REVIEW

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Iron in multiple sclerosis – from pathophysiology to disease progression – a narrative literature review

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Multiple sclerosis (MS) is a chronic autoimmune illness characterized by demyelination and neurodegeneration, which causes physical disability and severe alterations in the neurological system, including gliosis and neuron loss. The disease primarily affects myelinated parts of the central nervous system (CNS), such as the optic nerves, cerebellum, brain stem, and spinal cord. T cells play an important role in MS pathogenesis by inducing demyelination, and risk factors include genetic predisposition, environmental effects, and lifestyle decisions. The prevalence of MS is rising, especially among women and the elderly population. Iron dysregulation is a critical element in MS pathogenesis, with excess iron causing neurodegeneration *via* ferroptosis and immune response modulation. Excess iron amplifies inflammation by triggering the activation of macrophages with inflammatory properties, and promoting microglial polarization toward the pro-inflammatory phenotype. This causes increased oxidative stress, mitochondrial malfunction, and the release of reactive oxygen species, which harm neurons. Furthermore, proinflammatory cytokines like IL-6 regulate iron metabolism and encourage the formation of Th17 cells, which exacerbates CNS inflammation. Macrophages and microglia, which are implicated in inflammatory responses, collect iron during MS, exacerbating neuroinflammation and demyelination. Disrupted iron homeostasis is a major contributor to MS pathology, with iron deficiency affecting immunological function and changing T-cell responses, both of which are necessary for disease progression. Lumbar puncture, oligoclonal bands analysis, and magnetic resonance imaging are all used to diagnose MS and confirm disease activity and progression. The blood-brain barrier is frequently disrupted in MS, allowing the influx of inflammatory cells. The aim of this paper is to demonstrate the cause-effect relationship between the amount of iron and the health status of patients with MS.

Key words: demyelination, iron, macrophages, microglia, multiple sclerosis, neurodegeneration, neuroinflammation, oxidative stress, reactive oxygen species

INTRODUCTION

The leading cause of nontraumatic neurological dysfunction in young adults is multiple sclerosis (MS). MS is an autoimmune disease of demyelination and neurodegeneration. In addition to its serious impact on physical disability, this disease also causes numerous changes affecting the nervous system, such as gliosis and neuronal loss in the central nervous system (CNS) (Hauser & Cree, 2020; Travers et al., 2022; Haki et al., 2024). Structures of the nervous system, such as the optic nerves, cerebellum, brain stem, and spinal cord, are among the heavily myelinated areas of the nervous system that are particularly affected by MS, due to the progressive process of destruction of the myelinated regions (Dhanapalaratnam et al., 2022). Of particular importance in this regard are immunogenic T cells responsible for demyelination, resulting in the destruction of myelinated axons of the CNS (Haki et al., 2024). As a result, some patients experience sensorimotor symptoms such as tremors and vision loss, which are the most noticeable clinical symptoms (Makhoul et al., 2020; Stoiloudis et al., 2022). The first symptoms of MS usually appear between the ages

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of 20 and 40. However, a growing number of studies show that the epidemiology is changing, with older people experiencing higher incidence and prevalence. Numerous statistics show that MS is becoming more common and widespread worldwide, especially among women. Multiple studies have shown that girls are more likely to develop MS in childhood than boys (Gonzalez-Lorenzo et al., 2024; Zhang et al., 2024; García López et al., 2024; Fernández et al., 2024).

It is estimated that 2.9 million people worldwide suffer from this disease. The annual incidence is about 5-6 per 100,000 people, and the prevalence in the northern regions of North America and Europe is about 0.1%-0.2% of the population. This indicates that the population of people suffering from MS is constantly growing (Valadkeviciene et al., 2019; Sandesjö et al., 2024). Important risk factors for the development of MS include genetic predisposition, environmental variables, lifestyle factors and their interactions (Olsson et al., 2017). The onset of MS is also believed to be influenced by factors like smoking, sunshine, and viral infections (Holz et al., 2024). Up to 30% of monozygotic twins have MS, and 12.6% of all MS patients have familial instances of the disease (Sadovnick et al., 1993).

Genetic predisposition plays a crucial role in the development of MS, with various genes influencing an individual's susceptibility to the disease. The *HLA-DRB1* gene, located on chromosome 6, is the most strongly associated with MS, as certain variants of this gene are believed to increase the likelihood of the immune system attacking the body's own tissues, a key characteristic of MS (Brynedal et al., 2007). Additionally, other genes involved in immune regulation, inflammation and cellular repair mechanisms, such as the *IL7R* gene, contribute to a polygenic risk model, where multiple genetic variations collectively influence the overall risk of developing MS (Zuvich et al., 2010). Among the inflammasomes, the nucleotide-binding oligomerization domain-, leucine-rich repeat- and pyrin domain-containing 3 (NLRP3) inflammasome, which contains the nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain, is well-characterized and contributes to several neurological diseases, including MS (Cui et al., 2022). It is suggested that the NLRP3 inflammasome, a protein complex responsible for activating the inflammatory response, and the cytokine IL-1β, one of the main mediators of the inflammatory process, may be involved in how patients respond to interferon beta treatment (Cui et al., 2022). In practice, this means that these molecules may be key in regulating the inflammatory response in MS patients, and their activity may affect the effectiveness of the treatment (Malhotra et al., 2015). Ethnic differences have been noted to influence the study results, with a stronger association observed in the Latin American population. The frequency of NLRP3 polymorphisms may vary by ethnic group (Wu et al., 2021).

Pathophysiology of multiple sclerosis

Hemoglobin

The WHO's 1968 definition of anemia's cut-off hemoglobin values applies to all adults (hemoglobin <12g/dL for women and hemoglobin <13g/dL for men), but it does not specifically address the elderly population (Otálora-Alcaraz et al., 2025). Hemoglobin is a protein composed of four subunits: two alpha and two beta subunits, each containing a heme group attached to an iron atom (Pires et al., 2023). In the serum, both heme and non-heme forms of iron are present. Heme is released during hemolysis, utilized in metabolic processes, and found in high concentrations within erythrocytes. To prevent the harmful pro-oxidant effects of free heme, the blood protein haptoglobin binds to the released hemoglobin and its iron (Schaer et al., 2014). Hemoglobin can cross the compromised blood-brain barrier (BBB) to reach the CNS. In progressive diseases, the breakdown products of hemoglobin, such as iron and heme, contribute to neurodegeneration and brain atrophy (Lewin et al., 2016).

Haptoglobin

Due to the inflammatory nature of certain diseases, various inflammatory markers, including the proinflammatory cytokine IL-6, have been linked to disease symptoms and pathophysiology (Yan et al., 2012). IL-6, produced by hepatocytes and white adipose tissue, induces the expression of haptoglobin (Li et al., 2020). This acute-phase protein binds tightly to hemoglobin released during red blood cell turnover, reducing iron loss, preventing renal injury, and mitigating heme-induced inflammation (Sarpong-Kumankomah et al., 2022). In multiple sclerosis patients, haptoglobin also plays a protective role by acting as a first line of defense against oxidative damage to myelin. This is especially important given the high fragility of erythrocytes in MS, which leads to increased hemoglobin release, alters the BBB, and damages myelin proteins (Bamm & Harauz, 2014; Altinoz et al., 2016). The BBB, along with the blood-cerebrospinal fluid (CSF) barrier, restricts iron transport from the

blood to the brain (Engelhardt & Sorokin, 2009). Iron is believed to enter the brain through transferrin receptor-mediated endocytosis in brain capillaries and is released back into circulation *via* the CSF (Moos et al., 2006). Elevated iron levels are implicated in protein aggregation in neurodegenerative diseases, further complicating the pathophysiology of MS (Harrison & Arosio, 1996).

Ferritin

Ferritin serves as a major iron storage protein with the capacity to store up to 4,500 iron atoms within its hollow spherical structure, composed of 24 heavy and light chains (Wilkinson & Pantopoulos, 2014). Ferritin mRNA expression is regulated by the iron-responsive element (IRE)-iron regulatory protein (IRP) system, which responds to cellular iron levels (Arosio et al., 2017). In pathological conditions, ferritin levels increase significantly as iron accumulates within cells (Jhelum & David, 2022). Iron histochemistry can detect CNS iron deposition, and ferritin is a sensitive marker of iron presence (Jhelum et al., 2023). While ferritin itself is inert, it can become harmful when redox-active agents mobilize iron through ferritinophagy (Santana-Codina & Mancias, 2018). The protein nuclear receptor coactivator 4 (NCOA4) facilitates the transport of ferritin to autophagosomes for degradation. Overexpression of NCOA4 in pathological contexts can result in the release of redox-active iron, which is cytotoxic (David et al., 2023).

Ferroptotic mechanisms

Ferroptosis is an iron-dependent, controlled form of cell death that occurs in MS (Santana-Codina & Mancias, 2018). This process is characterized by mitochondrial shrinkage, iron accumulation, severe lipid peroxidation, and increased membrane density without apparent rupture. Notably, the nucleus remains normal, with no chromatin condensation (Li et al., 2020a; Tang & Kroemer, 2020). Ferroptosis is triggered by oxidative changes in the intracellular environment (Yu et al., 2017). Excessive lipid peroxidation is considered the key mechanism of ferroptotic cell death, distinguishing it from other forms of regulated cell death (Wiernicki et al., 2020). However, both iron overload and a deficiency in the glutathione (GSH) pathway contribute equally to its initiation (Jhelum et al., 2023). Iron plays a critical role in maintaining healthy oligodendrocytes and myelin and may be essential for remyelination (Cheli et al., 2020). In MS, iron levels are dysregulated, with an accumulation of iron in gray matter (GM) and a reduction in white matter (WM) (Hametner et al., 2018). After oligodendrocyte death, iron is released and can accumulate in neurons, potentially leading to neurotoxicity (Salvador et al., 2010; Levi et al., 2024). Excess iron, typically stored in ferritin, can be mobilized to generate free radicals, exacerbating oxidative damage. This dysregulation of cellular iron metabolism results in elevated bioactive iron, which drives the process of ferroptosis. Ferroptosis occurs when iron-mediated free radicals promote lipid peroxidation, especially in the presence of insufficient GSH-mediated antioxidant defenses (Fan et al., 2022; Wang et al., 2024). Polyunsaturated fatty acids in cell membranes are particularly susceptible to oxidation under these conditions (Ayala et al., 2014). In MS patients, brain tissue shows greater damage to myelin lipids than myelin proteins (Barnes-Vélez et al., 2022; Kister & Kister, 2023). A reduction in GSH, an important antioxidant, leads to the accumulation of lipid radicals and a loss of cell viability. This depletion of GSH in MS patients may also result in a decrease in glutathione peroxidase 4 (GPX4), an enzyme crucial for neutralizing lipid peroxides (Hu et al., 2019). Ferroptosis is exacerbated by chronic oxidative stress. In MS lesions, there is significant immune cell infiltration, which increases immune cell presence in the brain tissue compared to normal brain tissue. Higher ferroptosis scores have been correlated with phagocytic activation in WM lesions (Wu et al., 2024). Iron and lipid peroxides are central to the initiation of ferroptosis, with iron acting as a catalytic regulator. Ferroptosis can be inhibited by iron chelators like deferiprone or lipophilic antioxidants such as α-tocopherol. Additionally, reactive oxygen species (ROS) generated by the iron-catalyzed Fenton reaction contribute to ferroptosis onset (Feng et al., 2023).

MS diagnosis

Lumbar puncture and oligoclonal bands

A lumbar puncture is a key diagnostic test for MS (Ford, 2020). It involves drawing a sample of CSF from the subarachnoid space in the lumbar region to assess abnormalities linked to the disease (Gomes, 2022). One of the primary markers examined during this procedure is the presence of oligoclonal IgG bands (OCB), which suggest local antibody production in the CNS, a hallmark of MS-associated inflammation (Hümmert et al., 2019). Detection of OCB is strongly indicative of MS, as it is present in approximately 90%

of MS patients, although it is not exclusive to MS and can appear in other inflammatory disorders (Katsarogiannis et al., 2023). The revised McDonald criteria include OCB detection in CSF as a standard step in diagnosing MS (Kim, 2022). While OCB is not required for a definitive diagnosis, its presence, especially in combination with other diagnostic tools such as magnetic resonance imaging (MRI), provides crucial supporting evidence for MS (Joseph et al., 2009). Several types of OCB exist, with the most common being type 2 and occasionally type 3 (Sánchez-Vera et al., 2023). However, it is important to note that the presence of OCB in the CSF does not rule out non-inflammatory neurological diseases. Some neurological conditions, even those that are non-inflammatory, may also show OCBs, emphasizing the need for a comprehensive diagnostic approach (Pannewitz-Makaj et al., 2020). Despite its high diagnostic value, a lumbar puncture is an invasive procedure that carries potential risks, which must be considered before proceeding with the test (Graner et al., 2020).

Free kappa chains

Free kappa chains (κ-FLC), proteins produced by plasma cells and components of immunoglobulins (Rao et al., 2012), are another sign used to diagnose MS. Determining κ-FLC levels in CSF can reveal inflammatory activity in the CNS (Di Filippo et al., 2024). Elevated amounts of these chains in MS patients may indicate the existence of locally generated antibodies and disease activity. Recently, κ-FLC has emerged as a biomarker for disease monitoring and chronic inflammation assessment (Gudowska-Sawczuk & Mroczko, 2023). κ-FLCs, like other proteins, can be taken from blood or generated in the subarachnoid space under pathological conditions, which is especially important in MS (Hegen et al., 2022). Testing for κ-FLC using nephelometry or turbidimetry is simple, accurate, and cost-effective. Elevated κ-FLC levels in CSF can predict disease progression to clinical MS (Arrambide et al., 2022).

