Nutritional Neurosciences

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Brain-Iron Cross Talk

Springer

Nutritional Neurosciences

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This book series aims to publish volumes focusing on both basic and clinical research in the field of nutritional neuroscience with a focus on delineating the effect of nutrition on brain function and behavior. The books will examine the role of different nutrients, food agents and supplements (both macro and micro) on brain health, neurodevelopment, neurochemistry, and behaviour. The books will examine the influence of diet, including phytochemicals, antioxidants, dietary supplements, food additives, and other nutrients on the physiology and metabolism of neurons, neurotransmitters and their receptors, cognition, behavior, and hormonal regulations.

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Brain-Iron Cross Talk

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It is with genuine gratitude and warm regard that I dedicate this work to Menoufia Medical School: Thank you so much for unending financial and logistical support during my Ph.D. Journey and afterward during my sabbatical leave. I could not do any of this without your love and glory.

Wael Mohamed
Pahang
Malaysia

Foreword

Iron is an essential micronutrient for humans and plays a vital role in most brain physiological processes, including neurotransmitter synthesis, myelination of neurons, as well as mitochondrial function. There is a precise and well-ordered mechanism to regulate iron in the brain. Disruption of iron homeostasis in the brain, both conditions of iron overload and iron deficiencies are detrimental to the brain, as they can affect brain plasticity, cognitive function, and social behavior, which eventually contributes to the development of a diverse set of neuro-pathologies. These include mood, neurodevelopmental and neurodegenerative disorders.

The book *Brain-Iron Cross Talk* edited by Dr. Wael Mohamed, Dr. Nicola Luigi Bragazzi, and Dr. Richard M. Kostrzewa provides an excellent compilation of advanced works delineating the multilevel impacts of iron neurochemistry in the brain, starting from cellular levels to clinical manifestations. The contribution by authors includes discussion on the potential nutritional therapeutic opportunities targeting brain degenerative diseases induced by iron overload, the relation between Mediterranean Diet and Alzheimer's disease, the iron neurochemistry in the progression of Parkinson's disease, the homeostasis of iron and calcium and related ferroptosis, the dysregulation of iron homeostasis and its implication in multiple sclerosis and epilepsy, the role of iron after subarachnoid hemorrhage, and the complex relationship between iron deficiency and psychiatric disorders.

This book forms a valuable addition to the existing body of knowledge and is especially intended for students, scholars, neuroscientists, and clinicians who wish to deepen their understanding about the intricate cross talk between the iron and the brain.

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August 2022

Preface

> To study the phenomenon of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all.
>
> William Osler (1849–1919)

Recently, the impact of nutrition and food intake has been highly investigated to study its impact on our brain function and its development as it was shown that the diet we take will determine the outcome of certain brain disorders such as in brain injury and stroke. Along with its effects on cardiovascular diseases and cancer development, nutrition and diet have been shown to be involved in preserving our mental cognitive function and behavior. Recent studies have implicated the development or exacerbation of certain neurological disorders to imbalance in our nutritional intake and our diet especially iron. The current *Brain-Iron Cross Talk* book will be published by Springer Nature under the Nutritional Neurosciences series (https://www.springer.com/series/16639). The aim of this project is to assemble global perspectives concerning the relationship between iron and the brain. This book will be part of the Nutritional Neurosciences series that covers multiple domains within nutritional neuroscience. The inclusion of iron in this prestigious series will help introduce new readers to the sub-discipline and increase the number of global conversation partners.

In the human body, iron is the most plentiful trace element. It is well known that iron is an essential component of the oxygen conveying hemoglobin. Iron also participates in the tricarboxylic acid cycle and in oxidative phosphorylation as a component of various enzymes. Iron in the nervous system is often involved in the catecholamine neurotransmitter synthesis and is involved in myelin assembly. Previous studies have shown that iron deficiency in the brain triggers mental impairment for infants and young children, for example, verbal and body coordination delays and psychomotor disorders. However, if iron is accumulated excessively in the aged brain, the resulting disorders, including Alzheimer's, Parkinson's, or Friedreich's ataxia, are closely related. Therefore, the mechanism and control of brain iron

metabolism should be researched and understood thoroughly. On this basis, it is important to explore the relationship between brain iron control and the incidence of nervous system diseases and discover new iron metabolism-related therapeutic targets in order to break down the limitation of nervous system diseases prevention and treatment.

