels during AD**, **whether preceded or not by AD**"

A delicate balance: Iron metabolism and diseases of the brain (51) Free full text

This is a 2013-reported review from Austria. "**Iron is the most abundant transition metal within the brain**, **and is vital for a number of cellular processes including neurotransmitter synthesis**, **myelination of neurons**, **and mitochondrial function**. **Redox cycling between ferrous and ferric iron is utilized in biology for various electron transfer reactions essential to life**, **yet this same chemistry mediates deleterious reactions with oxygen that induce oxidative stress**. Consequently, **there is a precise and tightly controlled mechanism to regulate iron in the brain**. **When iron is dysregulated**, **both conditions of iron overload and iron deficiencies are harmful to the brain**. This review focuses on how iron metabolism is maintained in the brain, and **how an alteration to iron and iron metabolism adversely affects neurological function**."