MRI in the diagnosis of multiple sclerosis

In the brain, iron primarily builds up in certain areas, including the striatum (Ward et al., 2014), thalamus (Rodrigue et al., 2020), and caudate nucleus (Schipper, 2012). This metal is crucial for numerous biological functions in certain brain regions, such as metabolism and neurotransmitter activity. The protein ferritin is the primary form of iron storage in the brain, and as people age, its concentration rises (Beard, 2001). The globus pallidus, caudate nucleus, and substantia nigra are the basal nuclei with the largest concentrations of iron, which are implicated in the production of neurotransmitters, including glutamate and dopamine (Jamwal & Kumar, 2019). Other brain regions, particularly those impacted by myelin loss, may also experience iron buildup. Iron builds up in damaged places, particularly in the WM and demyelination-affected areas, in conditions like MS (LeVine et al., 2013). When myelin and oligodendrocytes are destroyed, activated microglia, involved in the brain's immune system accumulate iron, which can cause long-term inflammation and neurotoxicity (Yong, 2022). The placement of these alterations in deep brain nuclei is a sign of inflammatory activation, and they are frequently discernible on MRI scans, including T2-weighted sequences, where hyperintensity is apparent (Cacciaguerra et al., 2022). The main diagnostic criteria for MS based on MRI imaging are as follows:

- Temporal Dissemination: Lesions must be present at different points in time. This means that MRI changes should be observed at various stages during the disease, reflecting the relapsing-remitting nature of MS (Brownlee et al., 2025).
- Spatial Dissemination: Lesions should appear in at least two different locations in the CNS. Commonly affected areas include the periventricular regions, brainstem, cerebellum, and spinal cord (Filippi et al., 2019).
- Characteristic Demyelinating Lesions: The primary lesions in MS are demyelinating plaques, which typically show as bright spots on T2 or FLAIR MRI sequences. These lesions are most commonly seen on T2-weighted or Fluid-Attenuated Inversion Recovery (FLAIR) images. Active lesions may also be visible on contrast-enhanced T1 images, indicating inflammation or edema (Tillema & Pirko, 2013).
- Presence of New Active Lesions: New demyelinating lesions should be visible on MRI, ideally enhanced with contrast, indicating ongoing activity and inflammation (Kaunzner & Gauthier, 2017).
- Exclusion of Other Causes: The MRI should reveal changes consistent with MS and not be attributed to other neurological conditions (e.g., infections, tumors, or other demyelinating disorders) (Pirko & Noseworthy, 2007).

To diagnose MS, the McDonald criteria must be met. These criteria consider both spatial and temporal dissemination of lesions in the CNS and may involve the presence of new lesions on MRI, suggesting disease progression (Marcus & Waubant, 2013).

Table 1. Summary of possible methods of MS diagnosis.

Topic	Description
Lumbar Puncture	A diagnostic test for MS involving the collection of CSF from the subarachnoid space (Gomes, 2022). The presence of oligoclonal IgG bands, which indicate inflammation in the CNS, is expected (Katsarogiannis et al., 2023). Over 90% of MS patients present these bands (Hümmert et al., 2019).
Oligoclonal Bands (OCB)	OCB indicate the local production of antibodies in the CNS, which is characteristic of MS (Kim, 2022). The presence of OCB is a key indicator for MS diagnosis, especially when other test results are inconclusive (Kim, 2022). OCB is currently regarded as the gold standard for diagnosing MS (Pannewitz-Makaj et al., 2020).
Free Kappa Chains (κ-FLC)	Free kappa chains are proteins produced by plasma cells, with elevated levels in CSF indicating inflammatory activity in the CNS (Di Filippo et al., 2024). An increase in κ-FLC levels can predict disease progression and is used to monitor MS (Arrambide et al., 2022).
MRI in MS Diagnosis	Fe accumulates in the brain, especially in the basal nuclei, which may indicate damage caused by myelin loss in MS (Jamwal & Kumar, 2019). These changes are visible on MRI scans, particularly on T2-weighted sequences, where hyperintensity is observed (Cacciaguerra et al., 2022). Iron accumulation is associated with inflammatory activation and neurotoxicity (Yong, 2022).

Iron deficiency and weakened immune response

Iron deficiency can be caused by a low-iron diet, or a diet high in substances that inhibit iron absorption (Zimmermann & Hurrell, 2007). Healthy persons in high-income environments typically have serum iron levels ranging from 10-30 μmol/l and show minimal variation with age (Garcia-Casal et al., 2021). However, systemic iron availability may be "functionally" low due to chronically high hepcidin levels in the context of inflammation, which limit iron absorption by the duodenum and serum iron availability, regardless of ferritin iron storage (Cianetti et al., 2010). Iron is thought to be essential not only for DNA synthesis and RBC creation but also for immune system health (Miller, 2013; Roemhild et al., 2021; AlRajeh et al., 2022). The findings revealed that iron-deficient patients with low hemoglobin and/or ferritin levels had a significantly higher risk of recurrent infections. Clinical studies have revealed that iron availability plays a critical role in the development of T and B cell responses to infection and vaccination (Muchowska et al., 2019). They discovered that iron deficit patients had an increase in T-cell proliferation. Increased iron intake is required to fuel T-cell responses, which is consistent with iron's many roles in cellular metabolism (Andreini et al., 2018; Li et al., 2021). In an *in vitro* model of Th17 polarization, iron shortage affects the elimination of the main inhibitory histone methylation mark as well as differentiation (Teh et al., 2021). We found iron-interacting proteins in CD4+ and CD8+ T-cell proteomes that were differentially expressed during activation, implying that iron deficit may hamper pathways enriched for such proteins, such as histone demethylation. Iron requirements in T cells are immediately and significantly increased upon activation for usage in a variety of cellular processes, including demethylation and DNA synthesis (Jabara et al., 2016). *In vitro* studies of T-cells exposed to iron-depleted media or iron chelators show that iron is crucial for cell proliferation, activation, and production of effector molecules like granulocyte-macrophage colony-stimulating factor (GM-CSF) and interferon-γ (IFN-γ) (Leung et al., 2005; Yarosz et al., 2020). Hepcidin, an acute-phase protein, binds to ferroprotein in enterocytes, liver, and splenic macrophages and then degrades. Overall, its activity lowers blood iron levels by retaining iron in macrophages and inhibiting its absorption from the gastrointestinal tract. It can be deduced that hepcidin overexpression causes iron deficiency anemia, whereas low expression causes iron overload (Collins et al., 2008; Kowdley et al., 2021). Hepcidin has been discovered in mice to decrease antigen-specific CD8 T-cell responses, as well as T follicular helper cell, germinal center B cell, and plasma cell responses in the ovalbumin vaccination paradigm. Mice treated with minihepcidin have impaired T-cell ability to produce interferon-γ and TNF. In mice with a mutation in the gene producing the iron transporter transferrin receptor, the investigators discovered a deficiency in lymphocyte proliferation (Valentine et al., 2021). Iron supplementation has also been shown to reduce iron deficiency and improve vaccination responses in humans (Stoffel et al., 2020; Drakesmith et al., 2021). Because iron is necessary for T and B cells to function properly and because its absence interferes with T cell proliferation and the synthesis of effector molecules like interferon-γ, iron deficiency can impair immunity. Both *in vitro* and clinical studies have demonstrated that increased hepcidin activity, which restricts iron absorption, can worsen iron deficiency and compromise immunological responses.

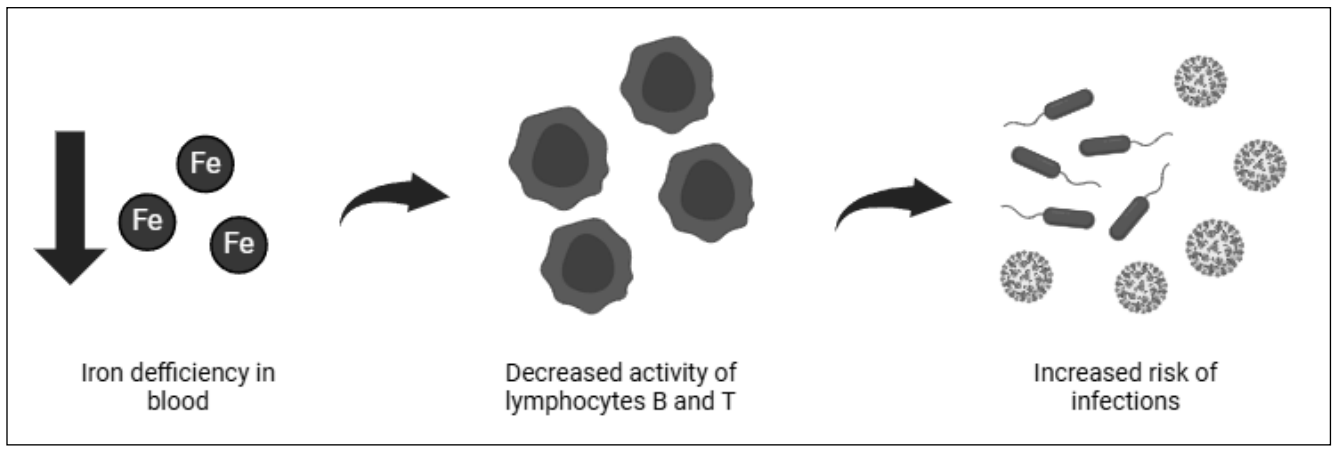

Fig. 1. The effect of iron deficiency on the immune response. A decrease in blood iron levels leads to reduced availability of this element to immune cells. In response to iron deficiency, T and B lymphocytes show increased proliferation, which symbolizes their activation. Additionally, hepcidin, by limiting iron absorption in the intestines, reduces the availability of this element, which weakens the immune response and increases the risk of infection.

Weakening of macrophage function

MS lesions are distinguished by the presence of various immune cells, such as lymphocytes, macrophages, and dendritic cells (Cheng et al., 2017; Cavallo, 2020). All of these cells are thought to play an important role in the development of MS lesions, and they do so through a variety of coordinated inflammatory pathways (Haase & Linker, 2021). Macrophages have a vital role in pathogen phagocytosis, the synthesis of cytokines that govern inflammatory responses, and the maintenance of the innate immune system (Hirayama et al., 2017). Macrophages are categorized into two types based on their activation state: those that are conventionally activated, with inflammatory functions, and those that are alternatively activated, playing a role in immune regulation (Strizova et al., 2023). In the context of MS, inflammatory alterations are related to macrophage activation, which can be distinguished depending on iron levels and other environmental factors (Mehta et al., 2013). For example, high levels of intracellular iron activate M1 macrophages, thereby reducing the number of anti-inflammatory M2 macrophages. Consequently, lower iron levels may limit M1 macrophage activation, leading to an enhanced inflammatory response and an imbalance between M1 and M2 macrophages (Feng et al., 2024). Chronic demyelinating lesions in MS show infiltration of myelin-laden macrophages, which causes deterioration of the myelin sheaths that surround neurons (Podbielska et al., 2013). These lesions are frequently linked with lymphocytic infiltrates, which work alongside macrophages in the demyelination process (Love, 2006). This mechanism is selective, as axons remain largely intact while macrophages destroy myelin (Park et al., 2020). Monocyte infiltration across the BBB is an important stage in the formation of these lesions (Zhang et al., 2025). In active demyelinating plaques, macrophages swallow myelin debris, causing additional damage to the myelin sheaths (Höftberger & Lassmann, 2017). This phenomenon is caused by the interaction between macrophages and myelin, which also involves T lymphocytes (Legroux & Arbour, 2015). The presence of monocytes in the perivascular space in progressive MS lesions stimulates the establishment of lymphoid tissue, which can produce pathogenic autoantibodies (Lassmann, 2018). In the context of experimental MS investigations, macrophages interact with myelin in response to BBB disruption, triggering myelin phagocytosis (Kopper & Gensel, 2018). Furthermore, interleukin-10 (IL-10) secreting B cells can stimulate microglia and macrophages, encouraging phagocytosis and remyelination. In this process, macrophages and microglia exhibit various activation patterns, which can be both pro-inflammatory and helpful in terms of controlling the inflammatory response (Touil et al., 2023). Myelin breakdown begins when IgG-positive macrophages come into touch with mostly intact myelin sheaths (Prineas & Parratt, 2021). There is additional evidence that microglia and macrophages collaborate to remove myelin and promote remyelination. It should be highlighted, however, that the specific involvement of these cells in the pathophysiology of MS, as well as the mechanisms that regulate their activation, are still being studied intensively (Mado et al., 2023; Baaklini et al., 2023). Iron deficiency can limit their ability to secrete cytokines and remove pathogens, making them more susceptible to infections.

The role of iron in microglia

Neuroinflammation is an inflammatory reaction in the CNS that is induced by both external and endogenous causes (Cronin et al., 2019). An early inflammatory response following CNS injury may be advantageous because it allows for the elimination of toxic chemicals and inhibits the progression of injury, hence aiding tissue repair (Kölliker-Frers et al., 2021). However, chronic inflammation in neurological illnesses causes damage to nervous system structures, and its long-term presence may contribute to neurodegeneration (Sochocka et al., 2017). Furthermore, as one gets older, the risk of acquiring neurodegenerative illnesses increases, and neuroinflammation plays an important role (Zhang et al., 2023). The CNS's original immune cells are microglia, which are formed from primary macrophages in the embryonic yolk sac (Kempuraj et al., 2016). Microglia are the innate immune system's initial line of defense, responsible for phagocytosis and the elimination of abnormal protein aggregates, dead cells, and other foreign particles (Colonna & Butovsky, 2017). Microglia activate M1 type microglia in response to inflammatory stimuli like lipopolysaccharide (LPS) and IFN-γ, producing proinflammatory cytokines like interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor (TNF-α), resulting in CNS tissue damage. IL-4 and IL-13 can transform microglia into the M2 type, producing anti-inflammatory factors like transforming growth factor-β, interleukin-4 (IL-4), IL-10, and interleukin-13 (IL-13). This supports nerve repair and regeneration, contributing to CNS homeostasis (Kwon & Koh, 2020; Shao et al., 2022; Guo et al., 2022; Qin et al., 2023). Iron buildup in microglia, caused by inflammatory cytokines, is a key part of the neuroinflammatory process (Li et al., 2024). Stimulating microglia with LPS, TNF-α, or IL-6 activates the production of proteins such as divalent metal transporter 1 (DMT1) and hepcidin, which transport and accumulate iron in these cells (Vela, 2018; Ward et al., 2022). Increased iron concentration in microglia causes TNF-α production, leading to inflammation (Rosenblum & Kosman, 2022). In multiple sclerosis, iron accumulation in microglia at the edges of demyelinating lesions leads to a shift toward a pro-inflammatory state, contributing to the worsening of pathogenic changes (McIntosh et al., 2019). Histological investigations have demonstrated that within these lesions, microglia collect iron, which produces more severe inflammation and intensifies the damage in CNS structures (Mehta et al., 2013). To summarize, iron buildup in microglia in chronic neuroinflammatory illnesses such as MS is an essential mechanism that contributes to the progression of CNS damage (Rock et al., 2004). Microglia, with their bidirectional function - both defensive and damaging - play an important part in the etiology of neuroinflammatory diseases. Future research into the mechanisms of iron buildup and the involvement of microglia in neuroinflammation may pave the way for new therapeutic approaches to slow the progression of neurodegenerative disorders.