Brain-Iron Cross Talk addresses cutting-edge areas of research of high significance for public health and translational medicine. The book discusses the comprehensive research history of iron and its significant role in the pathogenesis of the central nervous system (CNS) diseases. The book also identifies how iron supports function as well as the molecular mechanisms underlying their neuroprotectant activity. This topic is among the most interesting and challenging areas of contemporary translational biological and medical research, with implications for preventive and therapeutic approaches in age-related neurodegenerative disorders. This book explores the molecular mechanisms of brain iron including age-related metabolic pathways, mitochondrial nutrients, neurodegeneration and CNS disorders, cell signalling, and neuronal functions.

Coming from the background in the areas of neuropsychiatric health research, the editors (Drs. Mohammed, Bragazzi, and Kostrzewa) have decided to collaborate with other colleagues with expertise in areas of nutritional neuroscience to have a comprehensive book entitled *Brain-Iron Cross Talk* which included 13 chapters divided into two sections.

In the first section, entitled *Iron, Brain function, and Behavior* we have four chapters that describe various outcomes and effects of iron on brain functions (Sara Omer), neurodegenerative diseases (Haitham et al.), and Mediterranean diet (Abu Saleh et al.).

The second section of the book focuses on *brain disorders related to iron*. We are excited to have number of chapters that dissect how iron imbalance would modulate several known neurological disorders. In the first chapter, we discuss the iron relation to Parkinson's disease (Monika Kadian). In the next chapter, iron-calcium cross talk (Monika Kadian) is evaluated in terms of mechanisms and interaction; this is followed by an elegant chapter by Dr. Shi Hui et al., where they elaborate on iron and its relation to Alzheimer's disease. Other areas of discussion are introduced involving iron and multiple sclerosis where Arora et al. discussed the role of iron imbalance in multiple sclerosis. Interestingly, the following chapter discusses iron and epilepsy (Rajesh Thangarajan) followed by another overview chapter discussing iron and subarachnoid hemorrhage (Anika Zainab). This section is concluded with three chapters discussing nutrition in relation to psychiatric disorders (Haitham et al.), neurodevelopmental disorders (Rajesh Thangarajan), and finally iron and neuropathies (Asia Afzal).

Overall, this new book provides updated and novel concepts in the field of neurological disorders and its relation to the iron. The new compilation will be of high interest among researchers and clinical scientists involved in neuropsychiatry, nutrition, and biochemistry.

Finally, we thank all the authors for their significant effort in writing such excellent chapters for this new edition. We are also sincerely grateful to each author for their patience during the compilation and final editing of this book.

Kuantan, Malaysia — Wael Mohamed
Toronto, ON, Canada — Nicola Luigi Bragazzi
Johnson City, TN, USA — Richard M. Kostrzewa

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First, we would like to send a great appreciation for all the authors who contributed to this timely project. The high level of devotion and dedication between the authors and editors made writing this book an enjoyable journey. In addition, we also extend our gratefulness to the authors who are in the fields of medical psychiatry and neuropsychiatric research for delivering years of their experience and work in different areas psychiatric disorders to deliver such an elegant piece of work. The herein discussed topics and applications are of a great value in the areas of nutrition, psychiatry, neurological disorders, and neurodegeneration. Finally, we would like to thank the encouragement of many of our friends and colleagues for their unconditional love, encouragement, and inspiration throughout the endeavor of the project. Thank you.

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Editors and Contributors

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Wael Mohamed is a Psychiatrist Neuroscientist. He is leading a research team in Egypt for translational brain research focusing on neurodegenerative disorders, animal models, and clinical trials. His research interests are focused on understanding neurological diseases. Dr. Mohamed received his Ph.D. from PSU, USA, and is currently working as an Assistant Professor in IIUM Medical School, Malaysia. He has published over 64 peer-reviewed research articles related to neuroscience/psychiatry. Moreover, He authored for Springer, Taylor and Francis, and Elsevier, i.e., six books and many book chapters on nutritional neuroscience and neurodegenerative disorders.

Nicola Luigi Bragazzi received his MD in general medicine and surgery from Genoa University (Genoa, Italy) in 2011, his Ph.D. in biophysics from Marburg University (Marburg, Germany) in 2014, and his specialization in Public Health from Genoa University (Genoa, Italy) in 2017. He is a member of the Cochrane Association (Cochrane Reviewer) for the Cochrane Epilepsy Group. President Carlo Azeglio Ciampi awarded him Young Knight of the Italian Republic in 2005. Recently, in 2019, he has been nominated as one of the top five biomedical researchers worldwide aged less than 40 years in terms of several publications, articles in Q1 biomedical journals. He is currently working on infectious disease and vaccination modeling and extensive data mining in biomedicine at York University.