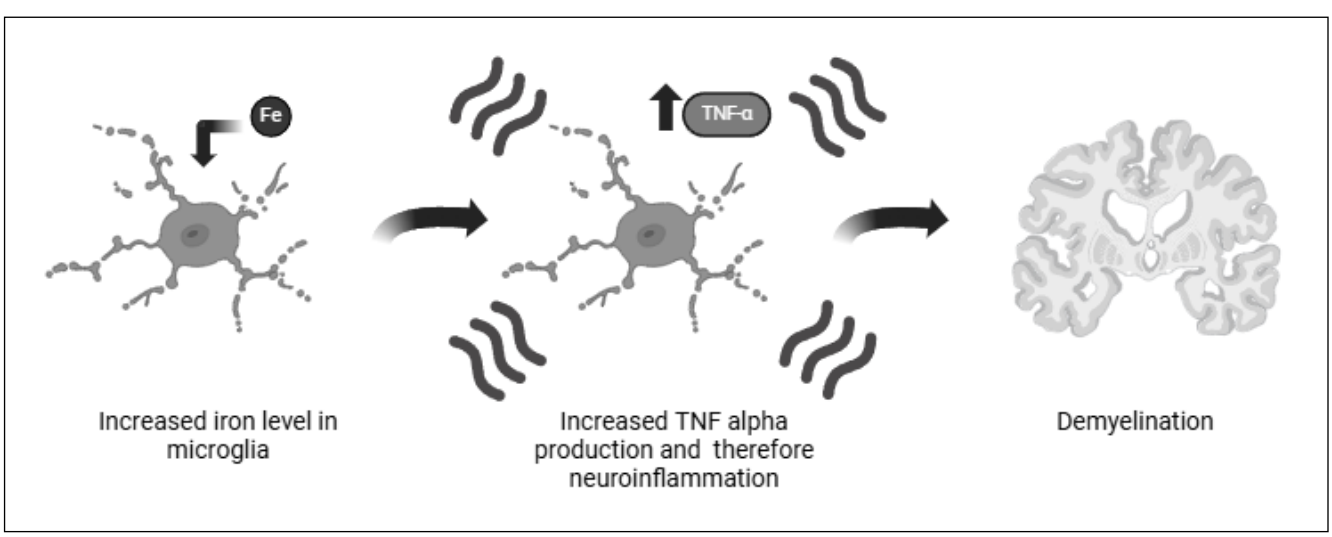

Fig. 2. The mechanism by which increased iron levels in microglia lead to the production of tumor necrosis factor alpha (TNF-α). Increased iron concentration in microglia stimulates an inflammatory response, which results in the activation of inflammation within the nervous system. This process leads to neuroinflammation and, consequently, to demyelination, which is particularly evident in diseases such as multiple sclerosis. Iron accumulation in microglia increases damage to brain and spinal cord structures, contributing to disease progression.

Mitochondrial dysfunction – reactive oxygen species origin

Oxidative stress results from excess iron in cells and tissues, which upsets redox equilibrium and promotes the growth of ROS (Williams et al., 2012). Age-related iron buildup in the human brain exacerbates the effects of oxidative damage and mitochondrial dysfunction, which also contribute to brain damage in aging and age-related ischemic vascular disorders (Galaris et al., 2019). Glutamate Ca2+ excitotoxicity, oxidative stress, and metabolic dysfunction are all brought on by ROS, which are produced when the CNS's divalent iron (Fe2+) content rises, for instance, as a result of microhemorrhages or the deterioration of oligodendrocytes and myelin (Chakrabarti et al., 2011). Iron is present in microglia/macrophages and astrocytes in active and chronic lesions, but it is also stored in oligodendrocytes and myelin in normal-appearing WM and GM in MS patients (Spaas et al., 2021). While iron is comparatively elevated in the perivascular tissue, it appears to decline with age in the subcortical WM of MS patients compared to healthy controls (Popescu et al., 2017). On the other hand, too much iron can cause neurotoxicity, inflammation, and oxidative stress, which can harm and damage the function of neurons. Cognitive impairment and disability in MS are exacerbated by iron deposition in the basal ganglia, which can happen concurrently with or independently of demyelination (Schweser et al., 2021).

ROS are created when electrons are moved from one material (the reactant) to another in an oxidation reaction. ROS constitute the most significant kind of radicals generated in biological systems. The three primary forms are hydroxyl radical (OH–), hydrogen peroxide (H_2O_2), and superoxide anion (O2–). While much larger concentrations of ROS can harm cellular components such as proteins, lipids, and nucleic acids, immune cells produce high local concentrations of ROS to destroy invaders (Williams et al., 2012). Oxidative species are produced in part by NADPH oxidase and the mitochondrial electron transport chain (Afzal et al., 2023). The trimeric Nrf2-Keap1-Cul3 complex regulates ROS levels in mammalian cells and the production of antioxidant enzymes. According to reports, ROS may play a role in the development and course of autoimmune illnesses such as MS (Dikalov, 2011).

The absence of the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, a crucial antioxidant transcription factor, is another feature shared by neurodegenerative and/or neurological diseases, such as MS. Nrf2 inhibits oxidative stress, neuroinflammation, and mitochondrial failure (Tavassolifar et al., 2020). Axonal degeneration, neuronal death, and a variety of neurological impairments that present with wildly disparate symptoms are all caused by demyelination. Therefore, in MS patients, primary demyelination results in neurodegeneration, which causes severe neurological damage and impairment (Villavicencio et al., 2021). By regulating the synthesis of adenosine triphosphate (ATP), redox balance, and intracellular free Ca2+ concentration in neuronal cells, mitochondria are essential organelles in charge of energy supply. In order to sustain and carry out membrane excitability, neurotransmission, and plasticity, as well as to regulate variations in (Ca2+), which aid in the release of neurotransmitters, neurons rely heavily on mitochondrial function (Correale et al., 2019).

When compared to age-matched healthy brain samples, post-mortem examination of MS brain tissues revealed fractured neurofilaments, decreased organelle content, and defective axoplasm (Duarte et al., 2023). It has also been observed that neurons with a higher mitochondrial content have significantly greater levels of organelle content compared to demyelinated axons, which results in impaired mitochondrial transport. In both CSF samples and animal models, MS-based studies have commonly proposed oxidative damage caused by elevated ROS and reactive nitrogen species (RNS) (Maldonado et al., 2022). The Nrf2 pathway, a transcription factor encoded by the nuclear factor erythroid 2-related factor 2 (*NFE2L2*) gene and a member of the Cap'n'Collar family of transcription factors, regulates the balance of ROS. These genes, which encode glutathione S-transferase (GST), glutamate-cysteine ligase (GCL), heme oxidase-1 (HO-1), NAD(P)H quinone oxidoreductase-1 (NQO1), and glutathione peroxidase, are a defense response to ROS overproduction (Campbell & Mahad, 2011). The Nrf2 pathway is unable to sustain ROS at physiological levels during redox abnormalities, such as those seen in MS (Tebay et al., 2015). However, there is mounting evidence that Nrf2 may play a role in persistent neuroinflammation. In fact, Nrf2 regulates nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) -dependent responses, another important route triggered by oxidative stress. Its activation constitutes a critical antioxidant checkpoint for astrocytes, conferring neuroprotective properties during neuroinflammation (Maldonado et al., 2022).

Lymphocyte CD3+ in MS pathogenesis

MS is caused by the loss of immunological tolerance to self-proteins, which results from the interplay of hereditary vulnerability and environmental

variables. This results in the production of autoreactive T and B cells, which are critical to the disease's progression (Maldonado et al., 2022). Th17 cells that produce glutamate, in particular, can cause damage to oligodendrocytes, resulting in an attack on myelin antigens. However, in MS, BBB function is compromised (Saha et al., 2020), which promotes T lymphocyte migration to the CNS. Special attention should be devoted to CD8+ T-cells, which have been found in both the CNS and the CSF (Lazibat et al., 2018). These cells accumulate in the CNS and are found in the blood of MS patients, confirming their function in the demyelination process (Larochelle et al., 2021; Nishihara et al., 2022). A decrease in the number of T-regulatory cells (Tregs) during the course of MS is associated with an increase in symptoms (Liu et al., 2022). Their number fluctuates with the stage of the disease, decreasing during relapses and increasing during remission (Pirko & Noseworthy, 2007). In turn, histological studies show the presence of leukocyte infiltrates in demyelinating plaques in the CNS, providing additional evidence for T-cell involvement in MS pathophysiology (Calahorra, et al., 2022). An increase in the number of CD20+ T-cells is particularly prominent in individuals with the primary progressive type of MS (PPMS), and it also correlates with the intensity of demyelination and disease severity in relapsing-remitting multiple sclerosis (RRMS) (Benallegue et al., 2022). Furthermore, extra iron in the body may alter the activation of T lymphocytes, particularly Th1 cells, which secrete proinflammatory cytokines like interferon-gamma. High iron levels stimulate uncontrolled activation of these cells, resulting in greater inflammation and additional nervous system damage (Findling et al., 2018). Iron overload can exacerbate MS by altering T lymphocyte activation, particularly Th1 cells, which contribute to inflammation and neurodegeneration. Elevated iron levels in the body may enhance the production of proinflammatory cytokines, further promoting myelin damage and disease progression.

Lymphocyte CD8+ in MS pathogenesis

Although T-cells are commonly acknowledged as the primary contributors to inflammatory demyelination in MS, emerging data suggests that B lymphocytes play an important role in the disease's pathogenesis (Maldonado et al., 2022). MS may be caused by B cells through various mechanisms, including antigen presentation to T-cells, which drives autoproliferation of brain-homing T-cells, production of proinflammatory cytokines and chemokines such as lymphotoxin-α, TNF-α, IL-6, and GM-CSF, which propagate inflammation throughout the CNS and generation of soluble toxic factors that damage oligodendrocytes and neurons. These pathways contribute to the persistent inflammation and neurodegeneration associated with MS (Pirko & Noseworthy, 2007; McLaughlin & Wucherpfennig, 2008; Lazibat et al., 2018; Findling et al., 2018; Milo, 2019; Saha et al., 2020; Larochelle et al., 2021; Ni et al., 2022; Nishihara et al., 2022; Liu et al., 2022; Calahorra, et al., 2022; Benallegue et al., 2022; von Essen et al., 2023). Excessive release of lymphotoxin-α, TNF-α, IL-6, and GM-CSF by B cells in patients' peripheral immune systems can worsen inflammatory processes (van Langelaar et al., 2020; Comi et al., 2021). There is also some evidence that B lymphocytes can produce autoantibodies against myelin, which contributes to disease development (de Gruijter et al., 2022). Clinical studies have proven the role of B cells in the development of MS, with anti-CD20 monoclonal antibody therapy demonstrating substantial efficacy in decreasing disease activity (Pala et al., 2018). MS patients' peripheral B cells produce anti-inflammatory cytokines such as IL-10, interleukin-35 (IL-35), and transforming growth factor β (TGF-β), perhaps maintaining immunological homeostasis (von Büdingen et al., 2011; de Sèze et al., 2023). Their presence in the brain and meninges, particularly in areas of demyelination, suggests a critical involvement in the local immune response, which may contribute to disease worsening (Gharibi et al., 2020). Iron overload may exacerbate inflammatory processes in MS by promoting oxidative stress, which damages oligodendrocytes and neurons. This increased oxidative stress can enhance the activation of B lymphocytes, worsening neuroinflammation and contributing to disease progression.

Toxic consequences of Fe

Neuronal metabolism associated with iron

Iron is a cofactor for the enzyme tyrosine hydroxylase (TH), which catalyzes the first and limiting step in dopamine production (Li et al., 2016). This enzyme requires iron (Fe^{2+}) to function, hence iron levels are directly tied to dopamine release. Additional TH activity is typical, resulting in the cofactor BH4, complicating the process of dopamine production (Lubetzki & Stankoff, 2014). The onset of iron deficiency can interfere with neuronal metabolism, resulting in dopaminergic dysfunction and associated behavioral issues, which may exacerbate MS symptoms in individuals with MS (Lozoff, 2011). In turn, dopamine in-

fluences the steering system, including in the context of MS, where it modulates the response, particularly in the regulation of Th17 cells (Xiao et al., 2021).

Dopamine has been found in studies to limit the release of proinflammatory cytokines by Th17 cells, which may have anti-inflammatory effects in MS. In this scenario, stimulation of the D2 dopamine receptor type inhibits the Th17 immune response (Juárez Olguín et al., 2016). Furthermore, dopamine influences the functioning of both the innate and adaptive immune systems, including effects on macrophages, dendritic cells, monocytes, and CD4+ and CD8+ T-cells that can generate dopamine and exhibit dopaminergic autoregulation (Melnikov et al., 2016). Dopamine affects neuropsychological symptoms in MS, including fatigue, cognitive impairment, and depression (Melnikov et al., 2022). Understanding the role of dopamine in the course of this disease, where dopamine can be identified based on the severity of individual neurological symptoms, and above all, because the occurrence of dopamine can be determined, as a result of which the release of proinflammatory cytokines will not be adequately inhibited has a direct impact on inflammation. This is crucial for the understanding of neuronal homeostasis and has consequences in the aftermath of MS prognosis, causing disease progression and harming brain structures and the spinal cord.

Inflammatory processes associated with IL-6, STAT3

Chronic inflammation in MS disrupts iron metabolism, which can lead to poor iron management. Macrophages and microglia, immune cells found in the CNS, release iron in response to inflammation, and incorrect management of this process can result in increased oxidative stress, which harms cells and tissues (Arreola et al., 2016). Proinflammatory cytokines, such as IL-6, stimulate the IL-6R-JAK2-STAT3 pathway, increasing the expression of hepcidin, an acute-phase protein that blocks iron release from macrophages and promotes iron retention in the body (Margoni et al., 2023). High levels of hepcidin cause inflammatory anemia defined by high serum ferritin and decreased erythropoiesis due to a lack of accessible iron (Williams et al., 2012). Furthermore, IL-6 is required for the development of T-cells into Th17 cells, which produce proinflammatory cytokines such as interleukin-17 (IL-17), interleukin-21 (IL-21), GM-CSF, granulocyte colony-stimulating factor (G-CSF), and interleukin-22 (IL-22). Th17 cells can pass the blood-brain barrier, causing neuroinflammation and demyelination in MS (Tesmer et al., 2008; Zepp et al., 2011; Pagani et al., 2019; Camaschella et al., 2020). Increased IL-6 levels in the CSF are associated with reduced synaptic plasticity, which leads to clinical signs of brain injury, such as cognitive impairment and exhaustion (Gruol, 2015). Furthermore, elevated levels of IL-6 in the peripheral circulation can worsen inflammation, increasing disease activity in MS (Stampanoni Bassi et al., 2020). As a result, modulating inflammatory cytokine levels, particularly IL-6, may have substantial therapeutic implications for regulating chronic inflammation and improving iron metabolism, both of which may help alleviate MS symptoms (Maggio et al., 2006).