Richard M. Kostrzewa is working as a Professor in the Department of Biomedical Sciences at James H. Quillen College of Medicine. His interests focus on highly selective neurotoxins as tools to uncover the ontogeny of monoaminergic systems in the brain and study nerve regeneration. He is involved in studying the reactive

elements of one neuronal phenotype subsequent to the destruction of an alternate neuronal phenotype. He is an Editor-in-Chief of the journal *Neurotoxicity Research* and Editor-in-Chief of the second edition of the *Handbook of Neurotoxicity*.

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Part I
Iron, Brain Function and Behavior

Chapter 1
Iron and Neuro-Cognition

Sara Hassan Omar

1 Introduction

Longer life expectancy has been seen in recent decades as a result of breakthroughs in health care. With longer lives, neurodegenerative illnesses will be the most common diseases globally as a result of aging, according to the 2011 "Global Health and Aging" study. Neurodegenerative disorders are still ambiguous but indeed they involve multifactorial interaction between elements like genetic factors, environmental, and natural factors (National Institute on Aging, 2011).

Iron is an essential element that plays a crucial role in biosynthesis and the development of neurotransmitters, myelination, and dendrites (Liu et al., 2018; Mohamed & Yamashita, 2022), the normal functioning of neurochemical circuits such as monoaminergic systems and glutamate and GABA homeostasis necessitates the presence of iron, hence, the metal is necessary for proper brain morphology, neurochemistry, and bioenergetics. Moreover, oxygen transport, cellular respiration, immunological function, nitric oxide metabolism, and DNA synthesis are all dependent on iron (Aboussaleh & Bikri, 2022; Ward et al., 2014). Therefore, homeostasis is among the variables that contribute to neurodegenerative illnesses. Copper, magnesium, and iron are the primary actors in homeostasis, with iron being the most prevalent and important trace element (Abbaspour et al., 2014), thus, it was unsurprising to find a link between the irregular iron levels in neurodegenerative illnesses in brains of Parkinson's and Alzheimer's patients (in particular regions such as the basal ganglia and the hippocampus (Allen et al., 2020; Ward et al., 2014).

Playing an integral part in metabolism, cell growth, and cell differentiation, iron must exist in the right amount in all organs, at all times. Consequently, the brain is

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required to display a fine delicate balance of that important metal at all times. Therefore, iron is delicately regulated in a process called iron homeostasis via a selective transport system in the brain through the brain guards on the blood-brain barrier (Ferreira et al., 2019; Tucker et al., 1990). This interesting element has two personalities; one that gains electrons (ferric to ferrous, or Fe3+ to Fe2+) and one that loses an electron (ferrous to ferric Fe2+ to Fe3+) (Ems et al., 2022). Heme and non-heme are the two forms of iron in the body. Oxygen binding and transport throughout the circulatory system, for example, take place on heme iron, the ferrous core of the hemoglobin molecule. In contrast to heme iron, which is only found in circulatory or accumulating blood, non-heme iron is found in almost all cells and is essential for many key activities such as ATP generation and DNA replication. Nonetheless, the non-heme iron buildup outside of binding complexes becomes an agent of oxidative stress (Daugherty & Raz, 2015).

Failing to maintain this fine balance, for example in iron shortage, impaired brain myelination in children was observed to cause long-term consequences for behavioral functioning. On the other hand, various illnesses, such as Alzheimer's, Parkinson's, supranuclear palsy, Huntington's disease, amyotrophic lateral sclerosis, and multiple system atrophy with striatonigral degeneration, have shown iron (ferritin) deposition (buildup) in afflicted brain areas (Mohamed & Yamashita, 2022; White et al., 2015). No wonder, this vital element was believed, long ago, to be a part of the elixir of life or the philosopher stone. Before even discovering its critical role within the majority of physiological processes and proteins in all organs, iron was one of the seven metals of alchemy (gold, silver, mercury, copper, lead, iron & tin); iron, the seventh element, taking the symbol of planet mars (Berthou et al., 2022).