Damage to the blood-brain barrier

Iron is essential for the BBBs proper function, particularly in the case of MS, where the disease's pathophysiology heavily relies on iron damage. By regulating the entry of chemicals and cells into the CNS, the BBB serves as a physical barrier for the brain (Schreiner et al., 2022). Damage to this barrier encourages inflammatory cells and cytotoxic chemicals to infiltrate, which exacerbates inflammation and damages brain structures in MS (Miljković & Spasojević, 2013). The BBB's integrity is jeopardized by iron, a strong catalyst for free-radical processes, which can raise oxidative stress (Rand et al., 2021). Additionally, extra iron in the brain might contribute to additional cellular damage and increase clinical symptoms in MS (Williams et al., 2012). Conversely, iron is essential for axonal myelination, and oligodendrocytes may store and transfer iron throughout the BBB because they employ ferritin-iron to build myelin. Myelination effectiveness may be impacted, and the disease's brain damage may worsen, if this process is disrupted, for example, by rupturing the BBB (Cheli et al., 2020). Therefore, maintaining appropriate brain function and preventing iron overload depend on the brain's iron levels being properly regulated.

Table 2. Summary of different pathways of Fe toxic influence on neuronal tissue.

Neuronal Metabolism and Iron	Inflammatory Processes (IL-6, STAT3)	Blood-Brain Barrier (BBB) Damage
- Iron is a cofactor for tyrosine hydroxylase (TH), essential for dopamine production (von Büdingen et al., 2011; de Sèze et al., 2023)	- Chronic inflammation disrupts iron metabolism in MS, leading to oxidative stress and cellular damage (Juárez Olguín et al., 2016)	- Iron is crucial for BBB function and plays a role in MS pathophysiology, as BBB damage allows immune cells and toxins to enter the CNS, worsening inflammation and brain damage (Gruol, 2015)
- Dopamine production and release are tied to iron levels, affecting various systems, including immune response (Gharibi et al., 2020)	- IL-6 activates the IL-6R-JAK2-STAT3 pathway, which increases hepcidin expression, causing iron retention and limiting available iron for erythropoiesis (Melnikov et al., 2016)	- Iron-induced oxidative stress can compromise BBB integrity, further exacerbating MS symptoms (Maggio et al., 2006)
- Dopamine modulates Th17 cell responses and proinflammatory cytokine release, potentially having anti-inflammatory effects in MS (Lubetzki & Stankoff, 2014)	- Elevated IL-6 levels contribute to Th17 cell development, which causes neuroinflammation and demyelination in MS (Arreola et al.. 2016; Margoni et al., 2023; Williams et al., 2012; Camaschella et al., 2020)	- Iron is also vital for myelination and is stored by oligodendrocytes for this process. Disruption of BBB or iron regulation can worsen brain damage in MS (Miljković & Spasojević, 2013)
- Dopamine impacts neuropsychological symptoms in MS, including cognitive impairment and depression (Xiao et al., 2021)	- High IL-6 levels in CSF and peripheral circulation are associated with increased disease activity, cognitive impairment, and exhaustion in MS (Pagani et al., 2019)	
- Deficiency or excess of dopamine can exacerbate neuroinflammation, impacting MS progression and neuronal homeostasis (Xiao et al., 2021)	- Modulating IL-6 levels may help alleviate MS symptoms by reducing inflammation and improving iron metabolism (Zepp et al., 2011)	

Animal models focused on iron metabolism and MS

Animal models (primarily rodents like mice or rats) are commonly used to study various aspects of iron metabolism and how it relates to MS (Wang et al., 2019). MS is a neuroinflammatory disease where the immune system attacks the protective covering of nerve fibers (myelin) (Tafti et al., 2024). The role of iron in MS pathology can be studied through these models by manipulating iron levels in the body and assessing the effects on MS symptoms (Stüber et al., 2016).

Experimental Autoimmune Encephalomyelitis (EAE) is one of the most common conditions studied in animal models for MS research. It mimics the demyelination process of MS. By manipulating iron levels (e.g., *via* iron supplementation or depletion), researchers can examine how changes in iron metabolism affect disease severity and progression in MS (Constantinescu et al., 2011). Iron is essential for myelin formation and function, but too much or too little can lead to detrimental effects (Wallace, 2016). Animal studies can explore the effects of iron overload or iron deficiency in the brain and spinal cord and how it affects inflammatory responses, oxidative stress, and neurodegeneration (Dash et al., 2025). There are models where animals have altered iron metabolism due to mutations in genes like ferroportin or hepcidin (which regulate iron absorption and distribution) (Nicolas et al., 2002). These models help in studying the relationship between iron dysregulation and MS-like symptoms or neurodegenerative conditions.

Cell-based models focused on iron metabolism and MS

Cell-based models are used to study the cellular processes involved in iron regulation, inflammation, and myelination (Santacreu-Vilaseca et al., 2025). Microglial and astrocyte cultures: Since microglia and astrocytes play a significant role in neuroinflammation, these cells are often studied in the context of MS (Mado et al., 2023). They are also crucial in the brain's handling of iron. Iron may influence the inflammatory response of microglia in MS models, and cell cultures can help understand this relationship (McCarthy et al., 2018). Oligodendrocyte precursor cells (OPCs): These cells are responsible for forming the myelin sheath (Benarroch, 2023). Iron is crucial for myelin production, and disruptions in iron homeostasis can affect OPC differentiation and myelination (Cheli et al., 2020). Cell models can be used to study the impact of iron on MS. Iron plays a role in redox reactions and can catalyze the production of reactive oxygen species (ROS) (Galaris et al., 2019). Elevated ROS levels contribute to cellular damage and neurodegeneration in MS (Ohl et al., 2016). *In vitro* models with neurons or glial cells can help examine how iron-induced oxidative stress influences MS progression (Czpakowska et al., 2024). Impairment of wound healing and fibrosis results in the buildup of cells and extracellular matrix constituents, with fibroblasts and their activated forms—myofibroblasts—present at injury sites (Klingberg et al., 2013). Disruptions in iron metabolism could influence the functioning of these cells, as iron plays a vital role in various inflam-

matory responses and healing processes (Ni et al., 2022). Fibroblasts in MS lesions contribute to extracellular matrix deposition and fibrosis. They produce collagen and fibronectin, contributing to the function of oligodendrocyte precursors (Lozinski et al., 2024). In MS, where there is damage to myelin and tissue within the CNS, alterations in iron metabolism may lead to disruptions in cell function, including that of fibroblasts, impacting repair processes and scar formation.

Pharmacological and non-pharmacological methods of modifying iron levels

The level of iron in the blood can be modified both through pharmacological and non- pharmacological methods. In the case of iron deficiency, it can be supplemented orally in the form of compounds such as iron sulfate, iron gluconate, or iron fumarate. This is the most commonly used way of modifying iron levels currently applied in medicine. The range between 50 mg and 200 mg of elemental iron per day for three to twelve weeks is usually necessary for effective iron substitution with oral supplements (Stoffel et al., 2017; Pantopoulos, 2024). In exceptional cases, intravenous iron supplementation may be used. This type of supplementation is typically indicated by poor tolerance to oral preparations, severe iron deficiency, impaired iron absorption from food, as well as women in advanced stages of pregnancy or heavy menstrual bleeding in women (Gupta et al., 2016; Pantopoulos, 2024). Furthermore, combined supplementation of iron with vitamin C can help improve iron absorption from the gastrointestinal tract due to its ability to convert ferric ions into ferrous ones. Vitamin C improves the absorption of iron even when the intake is modest compared to what is found in a typical diet (Li et al., 2020b; Doseděl et al., 2021).

Improved iron absorption can also be achieved through non-pharmacological methods. One such method may be modifying the diet. Products that contain notable amounts of iron include meat, fish, cereal products, and green plants such as spinach. By altering the diet to include the aforementioned items in meals, it is possible to support the increase of iron levels in the blood (Skolmowska et al., 2022). Avoiding products such as coffee and tea in the diet may help with iron supplementation. Studies have also shown that certain antinutritional factors found in these beverages, such as tannins and phytates, impair the bioavailability of essential nutrients (Shaw et al., 2022). Cryostimulation may affect iron levels through mechanisms such as improved circulation, reduced inflammation, or effects on metabolism, although this area still requires further research (Dulian et al., 2015). Intense physical activity itself may also contribute to increased iron loss due to sweat and tissue microtrauma, which is why iron deficiency is particularly common among athletes, especially those involved in endurance sports. Although there is currently no direct evidence that kinesiotherapy affects blood iron levels, this remains a subject of future research (Solberg & Reikvam, 2023).

DISCUSSION

The pathogenesis of multiple sclerosis involves disruptions to critical components of the nervous system, such as iron homeostasis, which are linked to neurodegeneration and impaired motor function. MS is a complex neurological disorder in which iron dysregulation may play a role in the disease's pathogenesis, potentially influencing its progression and increasing the risk of developing neurological damage. It is getting more and more serious globally, particularly in women. When hemoglobin is released into the body's main system, it causes neurodegeneration and brain shrinkage. In contrast, haptoglobin protects the body from hemoglobin release. An important regulatory component, ferritin is a source of iron storage, and when it malfunctions, can lead to neurotoxicity and disease damage. The disease progresses as a result of iron buildup and lipid peroxidation, which cause neurons to develop and myelin to be destroyed. Myelin deterioration and the formation of MS lesions are accelerated by oxidative stress and immunological activation brought on by dysregulation of the supply in MS. A low iron diet, or an application that prevents its absorption, can cause the deficit. The impact and burden on the immune system's operation and the deterioration of T and B lymphocytes have a crucial impact on the immune response.

Iron is necessary for the balance of macrophage types and for the utilization of macrophages, which power the immune response. A compromised response can result from inadequacies, raising the chance of autoimmune illnesses like MS. The CNS's defensive microglia are triggered by inflammation and have the ability to collect iron, which accelerates lymphocyte destruction. The buildup of components in microglia can deepen the structure of systemic systems in neuroinflammatory illnesses like MS. ROS can generate too much energy in cells by sending mitochondria and secreting ROS, which exacerbate neurodegenerative processes. The pathogenesis of MS is closely linked to alterations in iron homeostasis, ROS

production, and subsequent neuronal degeneration. Disruptions in iron regulation within the CNS can exacerbate inflammation and contribute to the progression of MS. The imbalance leads to the activation of autoreactive T and B lymphocytes, which play a crucial role in driving disease progression.

Special attention should be given to the role of CD8+ T cells, which accumulate in the CNS and contribute to demyelination. Additionally, B cells play a key role in MS pathophysiology by releasing proinflammatory cytokines and presenting antigens to T lymphocytes, further driving the inflammatory response. They are important when a local immune reaction takes place, which can happen as the disease progresses. They are found in the brain, particularly in cases of demyelination. Dopamine and inflammation cause iron to function as a neural mediator. Increased oxidative stress in MS can result from metabolic instability, which triggers the development of neurons and the disease. Hepcidin may act and cease operating as a result of chronic inflammation from MS that interferes with metabolic activity. Consequently, elevated IL-6 levels, a pro-inflammatory cytokine, can accelerate neurodegenerative and inflammatory processes, including demyelination in MS. Maintaining the BBB's integrity and controlling the amount of iron in the brain are essential for halting the disease's progression. A lumbar puncture to check for the presence of OCB in the cerebrospinal fluid is one of the procedures used to diagnose MS. When there is a high level of κ-FLC in CSF, it can be utilized as a biomarker to track the course of MS. The accumulation of iron in these locations, as seen in the MRI imaging, results from activation and neurotoxicity, indicating the disease's progressive nature.

CONCLUSIONS

MS is a chronic neurological disease characterized by neurodegeneration and autoimmune demyelination, particularly in young adults. Central to the pathophysiology of MS is the dysregulation of iron homeostasis, which contributes to neuronal damage. Key factors include the accumulation of iron in affected brain areas, leading to ferroptosis, a form of cell death associated with oxidative stress. This process accelerates neurodegeneration, exacerbating the loss of myelin and neurons. In addition to iron dysregulation, inflammatory responses and metabolic disruptions play significant roles in disease progression. The alteration of iron metabolism and the associated oxidative damage highlight the importance of targeting iron-related pathways as potential therapeutic strategies in MS.

REFERENCES

Afzal, S., Abdul Manap, A. S., Attiq, A., Albokhadaim, I., Kandeel, M., & Alhojaily, S. M. (2023). From imbalance to impairment: The central role of reactive oxygen species in oxidative stress-induced disorders and therapeutic exploration. *Frontiers in Pharmacology, 14*, 1269581. https://doi.org/10.3389/fphar.2023.1269581

AlRajeh, L., Zaher, A., Alghamdi, A., Alsheikh, R., & AlSultan, O. (2022). Effects of iron deficiency and its indicators on lymphocyte subsets: A study at King Fahd Hospital of the University, Saudi Arabia. *Journal of Blood Medicine, 13*, 61–67. https://doi.org/10.2147/JBM.S342321

Altinoz, M. A., Ozcan, E. M., Ince, B., & Guloksuz, S. (2016). Hemoglobins as new players in multiple sclerosis: Metabolic and immune aspects. *Metabolic Brain Disease, 31*(5), 983–992. https://doi.org/10.1007/s11011-016-9845-7

Andreini, C., Putignano, V., Rosato, A., & Banci, L. (2018). The human iron-proteome. *Metallomics, 10*(9), 1223–1231. https://doi.org/10.1039/c8mt00146d

Arosio, P., Elia, L., & Poli, M. (2017). Ferritin, cellular iron storage and regulation. *IUBMB Life, 69*(6), 414–422. https://doi.org/10.1002/iub.1621

Arreola, R., Alvarez-Herrera, S., Pérez-Sánchez, G., Becerril-Villanueva, E., Cruz-Fuentes, C., Flores-Gutierrez, E. O., Garcés-Alvarez, M. E., de la Cruz-Aguilera, D. L., Medina-Rivero, E., Hurtado-Alvarado, G., Quintero-Fabián, S., & Pavón, L. (2016). Immunomodulatory effects mediated by dopamine. *Journal of Immunology Research, 2016*, 3160486. https://doi.org/10.1155/2016/3160486

Arrambide, G., Espejo, C., Carbonell-Mirabent, P., Dieli-Crimi, R., Rodríguez-Barranco, M., Castillo, M., Auger, C., & Tintore, M. (2022). The kappa free light chain index and oligoclonal bands have a similar role in the McDonald criteria. *Brain, 145*(11), 3931–3942. https://doi.org/10.1093/brain/awac220

Ayala, A., Muñoz, M. F., & Argüelles, S. (2014). Lipid peroxidation: Production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. *Oxidative Medicine and Cellular Longevity, 2014*, 360438. https://doi.org/10.1155/2014/360438

Baaklini, C. S., Ho, M. F. S., Lange, T., Hammond, B. P., Panda, S. P., Zirngibl, M., & Plemel, J. R. (2023). Microglia promote remyelination independent of their role in clearing myelin debris. *Cell Reports, 42*(12), 113574. https://doi.org/10.1016/j.celrep.2023.113574

Barnes-Vélez, J. A., Aksoy Yasar, F. B., & Hu, J. (2022). Myelin lipid metabolism and its role in myelination and myelin maintenance. *Innovation (Camb), 4*(1), 100360. https://doi.org/10.1016/j.xinn.2022.100360

Bamm, V. V., & Harauz, G. (2014). Hemoglobin as a source of iron overload in multiple sclerosis: Does multiple sclerosis share risk factors with vascular disorders? *Cellular and Molecular Life Sciences, 71*(10), 1789–1798. https://doi.org/10.1007/s00018-014-1570-y

Beard, J. L. (2001). Iron biology in immune function, muscle metabolism, and neuronal functioning. *The Journal of Nutrition, 131*(2S-2), 568S–579S. https://doi.org/10.1093/jn/131.2.568S

Benallegue, N., Nicol, B., Lasselin, J., Bézie, S., Flippe, L., Regue, H., Vimond, N., Remy, S., Garcia, A., Le Frère, F., Anegon, I., Laplaud, D., & Guillonneau, C. (2022). Patients with severe multiple sclerosis exhibit functionally altered CD8+ regulatory T cells. *Neurology, Neuroimmunology & Neuroinflammation, 9*(6), e200016. https://doi.org/10.1212/NXI.0000000000200016

Benarroch, E. E. (2023). What are the roles of oligodendrocyte precursor cells in normal and pathologic conditions? *Neurology, 101*(21), 958–965. https://doi.org/10.1212/WNL.0000000000208000

Brownlee, W. J., Foster, M. A., Pontillo, G., Davagnanam, I., Collorone, S., Prados, F., Kanber, B., & Ciccarelli, O. (2025). Investigating whether dissemination in time is essential to diagnose relapsing multiple sclerosis. *Neurology, 104*(7), e210274. https://doi.org/10.1212/WNL.0000000000210274

Brynedal, B., Duvefelt, K., Jonasdottir, G., Roos, I. M., Akesson, E., Palmgren, J., & Hillert, J. (2007). HLA-A confers an HLA-DRB1 independent influence on the risk of multiple sclerosis. *PLoS ONE, 2*(7), e664. https://doi.org/10.1371/journal.pone.0000664

Cacciaguerra, L., Sechi, E., Rocca, M. A., Filippi, M., Pittock, S. J., & Flanagan, E. P. (2022). Neuroimaging features in inflammatory myelopathies: A review. *Frontiers in Neurology, 13*, 993645. https://doi.org/10.3389/fneur.2022.993645

Calahorra, L., Camacho-Toledano, C., Serrano-Regal, M. P., Ortega, M. C., & Clemente, D. (2022). Regulatory cells in multiple sclerosis: From blood to brain. *Biomedicines, 10*(2), 335. https://doi.org/10.3390/biomedicines10020335

Camaschella, C., Nai, A., & Silvestri, L. (2020). Iron metabolism and iron disorders revisited in the hepcidin era. *Haematologica, 105*(2), 260–272. https://doi.org/10.3324/haematol.2019.232124

Campbell, G. R., & Mahad, D. J. (2011). Mitochondria as crucial players in demyelinated axons: Lessons from neuropathology and experimental demyelination. *Autoimmune Diseases, 2011*, 262847. https://doi.org/10.4061/2011/262847

Cavallo, S. (2020). Immune-mediated genesis of multiple sclerosis. *Journal of Translational Autoimmunity, 3*, 100039. https://doi.org/10.1016/j.jtauto.2020.100039

Chakrabarti, S., Munshi, S., Banerjee, K., Thakurta, I. G., Sinha, M., & Bagh, M. B. (2011). Mitochondrial dysfunction during brain aging: Role of oxidative stress and modulation by antioxidant supplementation. *Aging Disease, 2*(3), 242–256.

Cheli, V. T., Correale, J., Paez, P. M., & Pasquini, J. M. (2020). Iron metabolism in oligodendrocytes and astrocytes, implications for myelination and remyelination. *ASN Neuro, 12*, 1759091420962681. https://doi.org/10.1177/1759091420962681

Cheng, Y., Sun, L., Xie, Z., Fan, X., Cao, Q., Han, J., & Jin, T. (2017). Diversity of immune cell types in multiple sclerosis and its animal model: Pathological and therapeutic implications. *Journal of Neuroscience Research, 95*(10), 1973–1983. https://doi.org/10.1002/jnr.24023

Cianetti, L., Gabbianelli, M., & Sposi, N. M. (2010). Ferroportin and erythroid cells: An update. *Advances in Hematology, 2010*, 404173. https://doi.org/10.1155/2010/404173

Comi, G., Bar-Or, A., Lassmann, H., Uccelli, A., Hartung, H. P., Montalban, X., Sørensen, P. S., Hohlfeld, R., & Hauser, S. L.; Expert Panel of the 27th Annual Meeting of the European Charcot Foundation. (2021). Role of B cells in multiple sclerosis and related disorders. *Annals of Neurology, 89*(1), 13–23. https://doi.org/10.1002/ana.25927

Collins, J. F., Wessling-Resnick, M., & Knutson, M. D. (2008). Hepcidin regulation of iron transport. *The Journal of Nutrition, 138*(11), 2284–2288. https://doi.org/10.3945/jn.108.096347

Colonna, M., & Butovsky, O. (2017). Microglia function in the central nervous system during health and neurodegeneration. *Annual Review of Immunology, 35*, 441–468. https://doi.org/10.1146/annurev-immunol-051116-052358

Constantinescu, C. S., Farooqi, N., O'Brien, K., & Gran, B. (2011). Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS). *British Journal of Pharmacology, 164*(4), 1079–1086. https://doi.org/10.1111/j.1476-5381.2011.01302.x

Correale, J., Marrodan, M., & Ysrraelit, M. C. (2019). Mechanisms of neurodegeneration and axonal dysfunction in progressive multiple sclerosis. *Biomedicines, 7*(1), 14. https://doi.org/10.3390/biomedicines7010014

Cronin, S. J. F., Woolf, C. J., Weiss, G., & Penninger, J. M. (2019). The role of iron regulation in immunometabolism and immune-related disease. *Frontiers in Molecular Biosciences, 6*, 116. https://doi.org/10.3389/fmolb.2019.00116

Cui, Y., Yu, H., Bu, Z., Wen, L., Yan, L., & Feng, J. (2022). Focus on the role of the NLRP3 inflammasome in multiple sclerosis: Pathogenesis, diagnosis, and therapeutics. *Frontiers in Molecular Neuroscience, 15*, 894298. https://doi.org/10.3389/fnmol.2022.894298

Czpakowska, J., Kałuża, M., Szpakowski, P., & Głąbiński, A. (2024). An overview of multiple sclerosis in vitro models. *International Journal of Molecular Sciences, 25*(14), 7759. https://doi.org/10.3390/ijms25147759

Dash, U. C., Bhol, N. K., Swain, S. K., Samal, R. R., Nayak, P. K., Raina, V., Panda, S. K., Kerry, R. G., Duttaroy, A. K., & Jena, A. B. (2025). Oxidative stress and inflammation in the pathogenesis of neurological disorders: Mechanisms and implications. *Acta Pharmaceutica Sinica B, 15*(1), 15–34. https://doi.org/10.1016/j.apsb.2024.10.004

David, S., Ryan, F., Jhelum, P., & Kroner, A. (2023). Ferroptosis in neurological disease. *Neuroscientist, 29*(5), 591–615. https://doi.org/10.1177/10738584221100183

de Gruijter, N. M., Jebson, B., & Rosser, E. C. (2022). Cytokine production by human B cells: Role in health and autoimmune disease. *Clinical & Experimental Immunology, 210*(3), 253–262. https://doi.org/10.1093/cei/uxac090

de Sèze, J., Maillart, E., Gueguen, A., Laplaud, D. A., Michel, L., Thouvenot, E., Zephir, H., Zimmer, L., Biotti, D., Liblau, R. (2023). Anti-CD20 therapies in multiple sclerosis: From pathology to the clinic. *Frontiers in Immunology, 14*, 1004795. https://doi.org/10.3389/fimmu.2023.1004795

Dhanapalaratnam, R., Markoulli, M., & Krishnan, A. V. (2022). Disorders of vision in multiple sclerosis. *Clinical and Experimental Optometry, 105*(1), 3–12. https://doi.org/10.1080/08164622.2021.1947745

Di Filippo, M., Gaetani, L., Centonze, D., Hegen, H., Kuhle, J., Teunissen, C. E., Tintoré, M., & Parnetti, L. (2024). Fluid biomarkers in multiple sclerosis: From current to future applications. *Lancet Regional Health Europe, 44*, 101009. https://doi.org/10.1016/j.lanepe.2024.101009

Dikalov, S. (2011). Cross talk between mitochondria and NADPH oxidases. *Free Radical Biology and Medicine, 51*(7), 1289–1301. https://doi.org/10.1016/j.freeradbiomed.2011.06.033

Doseděl, M., Jirkovský, E., Macáková, K., Krčmová, L. K., Javorská, L., Pourová, J., Mercolini, L., Remião, F., Nováková, L., Mladěnka, P., & On Behalf of The Oemonom. (2021). Vitamin C—Sources, physiological role, kinetics, deficiency, use, toxicity, and determination. *Nutrients, 13*(2), 615. https://doi.org/10.3390/nu13020615

Drakesmith, H., Pasricha, S. R., Cabantchik, I., Hershko, C., Weiss, G., Girelli, D., & Zimmermann, M. B. (2021). Vaccine efficacy and iron deficiency: An intertwined pair? *The Lancet Haematology, 8*(9), e666–e669. https://doi.org/10.1016/S2352-3026(21)00201-5

Duarte, F. V., Ciampi, D., & Duarte, C. B. (2023). Role of mitochondrial dysfunction in neuroinflammation: Implications for neurodegenerative diseases. *Molecular Neurobiology, 60*(5), 2414–2431. https://doi.org/10.1007/s12035-023-02917-2

Dulian, K., Laskowski, R., Grzywacz, T., Kujach, S., Flis, D. J., Smaruj, M., & Ziemann, E. (2015). The whole body cryostimulation modifies irisin concentration and reduces inflammation in middle-aged, obese men. *Cryobiology, 71*(3), 398–404. https://doi.org/10.1016/j.cryobiol.2015.10.143

Engelhardt, B., & Sorokin, L. (2009). The blood-brain and the blood-cerebrospinal fluid barriers: Function and dysfunction. *Seminars in Immunopathology, 31*(4), 497–511. https://doi.org/10.1007/s00281-009-0177-0

Fan, X., Li, A., Yan, Z., Geng, X., Lian, L., Lv, H., Gao, D., & Zhang, J. (2022). From iron metabolism to ferroptosis: Pathologic changes in coronary heart disease. *Oxidative Medicine and Cellular Longevity, 2022*, 6291889. https://doi.org/10.1155/2022/6291889

Feng, S., Tang, D., Wang, Y., Li, X., Bao, H., Tang, C., Dong, X., Li, X., Yang, Q., Yan, Y., Yin, Z., Shang, T., Zheng, K., Huang, X., Wei, Z., Wang, K., & Qi, S. (2023). The mechanism of ferroptosis and its related diseases. *Molecular Biomedicine, 4*(1), 33. https://doi.org/10.1186/s43556-023-00142-2

Feng, Z., Meng, F., Huo, F., Zhu, Y., Qin, Y., Gui, Y., & Wu, J. (2024). Inhibition of ferroptosis rescues M2 macrophages and alleviates arthritis by suppressing the HMGB1/TLR4/STAT3 axis in M1 macrophages. *Redox Biology, 75*, 103255. https://doi.org/10.1016/j.redox.2024.103255

Fernández, Ó., Sörensen, P. S., Comi, G., Vermersch, P., Hartung, H. P., Leocani, L., Berger, T., Van Wijmeersch, B., Oreja-Guevara, C. (2024). Managing multiple sclerosis in individuals aged 55 and above: A compre-

hensive review. *Frontiers in Immunology, 15*, 1379538. https://doi.org/10.3389/fimmu.2024.1379538

Filippi, M., Preziosa, P., Banwell, B. L., Barkhof, F., Ciccarelli, O., De Stefano, N., Geurts, J. J. G., & Rocca, M. A. (2019). Assessment of lesions on magnetic resonance imaging in multiple sclerosis: Practical guidelines. *Brain, 142*(7), 1858–1875. https://doi.org/10.1093/brain/awz144

Findling, O., Rust, H., Yaldizli, Ö., Timmermans, D. P. H., Scheltinga, A., & Allum, J. H. J. (2018). Balance Changes in Patients With Relapsing-Remitting Multiple Sclerosis: A Pilot Study Comparing the Dynamics of the Relapse and Remitting Phases. *Frontiers in neurology*, *9*, 686. https://doi.org/10.3389/fneur.2018.00686

Ford, H. (2020). Clinical presentation and diagnosis of multiple sclerosis. *Clinical Medicine (London), 20*(4), 380–383. https://doi.org/10.7861/clinmed.2020-0292

Galaris, D., Barbouti, A., & Pantopoulos, K. (2019). Iron homeostasis and oxidative stress: An intimate relationship. *Biochimica et Biophysica Acta - Molecular Cell Research, 1866*(12), 118535. https://doi.org/10.1016/j.bbamcr.2019.118535

Garcia-Casal, M. N., Pasricha, S. R., Martinez, R. X., Lopez-Perez, L., & Peña-Rosas, J. P. (2021). Serum or plasma ferritin concentration as an index of iron deficiency and overload. *Cochrane Database of Systematic Reviews, 5*(5), CD011817. https://doi.org/10.1002/14651858.CD011817.pub2

García López, F. J., García-Merino, A., Alcalde-Cabero, E., & de Pedro-Cuesta, J. (2024). Incidence and prevalence of multiple sclerosis in Spain: A systematic review. *Neurologia,* 39(8), 639–650. https://doi.org/10.1016/j.nrleng.2022.02.004

Gharibi, T., Babaloo, Z., Hosseini, A., Marofi, F., Ebrahimi-Kalan, A., Jahandideh, S., Baradaran, B. (2020). The role of B cells in the immunopathogenesis of multiple sclerosis. *Immunology, 160*(4), 325–335. https://doi.org/10.1111/imm.13198

Gomes, H. R. (2022). Cerebrospinal fluid analysis: Current diagnostic methods in central nervous system infectious diseases. Arquivos de Neuropsiquiatria, 80(5 Suppl 1), 290–295. https://doi.org/10.1590/0004-282X--ANP-2022-S114