Indeed, the above-mentioned brain disorders severely impact cognitive functions such as language, personality, and many other traits. The area of cognitive neuroscience is undeniably the arena where research and exaggerated claims about science can be difficult to decipher. For instance, attention, concentration, executive functions, memory, language, visuospatial abilities, abstraction, computation, awareness, attitude, anxiety, aggression, and direction, were proven recently to be associated with elevated brain iron in the parietal and prefrontal cortex (Chen et al., 2019; Thomas et al., 2020). Interestingly, a research team from the university college of London (UCL) was able to image the elevated brain levels in the brain and use them as markers of poor cognitive outcome in Parkinson's disease without dementia. Moreover, the anatomically specific alterations in the hippocampus and thalamus were also imaged and proved to be linked to that higher brain iron in the putamen which is also associated with lower motor performance. The team used quantitative susceptibility mapping (QSM) and susceptibility-weighted imaging (SWI) which are MRI techniques that detect and depict changes in the magnetization that is produced in tissues (Chen et al., 2019; Thomas et al., 2020).

The Montreal Cognitive Assessment (MoCA) was used to test cognition, whereas motor function was assessed using the Movement Disorder Society Unified Parkinson's Disease Rating Scale motor component 3 (MDS-UPDRS-III). Visual tasks were used to measure visual perception as well (Thomas et al., 2020).

So, one could argue that the biological effects of a nutrient-deficient diet with a particular interest in iron, and their impacts on neurophysiological mechanisms and cognition overlap. These interactions between biological, psychological, and social dimensions of nutrient deficiency, subsequent multi-organ disruption of iron homeostasis, and its effects on motor deficits, cognitive impairments, and social behavior modifications shall be examined in the coming sections.

2 Delicate Regulation of Iron in the Brain

Because oxidative metabolism of neural cells, neurotransmitter production, myelination, and synaptic plasticity are all influenced by iron, the delicately regulated iron content within the brain is maintained by several feedback loops (Hare et al., 2013).

Iron is carried across the barrier on transferrin (Tf), then internalized by attaching to the Tf receptor on brain capillary endothelial cells (BCECs), and subsequently stored as ferritin. The blood-brain barrier (BBB) operates as a hydrophobic barrier, blocking both hydrophilic Fe2Tf diffusion and non-transferrin bound iron (NTBI) migration into the systema-nervosum. It was not until 2011 when published studies provided a precise description of iron transport across the brain. Intake of iron within the developing rat brain was noticed to be rapid. This was attributed to the increased expression of transferrin receptor 1 (TfR1) in BCECs. Thus, this route becomes the most crucial iron regulating mechanism until the BBB is sealed, after which iron intake diminishes (Moos et al., 2007).

The BBB expression of ferroportin and circulating ferroxidases (enzymes that catalyze Fe2+ oxidation to Fe3+) like ceruloplasmin was suspected to be connected to another route for Non-transferrin bound iron absorption (Moos & Rosengren Nielsen, 2006). It is unclear if the iron in BCEC endosomes is released into the cytoplasm. Possibly, the endosome travels via the BCEC and the cytosol is left intact while Fe3+ is delivered directly into the brain for distribution to cells (transcytosis) (Moos et al., 2007; Moos & Rosengren Nielsen, 2006).

A higher percentage of non-transferrin-bound iron circulates there since the cerebrospinal fluid (CSF) is substantially higher in the systema-nervosum, compared to the periphery (Hare et al., 2013). Astrocytes also operate to ensure the rapid oxidation of any circulating Fe2+ to Fe3+ is taking place. This is to avoid the formation of harmful reactive oxygen species (ROS) through Fenton chemistry (Abbott et al., 2006; Hare et al., 2013; Wu et al., 2004).

The amount of iron in the brain has a significant influence on energy metabolism. In prenatal iron shortage, for example, cytochrome-c-oxidase is decreased, resulting in altered hippocampus metabolic activity. Tf is in charge of practically all iron exchange and transit in the body, with around 3–4 mg of iron bound to Tf circulating in a healthy adult (de Ungria et al., 2000). Non-transferrin-bound iron constitutes less than 1% of all circulating iron. A ferroxidase loads two Fe3+ ions onto a single Tf unit, which is subsequently shunted into the interstitium by ferroportin, with only

about 30% of all circulating Tf units occupied at any given moment (only in severe iron overload circumstances) (de Ungria et al., 2000).

3 Iron Buildup and Neurodegenerative Diseases

Neurodegenerative illnesses are positively linked to aging. The aging process may play a role in several breakdowns of the iron regulation system in illness. Age-related iron retention has also been positively linked to behavioral impairments such as cognitive decline and motor impairment, suggesting that it may play a role in age-related decline.

As mentioned above, various neurodegenerative disorders have shown iron deposition in the nervous system. Among them is Friedreich's ataxia, which is a well-studied iron metabolism condition that was first, described between the years 1863 and 1877, by the German neurologist Nicholaus Friedreich.