Gonzalez-Lorenzo, M., Ridley, B., Minozzi, S., Del Giovane, C., Peryer, G., Piggott, T., Foschi, M., Filippini, G., Tramacere, I., Baldin, E., Nonino, F. (2024). Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: A network meta-analysis. *Cochrane Database of Systematic Reviews, 1*(1), CD011381. https://doi.org/10.1002/14651858.CD011381.pub3

Graner, M., Pointon, T., Manton, S., Green, M., Dennison, K., Davis, M., Braiotta, G., & Yu, X. (2020). Oligoclonal IgG antibodies in multiple sclerosis target patient-specific peptides. *PLOS ONE, 15*(2), e0228883. https://doi.org/10.1371/journal.pone.0228883

Gruol, D. L. (2015). IL-6 regulation of synaptic function in the CNS. Neuropharmacology, 96(Pt A), 42–54. https://doi.org/10.1016/j.neuropharm.2014.10.023

Gudowska-Sawczuk, M., & Mroczko, B. (2023). Free light chains κ and λ as new biomarkers of selected diseases. International *Journal of Molecular Sciences, 24*(11), 9531. https://doi.org/10.3390/ijms24119531

Guo, L., Choi, S., Bikkannavar, P., & Cordeiro, M. F. (2022). Microglia: Key players in retinal ageing and neurodegeneration. *Frontiers in Cellular Neuroscience, 16*, 804782. https://doi.org/10.3389/fncel.2022.804782

Gupta, A., Pratt, R. D., & Crumbliss, A. L. (2016). Ferrous iron content of intravenous iron formulations. *Biometals, 29*(3), 411–415. https://doi.org/10.1007/s10534-016-9923-7

Haase, S., & Linker, R. A. (2021). Inflammation in multiple sclerosis. *Therapeutic Advances in Neurological Disorders, 14*, 17562864211007687. https://doi.org/10.1177/17562864211007687

Haki, M., Al-Biati, H. A., Al-Tameemi, Z. S., Ali, I. S., & Al-Hussaniy, H. A. (2024). Review of multiple sclerosis: Epidemiology, etiology, pathophysiology, and treatment. *Medicine (Baltimore), 103*(8), e37297. https://doi.org/10.1097/MD.0000000000037297

Hametner, S., Dal Bianco, A., Trattnig, S., & Lassmann, H. (2018). Iron related changes in MS lesions and their validity to characterize MS lesion types and dynamics with ultra-high field magnetic resonance imaging. *Brain Pathology, 28*(5), 743–749. https://doi.org/10.1111/bpa.12643

Harrison, P. M., & Arosio, P. (1996). The ferritins: Molecular properties, iron storage function and cellular regulation. *Biochimica et Biophysica Acta, 1275*(3), 161–203. https://doi.org/10.1016/0005-2728(96)00022-9

Hauser, S. L., & Cree, B. A. C. (2020). Treatment of multiple sclerosis: A review. *American Journal of Medicine, 133*(12), 1380-1390.e2. https://doi.org/10.1016/j.amjmed.2020.05.049

Hegen, H., Berek, K., & Deisenhammer, F. (2022). Cerebrospinal fluid kappa free light chains as biomarkers in multiple sclerosis—from diagnosis to prediction of disease activity. *Wiener Medizinische Wochenschrift,* 172(15–16), 337–345. https://doi.org/10.1007/s10354-022-00912-7

Hirayama, D., Iida, T., & Nakase, H. (2017). The phagocytic function of macrophages—Enforcing innate immunity and tissue homeostasis. *International Journal of Molecular Sciences, 19*(1), 92. https://doi.org/10.3390/ijms19010092

Holz, A., Obi, N., Ahrens, W., Berger, K., Bohn, B., Brenner, H., Becher, H. (2024). Childhood and adolescence factors and multiple sclerosis: Results from the German National Cohort (NAKO). *BMC Neurology, 24*(1), 123. https://doi.org/10.1186/s12883-024-03620-4

Hu, C. L., Nydes, M., Shanley, K. L., Morales Pantoja, I. E., Howard, T. A., & Bizzozero, O. A. (2019). Reduced expression of the ferroptosis inhibitor glutathione peroxidase-4 in multiple sclerosis and experimental autoimmune encephalomyelitis. *Journal of Neurochemistry, 148*(3), 426–439. https://doi.org/10.1111/jnc.14604

Höftberger, R., & Lassmann, H. (2017). Inflammatory demyelinating diseases of the central nervous system. In Handbook of Clinical Neurology (Vol. 145, pp. 263–283). https://doi.org/10.1016/B978-0-12-802395-2.00019-5

Hümmert, M. W., Wurster, U., Bönig, L., Schwenkenbecher, P., Sühs, K. W., Alvermann, S., Gingele, S., Skripuletz, T., & Stangel, M. (2019). Investigation of oligoclonal IgG bands in tear fluid of multiple sclerosis patients. *Frontiers in Immunology, 10*, 1110. https://doi.org/10.3389/fimmu.2019.01110

Jabara, H. H., Boyden, S. E., Chou, J., Ramesh, N., Massaad, M. J., Benson, H., & Geha, R. S. (2016). A missense mutation in TFRC, encoding transferrin receptor 1, causes combined immunodeficiency. *Nature Genetics, 48*(1), 74–78. https://doi.org/10.1038/ng.3465

Jamwal, S., & Kumar, P. (2019). Insight into the emerging role of striatal neurotransmitters in the pathophysiology of Parkinson's disease and Huntington's disease: A review. *Current Neuropharmacology, 17*(2), 165–175. https://doi.org/10.2174/1570159X16666180302115032

Jhelum, P., & David, S. (2022). Ferroptosis: Copper-iron connection in cuprizone-induced demyelination. *Neural Regeneration Research, 17*(1), 89–90. https://doi.org/10.4103/1673-5374.314300

Jhelum, P., Zandee, S., Ryan, F., Zarruk, J. G., Michalke, B., Venkataramani, V., Curran, L., Klement, W., Prat, A., & David, S. (2023). Ferroptosis induces detrimental effects in chronic EAE and its implications for progressive MS. *Acta Neuropathologica Communications, 11*(1), 121. https://doi.org/10.1186/s40478-023-01617-7

Joseph, F. G., Hirst, C. L., Pickersgill, T. P., Ben-Shlomo, Y., Robertson, N. P., & Scolding, N. J. (2009). CSF oligoclonal band status informs prognosis in multiple sclerosis: A case control study of 100 patients. *Journal of Neurology, Neurosurgery & Psychiatry, 80*(3), 292–296. https://doi.org/10.1136/jnnp.2008.150896

Juárez Olguín, H., Calderón Guzmán, D., Hernández García, E., & Barragán Mejía, G. (2016). The role of dopamine and its dysfunction as a consequence of oxidative stress. *Oxidative Medicine and Cellular Longevity, 2016*, 9730467. https://doi.org/10.1155/2016/9730467

Katsarogiannis, E., Landtblom, A. M., Kristoffersson, A., Wikström, J., Semnic, R., & Berntsson, S. G. (2023). Absence of oligoclonal bands in multiple sclerosis: A call for differential diagnosis. *Journal of Clinical Medicine, 12*(14), 4656. https://doi.org/10.3390/jcm12144656

Kaunzner, U. W., & Gauthier, S. A. (2017). MRI in the assessment and monitoring of multiple sclerosis: An update on best practice. *Therapeutic Advances in Neurological Disorders, 10*(6), 247–261. https://doi.org/10.1177/1756285617708911

Kempuraj, D., Thangavel, R., Natteru, P. A., Selvakumar, G. P., Saeed, D., Zahoor, H., Zaheer, S., Iyer, S. S., & Zaheer, A. (2016). Neuroinflammation induces neurodegeneration. *Journal of Neurology, Neurosurgery & Spine, 1*(1), 1003.

Kim, K. T. (2022). Lumbar puncture: Considerations, procedure, and complications. *Encephalitis, 2*(4), 93–97. https://doi.org/10.47936/encephalitis.2022.00045

Kister, A., & Kister, I. (2023). Overview of myelin, major myelin lipids, and myelin-associated proteins. *Frontiers in Chemistry, 10*, 1041961. https://doi.org/10.3389/fchem.2022.1041961

Klingberg, F., Hinz, B., & White, E. S. (2013). The myofibroblast matrix: implications for tissue repair and fibrosis. *The Journal of pathology, 229*(2), 298–309. https://doi.org/10.1002/path.4104

Kopper, T. J., & Gensel, J. C. (2018). Myelin as an inflammatory mediator: Myelin interactions with complement, macrophages, and microglia in spinal cord injury. *Journal of Neuroscience Research, 96*(6), 969–977. https://doi.org/10.1002/jnr.24114

Kowdley, K. V., Gochanour, E. M., Sundaram, V., Shah, R. A., & Handa, P. (2021). Hepcidin signaling in health and disease: Ironing out the details. *Hepatology Communications, 5*(5), 723–735. https://doi.org/10.1002/hep4.1717

Kwon, H. S., & Koh, S. H. (2020). Neuroinflammation in neurodegenerative disorders: The roles of microglia and astrocytes. *Translational Neurodegeneration, 9*(1), 42. https://doi.org/10.1186/s40035-020-00221-2

Kölliker-Frers, R., Udovin, L., Otero-Losada, M., Kobiec, T., Herrera, M. I., Palacios, J., & Capani, F. (2021). Neuroinflammation: An integrating overview of reactive-neuroimmune cell interactions in health and disease. *Mediators of Inflammation, 2021*, 9999146. https://doi.org/10.1155/2021/9999146

Larochelle, C., Wasser, B., Jamann, H., Löffel, J. T., Cui, Q. L., Tastet, O., Schillner, M., Luchtman, D., Birkenstock, J., Stroh, A., Antel, J., Bittner, S., Zipp, F. (2021). Pro-inflammatory T helper 17 directly harms oligodendrocytes in neuroinflammation. *Proceedings of the National Academy of Sciences of the United States of America, 118*(34), e2025813118. https://doi.org/10.1073/pnas.2025813118

Lassmann, H. (2018). Multiple sclerosis pathology. *Cold Spring Harbor Perspectives in Medicine, 8*(3), a028936. https://doi.org/10.1101/cshperspect.a028936

Lazibat, I., Rubinić Majdak, M., & Županić, S. (2018). Multiple sclerosis: New aspects of immunopathogenesis. *Acta Clinica Croatica, 57*(2), 352–361. https://doi.org/10.20471/acc.2018.57.02.17

Legroux, L., & Arbour, N. (2015). Multiple sclerosis and T lymphocytes: An entangled story. *Journal of Neuroimmune Pharmacology, 10*(4), 528–546. https://doi.org/10.1007/s11481-015-9614-0

Leung, S., Holbrook, A., King, B., Lu, H. T., Evans, V., Miyamoto, N., & Perez, D. (2005). Differential inhibition of inducible T cell cytokine secretion by potent iron chelators. *Journal of Biomolecular Screening, 10*(2), 157–167. https://doi.org/10.1177/1087057104272394

Levi, S., Ripamonti, M., Moro, A. S., & Cozzi, A. (2024). Iron imbalance in neurodegeneration. *Molecular Psychiatry, 29*(4), 1139–1152. https://doi.org/10.1038/s41380-023-02399-z

LeVine, S. M., Bilgen, M., & Lynch, S. G. (2013). Iron accumulation in multiple sclerosis: An early pathogenic event. *Expert Review of Neurotherapeutics, 13*(3), 247–250. https://doi.org/10.1586/ern.13.14

Lewin, A., Hamilton, S., Witkover, A., Langford, P., Nicholas, R., Chataway, J., & Bangham, C. R. M. (2016). Free serum hemoglobin is associated with brain atrophy in secondary progressive multiple sclerosis. *Wellcome Open Research, 1*, 10. https://doi.org/10.12688/wellcomeopenres.9967.2

Li, H., Li, B., & Zheng, Y. (2024). Role of microglia/macrophage polarization in intraocular diseases: A review. *International Journal of Molecular Medicine, 53*(5), 45. https://doi.org/10.3892/ijmm.2024.5369

Li, L., Xia, Y., Yuan, S., Li, F., Xie, X., Luo, Y., & He, R. (2021). Iron deprivation restrains the differentiation and pathogenicity of T helper 17 cell. *Journal of Leukocyte Biology, 110*(6), 1057–1067. https://doi.org/10.1002/JLB.3MA0821-015R

Li, N., Zhao, G., Wu, W., Zhang, M., Liu, W., Chen, Q., & Wang, X. (2020a). The efficacy and safety of vitamin C for iron supplementation in adult patients with iron deficiency anemia: A randomized clinical trial. *JAMA Network Open, 3*(11), e2023644. https://doi.org/10.1001/jamanetworkopen.2020.23644

Li, R., Rezk, A., Healy, L. M., Muirhead, G., Prat, A., Gommerman, J. L., Bar-Or, A.; MSSRF Canadian B Cells in MS Team. (2016). Cytokine-defined B cell responses as therapeutic targets in multiple sclerosis. *Frontiers in Immunology, 6*, 626. https://doi.org/10.3389/fimmu.2015.00626

Li, S. C., Lee, C. C., Hsu, C. M., Huang, H. B., & Su, Y. C. (2020b). IL-6 induces haptoglobin expression through activating STAT3 in human head and neck cancer. *Journal of Oral Pathology & Medicine, 49*(1), 49-54. https://doi.org/10.1111/jop.12958

Liu, R., Du, S., Zhao, L., Jain, S., Sahay, K., Rizvanov, A., Lezhnyova, V., Khaibullin, T., Martynova, E., Khaiboullina, S., & Baranwal, M. (2022). Autoreactive lymphocytes in multiple sclerosis: Pathogenesis and treatment target. *Frontiers in Immunology, 13*, 996469. https://doi.org/10.3389/fimmu.2022.996469

Love, S. (2006). Demyelinating diseases. *Journal of Clinical Pathology, 59*(11), 1151–1159. https://doi.org/10.1136/jcp.2005.031195

Lozinski, B. M., Ghorbani, S., & Yong, V. W. (2024). Biology of neurofibrosis with focus on multiple sclerosis. *Frontiers in Immunology, 15*, 1370107. https://doi.org/10.3389/fimmu.2024.1370107

Lozoff, B. (2011). Early iron deficiency has brain and behavior effects consistent with dopaminergic dysfunction. *The Journal of Nutrition, 141*(4), 740S–746S. https://doi.org/10.3945/jn.110.131169

Lubetzki, C., & Stankoff, B. (2014). Demyelination in multiple sclerosis. *Handbook of Clinical Neurology, 122*, 89–99. https://doi.org/10.1016/B978-0-444-52001-2.00004-2

Mado, H., Adamczyk-Sowa, M., & Sowa, P. (2023). Role of microglial cells in the pathophysiology of MS: Synergistic or antagonistic? *International Journal of Molecular Sciences, 24*(3), 1861. https://doi.org/10.3390/ijms24031861

Maggio, M., Guralnik, J. M., Longo, D. L., & Ferrucci, L. (2006). Interleukin-6 in aging and chronic disease: A magnificent pathway. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 61*(6), 575–584. https://doi.org/10.1093/gerona/61.6.575

Makhoul, K., Ahdab, R., Riachi, N., Chalah, M. A., & Ayache, S. S. (2020). Tremor in multiple sclerosis—An overview and future perspectives. *Brain Sciences, 10*(10), 722. https://doi.org/10.3390/brainsci10100722

Maldonado, P. P., Guevara, C., Olesen, M. A., Orellana, J. A., Quintanilla, R. A., & Ortiz, F. C. (2022). Neurodegeneration in multiple sclerosis: The role of Nrf2-dependent pathways. *Antioxidants (Basel), 11*(6), 1146. https://doi.org/10.3390/antiox11061146

Malhotra, S., Río, J., Urcelay, E., Nurtdinov, R., Bustamante, M. F., Comabella, M. (2015). NLRP3 inflammasome is associated with the response to IFN-β in patients with multiple sclerosis. *Brain, 138*(Pt 3), 644–652. https://doi.org/10.1093/brain/awu388

Marcus, J. F., & Waubant, E. L. (2013). Updates on clinically isolated syndrome and diagnostic criteria for multiple sclerosis. *The Neurohospitalist, 3*(2), 65–80. https://doi.org/10.1177/1941874412457183

Margoni, M., Preziosa, P., Rocca, M. A., & Filippi, M. (2023). Depressive symptoms, anxiety and cognitive impairment: Emerging evidence in multiple sclerosis. *Translational Psychiatry, 13*(1), 264. https://doi.org/10.1038/s41398-023-02555-7

McCarthy, R. C., Sosa, J. C., Gardeck, A. M., Baez, A. S., Lee, C. H., & Wessling-Resnick, M. (2018). Inflammation-induced iron transport and metabolism by brain microglia. *Journal of Biological Chemistry, 293*(20), 7853–7863. https://doi.org/10.1074/jbc.RA118.001949

McIntosh, A., Mela, V., Harty, C., Minogue, A. M., Costello, D. A., Kerskens, C., & Lynch, M. A. (2019). Iron accumulation in microglia triggers a cascade

of events that leads to altered metabolism and compromised function in APP/PS1 mice. *Brain Pathology, 29*(5), 606–621. https://doi.org/10.1111/bpa.12704

McLaughlin, K. A., & Wucherpfennig, K. W. (2008). B cells and autoantibodies in the pathogenesis of multiple sclerosis and related inflammatory demyelinating diseases. *Advances in Immunology, 98*, 121–149. https://doi.org/10.1016/S0065-2776(08)00404-5

Mehta, V., Pei, W., Yang, G., Li, S., Swamy, E., Boster, A., & Pitt, D. (2013). Iron is a sensitive biomarker for inflammation in multiple sclerosis lesions. *PLoS ONE,* 8(3), e57573. https://doi.org/10.1371/journal.pone.0057573

Melnikov, M., Belousova, O., Murugin, V., Pashenkov, M., & Boyko, A. (2016). The role of dopamine in modulation of Th-17 immune response in multiple sclerosis. *Journal of Neuroimmunology, 292*, 97–101. https://doi.org/10.1016/j.jneuroim.2016.01.020

Melnikov, M., Sviridova, A., Rogovskii, V., Kudrin, V., Murugin, V., Boyko, A., & Pashenkov, M. (2022). The role of D2-like dopaminergic receptor in dopamine-mediated modulation of Th17-cells in multiple sclerosis. *Current Neuropharmacology, 20*(8), 1632–1639. https://doi.org/10.2174/1570159X19666210823103859

Miljković, D., & Spasojević, I. (2013). Multiple sclerosis: Molecular mechanisms and therapeutic opportunities. *Antioxidants & Redox Signaling, 19*(18), 2286–2334. https://doi.org/10.1089/ars.2012.5068

Miller, J. L. (2013). Iron deficiency anemia: A common and curable disease. *Cold Spring Harbor Perspectives in Medicine, 3*(7), a011866. https://doi.org/10.1101/cshperspect.a011866

Milo, R. (2019). Therapies for multiple sclerosis targeting B cells. *Croatian Medical Journal, 60*(2), 87–98. https://doi.org/10.3325/cmj.2019.60.87

Moos, T., Skjoerringe, T., Gosk, S., & Morgan, E. H. (2006). Brain capillary endothelial cells mediate iron transport into the brain by segregating iron from transferrin without the involvement of divalent metal transporter 1. *Journal of Neurochemistry, 98*(6), 1946–1958. https://doi.org/10.1111/j.1471-4159.2006.04023.x

Muchowska, K. B., Varma, S. J., & Moran, J. (2019). Synthesis and breakdown of universal metabolic precursors promoted by iron. *Nature, 569*(7754), 104–107. https://doi.org/10.1038/s41586-019-1151-1

Ni, S., Yuan, Y., Kuang, Y., & Li, X. (2022). Iron metabolism and immune regulation. Frontiers in Immunology, 13, 816282. https://doi.org/10.3389/fimmu.2022.816282

Nicolas, G., Bennoun, M., Porteu, A., Mativet, S., Beaumont, C., Grandchamp, B., Sirito, M., Sawadogo, M., Kahn, A., & Vaulont, S. (2002). Severe iron deficiency anemia in transgenic mice expressing liver hepcidin. *Proceedings of the National Academy of Sciences of the United States of America, 99*(7), 4596–4601. https://doi.org/10.1073/pnas.072632499

Nishihara, H., Perriot, S., Gastfriend, B. D., Steinfort, M., Cibien, C., Soldati, S., Matsuo, K., Guimbal, S., Mathias, A., Palecek, S. P., Shusta, E. V., Pasquier, R. D., & Engelhardt, B. (2022). Intrinsic blood-brain barrier dysfunction contributes to multiple sclerosis pathogenesis. *Brain, 145*(12), 4334–4348. https://doi.org/10.1093/brain/awac019

Ohl, K., Tenbrock, K., & Kipp, M. (2016). Oxidative stress in multiple sclerosis: Central and peripheral mode of action. *Experimental Neurology, 27*7, 58–67. https://doi.org/10.1016/j.expneurol.2015.11.010

Olsson, T., Barcellos, L. F., & Alfredsson, L. (2017). Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nature Reviews Neurology, 13*(1), 25–36. https://doi.org/10.1038/nrneurol.2016.187

Otálora-Alcaraz, A., Reilly, T., Oró-Nolla, M., Sun, M. C., Costelloe, L., Kearney, H., Patra, P. H., Downer, E. J. (2025). The NLRP3 inflammasome: A central player in multiple sclerosis. *Biochemical Pharmacology, 232*, 116667. https://doi.org/10.1016/j.bcp.2024.116667

Pagani, A., Nai, A., Silvestri, L., & Camaschella, C. (2019). Hepcidin and anemia: A tight relationship. *Frontiers in Physiology, 10*, 1294. https://doi.org/10.3389/fphys.2019.01294

Pala, O., Diaz, A., Blomberg, B. B., & Frasca, D. (2018). B lymphocytes in rheumatoid arthritis and the effects of anti-TNF-α agents on B lymphocytes: A review of the literature. Clinical Therapeutics, 40(6), 1034–1045. https://doi.org/10.1016/j.clinthera.2018.04.016

Pannewitz-Makaj, K., Wurster, U., Jendretzky, K. F., Gingele, S., Sühs, K. W., Stangel, M., Skripuletz, T., & Schwenkenbecher, P. (2020). Evidence of oligoclonal bands does not exclude non-inflammatory neurological diseases. *Diagnostics (Basel), 11*(1), 37. https://doi.org/10.3390/diagnostics11010037

Pantopoulos, K. (2024). Oral iron supplementation: New formulations, old questions. *Haematologica, 109*(9), 2790–2801. https://doi.org/10.3324/haematol.2024.284967

Park, H. T., Kim, Y. H., Lee, K. E., & Kim, J. K. (2020). Behind the pathology of macrophage-associated demyelination in inflammatory neuropathies: Demyelinating Schwann cells. *Cellular and Molecular Life Sciences, 77*(13), 2497–2506. https://doi.org/10.1007/s00018-019-03431-8

Pires, I. S., Berthiaume, F., & Palmer, A. F. (2023). Engineering therapeutics to detoxify hemoglobin, heme, and iron. *Annual Review of Biomedical Engineering, 25*, 1–21. https://doi.org/10.1146/annurev-bioeng-081622--031203

Pirko, I., & Noseworthy, J. H. (2007). Demyelinating disorders of the central nervous system. In Textbook of Clinical Neurology (pp. 1103–1133). https://doi.org/10.1016/B978-141603618-0.10048-7

Podbielska, M., Banik, N. L., Kurowska, E., & Hogan, E. L. (2013). Myelin recovery in multiple sclerosis: The challenge of remyelination. *Brain Sciences,* 3(3), 1282–1324. https://doi.org/10.3390/brainsci3031282

Popescu, B. F., Frischer, J. M., Webb, S. M., Tham, M., Adiele, R. C., Robinson, C. A., Fitz-Gibbon, P. D., Weigand, S. D., Metz, I., Nehzati, S., George, G. N., Pickering, I. J., Brück, W., Hametner, S., Lassmann, H., Parisi, J. E., Yong, G., & Lucchinetti, C. F. (2017). Pathogenic implications of distinct patterns of iron and zinc in chronic MS lesions. *Acta Neuropathologica, 134*(1), 45–64. https://doi.org/10.1007/s00401-017-1696-8

Prineas, J. W., & Parratt, J. D. E. (2021). Multiple sclerosis: Microglia, monocytes, and macrophage-mediated demyelination. *Journal of Neuropathology & Experimental Neurology, 80*(10), 975–996. https://doi.org/10.1093/jnen/nlab083

Qin, J., Ma, Z., Chen, X., & Shu, S. (2023). Microglia activation in central nervous system disorders: A review of recent mechanistic investigations and development efforts. *Frontiers in Neurology, 14*, 1103416. https://doi.org/10.3389/fneur.2023.1103416

Rand, D., Ravid, O., Atrakchi, D., Israelov, H., Bresler, Y., Shemesh, C., Omesi, L., Liraz-Zaltsman, S., Gosselet, F., Maskrey, T. S., Beeri, M. S., Wipf, P., & Cooper, I. (2021). Endothelial iron homeostasis regulates blood-brain barrier integrity via the HIF2α–VE-cadherin pathway. *Pharmaceutics, 13*(3), 311. https://doi.org/10.3390/pharmaceutics13030311

Rao, M., Lamont, J. L., Chan, J., Concannon, T. W., Comenzo, R., Ratichek, S. J., & Avendano, E. E.(2012). Serum free light chain analysis for the diagnosis, management, and prognosis of plasma cell dyscrasias: Future research needs. Agency for Healthcare Research and Quality (US). https://pubmed.ncbi.nlm.nih.gov/23678513

Rock, R. B., Gekker, G., Hu, S., Sheng, W. S., Cheeran, M., Lokensgard, J. R., & Peterson, P. K. (2004). Role of microglia in central nervous system infections. *Clinical Microbiology Reviews, 17*(4), 942–964. https://doi.org/10.1128/CMR.17.4.942-964.2004

Rodrigue, K. M., Daugherty, A. M., Foster, C. M., & Kennedy, K. M. (2020). Striatal iron content is linked to reduced fronto-striatal brain function under working memory load. *NeuroImage, 21*0, 116544. https://doi.org/10.1016/j.neuroimage.2020.116544

Roemhild, K., von Maltzahn, F., Weiskirchen, R., Knüchel, R., von Stillfried, S., & Lammers, T. (2021). Iron metabolism: Pathophysiology and pharmacology. *Trends in Pharmacological Sciences, 42*(8), 640–656. https://doi.org/10.1016/j.tips.2021.05.001

Rosenblum, S. L., & Kosman, D. J. (2022). Aberrant cerebral iron trafficking co-morbid with chronic inflammation: Molecular mechanisms and pharmacologic intervention. *Frontiers in Neurology, 13*, 855751. https://doi.org/10.3389/fneur.2022.855751

Sadovnick, A. D., Armstrong, H., Rice, G. P., Bulman, D., Hashimoto, L., et al. (1993). A population-based study of multiple sclerosis in twins: Update. *Annals of Neurology, 33*(3), 281–285. https://doi.org/10.1002/ana.410330309

Saha, S., Buttari, B., Panieri, E., Profumo, E., & Saso, L. (2020). An overview of the Nrf2 signaling pathway and its role in inflammation. *Molecules, 25*(22), 5474. https://doi.org/10.3390/molecules25225474

Salvador, G. A., Uranga, R. M., & Giusto, N. M. (2010). Iron and mechanisms of neurotoxicity. *International Journal of Alzheimer s Disease, 2011*, 720658. https://doi.org/10.4061/2011/720658

Sánchez-Vera, I., Escudero, E., Muñoz, Ú., & Sádaba, M. C. (2023). IgM to phosphatidylcholine in multiple sclerosis patients: From the diagnosis to the treatment. *Therapeutic Advances in Neurological Disorders, 16*, 17562864231189919. https://doi.org/10.1177/17562864231189919

Sandesjö, F., Tremlett, H., Fink, K., Marrie, R. A., Zhu, F., Wickström, R., McKay, K. A. (2024). Incidence rate and prevalence of pediatric-onset multiple sclerosis in Sweden: A population-based register study. *European Journal of Neurology, 31*(5), e16253. https://doi.org/10.1111/ene.16253

Santana-Codina, N., & Mancias, J. D. (2018). The role of NCOA4-mediated ferritinophagy in health and disease. *Pharmaceuticals (Basel), 11*(4), 114. https://doi.org/10.3390/ph11040114

Sarpong-Kumankomah, S., Knox, K. B., Kelly, M. E., Hunter, G., Popescu, B., Gailer, J. (2022). Quantification of human plasma metalloproteins in multiple sclerosis, ischemic stroke, and healthy controls reveals an association of haptoglobin-hemoglobin complexes with age. *PLoS ONE, 17*(1), e0262160. https://doi.org/10.1371/journal.pone.0262160

Schaer, D. J., Vinchi, F., Ingoglia, G., Tolosano, E., & Buehler, P. W. (2014). Haptoglobin, hemopexin, and related defense pathways—Basic science, clinical perspectives, and drug development. *Frontiers in Physiology, 5*, 415. https://doi.org/10.3389/fphys.2014.00415

Schipper, H. M. (2012). Neurodegeneration with brain iron accumulation—clinical syndromes and neuroimaging. *Biochimica et Biophysica Acta, 1822*(3), 350–360. https://doi.org/10.1016/j.bbadis.2011.06.016