3.1 Friedreich's Ataxia

This condition was characterized by atrophy of the posterior columns of the spinal cord, resulting in sensory loss and progressive ataxia, combined with muscular weakness in patients. The condition was also frequently linked with cardiomyopathy. Mutations in the mitochondrial protein frataxin cause this autosomal recessive degenerative illness. Besides, the massive sensory neuron degeneration and cardiomyopathy, Friedreich's ataxia includes brain shrinkage and iron buildup. According to recent studies, the role of frataxin is involved in iron homeostasis, operating as an intra-mitochondrial chaperone and storage protein for iron in mitochondria. It's also thought to have a role in the biogenesis of heme and iron-sulfur clusters. The frataxin mutant is unstable, and a significant decrease in protein might lead to intra-mitochondrial iron buildup and cytosolic iron insufficiency in mice and humans, suggesting that it may play a role in disease etiology. In mouse models, a high iron diet suppresses certain traits, such as heart hypertrophy (Llorens et al., 2019).

Friedreich's ataxia patients were shown to have a significant decline in a variety of cognitive domains over time. Over eight years, processing speed, fluency, and visuoconstructive ability often decline. This pattern is most likely caused by an increase in motor or verbal impairment. When compared to healthy controls, the longitudinal rate of iron concentration in Friedreich ataxia patients was significantly greater bilaterally. As the disease advanced, the iron content increased, and the development of cerebellar issues was linked to performance. Furthermore, the neuropsychological profile confirmed impairments in verbal fluency, working memory, and social cognition. Functional connectivity studies demonstrated higher co-activation within cerebellar and cortical regions, as well as weaker inter-regional coupling between the cerebellum and frontoinsular cortex for phonemic processing,

which was also linked to lower task performance. Cerebellar degeneration in Friedreich's ataxia is typically seen in deep dentate nuclei with significant-high iron concentrations, making MRI imaging difficult with its small size (Dogan et al., 2016; Hernández-Torres et al., 2021).

3.2 Wilson's Disease

Copper, like iron, is involved in neurodegenerative processes. Copper can induce alpha-synuclein (α-synuclein is a protein (soluble and unfolded) that accumulates in Lewy bodies) to clump together. Copper is involved in dopamine production since it acts as a co-factor for the enzyme dopamine beta-hydroxylase. In *Wilson's disease*, Iron builds up as a side effect of the disease (Pak et al., 2021). Wilson's illness involves copper and iron built up in the brain and the liver. Thereupon, the nervous system and mental health symptoms frequently manifest as early-onset Parkinson's disease. Symptoms include, speech impairment, difficulty in swallowing, or physical coordination issues like muscle spasms and uncontrollable movements are all due to the deposition of copper and iron in the nervous system. Meanwhile, among the mental health signs are anxiety, alterations in mood, attitude, psychosis, or depression Pak et al., 2021; Wilson's Disease, 2018).

Cognitive impairments have been recognized since Wilson's disease was early reported. Typically, Wilson's patients show subcortical dementia, a dementia pattern characterized by executive dysfunction, apathy, and depression. This is unlike the cortical dementias, which are characterized by aphasia, agnosia, apraxia, and forgetfulness, experienced in Alzheimer's disease. On cognitive tests, patients with only hepatic symptoms (with no neurodegenerative symptoms) perform the same as normal volunteer participants, whereas, patients with neurological symptoms perform worse than control groups. Furthermore, several researchers have documented memory impairments on all levels of the Rey Auditory-Verbal Learning Test (RAVLT), in patients with Wilson's disease, including a poorer capacity to learn and recall words. Likely, testing executive skills, demonstrated that patients with Wilson's disease perform worse than healthy controls. Tests that also assess thinking have revealed a difference between individuals with neurological symptoms and control groups. One research indicated that lower performance was noticed in both the verbal and nonverbal components. Hence, generally speaking, patients with Wilson's disease have shown poorer cognitive functions on global tests or scales (Frota et al., 2009).