Schreiner, T. G., Romanescu, C., & Popescu, B. O. (2022). The blood-brain barrier—a key player in multiple sclerosis disease mechanisms. *Biomolecules, 12*(4), 538. https://doi.org/10.3390/biom12040538

Schweser, F., Hagemeier, J., Dwyer, M. G., Bergsland, N., Hametner, S., Weinstock-Guttman, B., Zivadinov, R. (2021). Decreasing brain iron in multiple sclerosis: The difference between concentration and content in iron MRI. *Human Brain Mapping, 42*(5), 1463–1474. https://doi.org/10.1002/hbm.25306

Shao, F., Wang, X., Wu, H., Wu, Q., & Zhang, J. (2022). Microglia and neuroinflammation: Crucial pathological mechanisms in traumatic brain injury-induced neurodegeneration. *Frontiers in Aging Neuroscience, 14*, 825086. https://doi.org/10.3389/fnagi.2022.825086

Shaw, K. A., Zello, G. A., Rodgers, C. D., Warkentin, T. D., Baerwald, A. R., & Chilibeck, P. D. (2022). Benefits of a plant-based diet and considerations for the athlete. *European Journal of Applied Physiology, 122*(5), 1163–1178. https://doi.org/10.1007/s00421-022-04902-w

Skolmowska, D., Głąbska, D., Kołota, A., & Guzek, D. (2022). Effectiveness of dietary interventions in prevention and treatment of iron-deficiency anemia in pregnant women: A systematic review of randomized controlled trials. *Nutrients, 14*(15), 3023. https://doi.org/10.3390/nu14153023

Sochocka, M., Diniz, B. S., & Leszek, J. (2017). Inflammatory response in the CNS: Friend or foe? Molecular Neurobiology, 54(10), 8071–8089. https://doi.org/10.1007/s12035-016-0297-1

Solberg, A., & Reikvam, H. (2023). Iron status and physical performance in athletes. *Life (Basel), 13*(10), 2007. https://doi.org/10.3390/life13102007

Spaas, J., van Veggel, L., Schepers, M., Tiane, A., van Horssen, J., Wilson, D. M. III, Moya, P. R., Piccart, E., Hellings, N., Eijnde, B. O., Derave, W., Schreiber, R., & Vanmierlo, T. (2021). Oxidative stress and impaired oligodendrocyte precursor cell differentiation in neurological disorders. *Cellular and Molecular Life Sciences, 78*(10), 4615–4637. https://doi.org/10.1007/s00018-021-03802-0

Stampanoni Bassi, M., Iezzi, E., Drulovic, J., Pekmezovic, T., Gilio, L., Furlan, R., Finardi, A., Marfia, G. A., Sica, F., Centonze, D., & Buttari, F. (2020). IL-6 in the cerebrospinal fluid signals disease activity in multiple sclerosis. *Frontiers in Cell and Neuroscience, 14*, 120. https://doi.org/10.3389/fncel.2020.00120

Stoffel, N. U., Cercamondi, C. I., Brittenham, G., Zeder, C., Geurts-Moespot, A. J., Swinkels, D. W., Moretti, D., & Zimmermann, M. B. (2017). Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: Two open-label, randomised controlled trials. *Lancet Haematology,* 4(11), e524–e533. https://doi.org/10.1016/S2352-3026(17)30182-5

Stoffel, N. U., Uyoga, M. A., Mutuku, F. M., Frost, J. N., Mwasi, E., Paganini, D., & Zimmermann, M. B. (2020). Iron deficiency anemia at the time of vaccination predicts decreased vaccine response and iron supplementation at time of vaccination increases humoral vaccine response: A birth cohort study and a randomized trial follow-up study in Kenyan infants. *Frontiers in Immunology, 11*, 1313 https://doi.org/10.3389/fimmu.2020.01313

Stoiloudis, P., Kesidou, E., Bakirtzis, C., Sintila, S. A., Konstantinidou, N., Grigoriadis, N. (2022). The role of diet and interventions on multiple sclerosis: A review. *Nutrients, 14*(6), 1150. https://doi.org/10.3390/nu14061150

Strizova, Z., Benesova, I., Bartolini, R., Novysedlak, R., Cecrdlova, E., Foley, L. K., & Striz, I. (2023). M1/M2 macrophages and their overlaps—Myth or reality? *Clinical Science, 137*(15), 1067–1093. https://doi.org/10.1042/CS20220531

Stüber, C., Pitt, D., & Wang, Y. (2016). Iron in multiple sclerosis and its noninvasive imaging with quantitative susceptibility mapping. *International Journal of Molecular Sciences, 17*(1), 100. https://doi.org/10.3390/ijms17010100

Tafti, D., Ehsan, M., & Xixis, K. L. (2024). Multiple Sclerosis. In StatPearls. StatPearls Publishing.

Tang, D., & Kroemer, G. (2020). Ferroptosis. *Current Biology, 3*0(21), R1292–R1297. https://doi.org/10.1016/j.cub.2020.09.068

Tavassolifar, M. J., Vodjgani, M., Salehi, Z., & Izad, M. (2020). The influence of reactive oxygen species in the immune system and pathogenesis of multiple sclerosis. *Autoimmune Diseases, 2020*, 5793817. https://doi.org/10.1155/2020/5793817

Tebay, L. E., Robertson, H., Durant, S. T., Vitale, S. R., Penning, T. M., Dinkova-Kostova, A. T., & Hayes, J. D. (2015). Mechanisms of activation of the transcription factor Nrf2 by redox stressors, nutrient cues, and energy status, and the pathways through which it attenuates degenerative disease. *Free Radical Biology and Medicine, 88*(Pt B), 108–146. https://doi.org/10.1016/j.freeradbiomed.2015.06.021

Teh, M. R., Frost, J. N., Armitage, A. E., & Drakesmith, H. (2021). Analysis of iron and iron- interacting protein dynamics during T-cell activation. *Frontiers in Immunology, 12*, 714613. https://doi.org/10.3389/fimmu.2021.714613

Tesmer, L. A., Lundy, S. K., Sarkar, S., & Fox, D. A. (2008). Th17 cells in human disease. *Immunological Reviews, 223*, 87–113. https://doi.org/10.1111/j.1600-065X.2008.00628.x

Tillema, J. M., & Pirko, I. (2013). Neuroradiological evaluation of demyelinating disease. *Therapeutic Advances in Neurological Disorders,* 6(4), 249–268. https://doi.org/10.1177/1756285613478870

Touil, H., Li, R., Zuroff, L., Moore, C. S., Healy, L., Cignarella, F., & Bar-Or, A. (2023). Cross-talk between B cells, microglia, and macrophages and implications for central nervous system compartmentalized inflammation and progressive multiple sclerosis. *EBioMedicine, 96*, 104789. https://doi.org/10.1016/j.ebiom.2023.104789

Travers, B. S., Tsang, B. K., & Barton, J. L. (2022). Multiple sclerosis: Diagnosis, disease-modifying therapy, and prognosis. *Australian Journal of General Practice, 51*(4), 199–206. https://doi.org/10.31128/AJGP-07-21-6103

Valadkeviciene, D., Kavaliunas, A., Kizlaitiene, R., Jocys, M., & Jatuzis, D. (2019). Incidence rate and sex ratio in multiple sclerosis in Lithuania. *Brain and Behavior, 9*(1), e01150. https://doi.org/10.1002/brb3.1150

Valentine, K. M., Mullins, G. N., Davalos, O. A., Seow, L. W., & Hoyer, K. K. (2021). CD8 follicular T cells localize throughout the follicle during germinal center reactions and maintain cytolytic and helper properties. *Journal of Autoimmunity, 123*, 102690. https://doi.org/10.1016/j.jaut.2021.102690

van Langelaar, J., Rijvers, L., Smolders, J., & van Luijn, M. M. (2020). B and T cells driving multiple sclerosis: Identity, mechanisms, and potential triggers. *Frontiers in Immunology, 11*, 760. https://doi.org/10.3389/fimmu.2020.00760

Vela, D. (2018). Hepcidin, an emerging and important player in brain iron homeostasis. *Journal of Translational Medicine, 16*(1), 25. https://doi.org/10.1186/s12967-018-1399-5

Villavicencio Tejo, F., & Quintanilla, R. A. (2021). Contribution of the Nrf2 pathway on oxidative damage and mitochondrial failure in Parkinson s and Alzheimer s disease. *Antioxidants (Basel), 10*(7), 1069. https://doi.org/10.3390/antiox10071069

von Büdingen, H. C., Bar-Or, A., & Zamvil, S. S. (2011). B cells in multiple sclerosis: Connecting the dots. *Current Opinion in Immunology, 23*(6), 713–720. https://doi.org/10.1016/j.coi.2011.09.003

von Essen, M. R., Talbot, J., Hansen, R. H. H., Chow, H. H., Lundell, H., Siebner, H. R., & Sellebjerg, F. (2023). Intrathecal CD8+CD20+ T cells in primary progressive multiple sclerosis. Neurology, *Neuroimmunology & Neuroinflammation, 10*(5), e200140. https://doi.org/10.1212/NXI.0000000000200140

Wallace, D. F. (2016). The regulation of iron absorption and homeostasis. *Clinical Biochemistry Reviews, 37*(2), 51–62. https://doi.org/10.1016/j.bbamcr.2019.118535

Wang, H., Huang, Z., Du, C., & Dong, M. (2024). Iron dysregulation in cardiovascular diseases. *Reviews in Cardiovascular Medicine, 25*(1), 16. https://doi.org/10.31083/j.rcm2501016

Wang, X., Garrick, M. D., & Collins, J. F. (2019). Animal models of normal and disturbed iron and copper metabolism. *The Journal of Nutrition, 149*(12), 2085–2100. https://doi.org/10.1093/jn/nxz172

Ward, R. J., Dexter, D. T., & Crichton, R. R. (2022). Iron, neuroinflammation, and neurodegeneration. *International Journal of Molecular Sciences, 23*(13), 7267. https://doi.org/10.3390/ijms23137267

Ward, R. J., Zucca, F. A., Duyn, J. H., Crichton, R. R., & Zecca, L. (2014). The role of iron in brain ageing and neurodegenerative disorders. *Lancet Neurology, 13*(10), 1045–1060. https://doi.org/10.1016/S1474-4422(14)70117-6

Wiernicki, B., Dubois, H., Tyurina, Y. Y., Hassannia, B., Bayir, H., Kagan, V. E., Vandenabeele, P., Wullaert, A., & Vanden Berghe, T. (2020). Excessive phospholipid peroxidation distinguishes ferroptosis from other cell death modes including pyroptosis. *Cell Death & Disease, 11*(10), 922. https://doi.org/10.1038/s41419-020-03118-0

Wilkinson, N., & Pantopoulos, K. (2014). The IRP/IRE system in vivo: Insights from mouse models. *Frontiers in Pharmacology, 5*, 176. https://doi.org/10.3389/fphar.2014.00176

Williams, R., Buchheit, C. L., Berman, N. E., & LeVine, S. M. (2012). Pathogenic implications of iron accumulation in multiple sclerosis. *Journal of Neurochemistry, 120*(1), 7–25. https://doi.org/10.1111/j.1471-4159.2011.07536.x

Wu, T., Ning, S., Zhang, H., Cao, Y., Li, X., Hao, J., & Wang, L. (2024). Role of ferroptosis in neuroimmunity and neurodegeneration in multiple sclerosis revealed by multi-omics data. *Journal of Cellular and Molecular Medicine, 28*(10), e18396. https://doi.org/10.1111/jcmm.18396

Wu, Z., Wu, S., & Liang, T. (2021). Association of NLRP3 rs35829419 and rs10754558 polymorphisms with risks of autoimmune diseases: A systematic review and meta-analysis. *Frontiers in Genetics, 12*, 690860. https://doi.org/10.3389/fgene.2021.690860

Xiao, G., Zhao, M., Liu, Z., Du, F., & Zhou, B. (2021). Zinc antagonizes iron-regulation of tyrosine hydroxylase activity and dopamine production in Drosophila melanogaster. *BMC Biology, 19*(1), 236. https://doi.org/10.1186/s12915-021-01168-0

Yan, J., Liu, J., Lin, C. Y., Australia and New Zealand Multiple Sclerosis Genetics Consortium (ANZGene), Csurhes, P. A., Pender, M. P., McCombe, P. A., Greer, J. M. (2012). Interleukin-6 gene promoter-572 C allele may play a role in rate of disease progression in multiple sclerosis. *International Journal of Molecular Sciences, 13*(10), 13667–13679. https://doi.org/10.3390/ijms131013667

Yarosz, E. L., Ye, C., Kumar, A., Black, C., Choi, E. K., Seo, Y. A., & Chang, C. H. (2020). Cutting edge: Activation-induced iron flux controls CD4 T cell proliferation by promoting proper IL-2R signaling and mitochondrial function. *Journal of Immunology, 204*(7), 1708–1713. https://doi.org/10.4049/jimmunol.1901399

Yong, V. W. (2022). Microglia in multiple sclerosis: Protectors turn destroyers. *Neuron, 110*(21), 3534–3548. https://doi.org/10.1016/j.neuron.2022.06.023

Yu, H., Guo, P., Xie, X., Wang, Y., & Chen, G. (2017). Ferroptosis, a new form of cell death, and its relationships with tumourous diseases. *Journal of Cellular and Molecular Medicine, 21*(4), 648–657. https://doi.org/10.1111/jcmm.13008

Zepp, J., Wu, L., & Li, X. (2011). IL-17 receptor signaling and T helper 17-mediated autoimmune demyelinating disease. *Trends in Immunology, 32*(5), 232–239. https://doi.org/10.1016/j.it.2011.02.007

Zhang, C., Liu, W., Wang, L., Wang, F., Li, J., Hao, J. (2024). Prevalence and burden of multiple sclerosis in China, 1990-2019: Findings from the Global Burden of Disease Study 2019. *Neurology, 102*(11), e209351. https://doi.org/10.1212/WNL.0000000000209351

Zhang, W., Xiao, D., Mao, Q., & Xia, H. (2023). Role of neuroinflammation in neurodegeneration development. *Signal Transduction and Targeted Therapy, 8*(1), 267. https://doi.org/10.1038/s41392- 023-01486-5

Zimmermann, M. B., & Hurrell, R. F. (2007). Nutritional iron deficiency. *The Lancet, 370*(9586), 511–520. https://doi.org/10.1016/S0140-6736(07)61235-5

Zuvich, R. L., McCauley, J. L., Oksenberg, J. R., Sawcer, S. J., De Jager, P. L., Haines, J. L. (2010). Genetic variation in the IL7RA/IL7 pathway increases multiple sclerosis susceptibility. *Human Genetics, 127*(5), 525–535. https://doi.org/10.1007/s00439-010-0789-4