This is attributed to the increased iron levels that were demonstrated in substantia nigra in patients with Wilson's disease. In the aforementioned study, susceptibility-weighted imaging was used to show the difference in magnetic susceptibility between magnetic material tissue and non-containing magnetic material tissue. Basically, the substantia nigra is a dopaminergic nucleus in the midbrain that plays an important role in regulating motor activity and reward functions as part of the basal ganglia circuitry. Moreover, the nigrostriatal pathway connects the substantia

nigra to the putamen, and this is crucial in motor impairments. On the other hand, the basal ganglia are also involved since it is a grouping of interconnected subcortical nuclei that mitigate and control functions ranging from voluntary movement, cognitive planning, emotions and reward functions, and even cognition and learning. The substantia nigra is typically thought to be the major input into the basal ganglia circuitry and an important component of these processes (Sonne et al., 2022).

3.3 Alzheimer's Disease (AD)

The Centers for Disease Control and Prevention reported a 50 percent increase in the death rates of Alzheimer's disease (AD) between 2000 and 2018. The primary causes of AD and the mechanism of neuronal death are unknown to this point, but the brain is characterized by neuronal cell death in the cerebral cortex and acetylcholine (a neurotransmitter) deficiency throughout various stages of AD (Alzheimer's Association et al., 2013; Omar et al., 2020). Accordingly, AD patients suffer from increasing dementia and the accumulation of plaques along with tau-containing neurofibrillary tangles in the afflicted brain regions. The presence of iron buildup in the AD cortex and hippocampus is consistent with the clinical picture of AD neurodegeneration. Furthermore, both plaques and tangles acquire iron, which is estimated to be three times the normal neuropil amount in plaques. The iron level in the hippocampus of individuals with AD was shown to be related to the mini-mental state examination and the length of the condition, indicating that iron may have a role in disease development. Several iron regulatory protein genes have been linked to sporadic Alzheimer's disease (Lei et al., 2020; Liu et al., 2018).

When iron metabolism is out of equilibrium in pathological conditions, it does not support brain homeostasis. Accordingly, it has a variety of impacts on brain function. Goodman (1953) discovered that iron levels in the AD patients' brains were elevated. Later, as imaging and sampling technologies got advanced, researchers were able to determine the particular locations of brain iron and plaques. Indeed, iron deposition and plaques aided in the progression of the illness in particular brain areas that are linked to neurodegenerative illnesses. Namely; cortex, caudate nucleus, and globus pallidus, as well as substantia nigra. Furthermore, in AD, iron, and tangles were found together, functioning as a pool of ROS within the neurons. In vitro, only Fe (III) can cause tau aggregation, which can be reversed by converting Fe(III) to Fe(II) or using iron chelators. Tau hyperphosphorylation can be induced by Fe (II) through activating the extracellular signal-regulated kinase or mitogen-activated protein kinase pathways (Lei et al., 2020; Liu et al., 2018).

Iron may contribute to pathology in AD in numerous ways: It may be responsible for the production of plaques and tangles since higher iron concentrations in senile plaques and co-localization with tangles were discovered. Iron promotes amyloid-β peptide aggregation in cell-free systems, which promotes neuronal toxicity. Iron is reduced by amyloid-β peptides, which increases thiobarbituric acid substance reactivity. The toxicity of amyloid-β peptide iron complexes may be due to the unique

structure of the induced amyloid aggregation, which is prone to activating cell death pathways. Iron may bind to tau and enhance tau aggregation and hyperphosphorylation (iron chelation can reverse this process) (Lei et al., 2020). Moreover, changes in proteins that regulate the iron life cycle may have a role in brain iron elevation as people get older. For example, regarding ferritin levels in the occipital (grey and white matter), the SN remains unaffected. The superior temporal gyrus white matter has shown lower expression of Tf, meanwhile higher expression in the occipital cortex white matter. Cp was shown to be enhanced in gray matter with age, but not in white matter, whereas Cp was found to be unaffected in SN in another study. Iron and ferritin levels in rat brains were observed to rise with age, but Tf levels remained constant. The mechanism behind age-related iron buildup is still unraveled; nonetheless, iron accumulation's selective sensitivity throughout aging might help explore the reasons behind iron elevation in several neurodegenerative disorders.

3.4 Case Study

Iron levels in the human brain were explored in a post-mortem investigation of age-related alterations and anatomical area differences in one research to establish the relationship between brain iron homeostasis and neurodegenerative illnesses. Samples were collected from men ($n = 27$; 67 ± 11 years old) and women ($n = 15$; 77 ± 12 years old) (Ramosa et al., 2014). Samples were collected from brains that had undergone forensic autopsies. The iron distribution in an adult human brain is extraordinarily variable, according to the findings from 14 brain locations in this study. Regardless of age group, the basal ganglia had the most abnormally high iron levels in the brain, and that was observed in a variety of diseases, including Parkinson's (PD) and AD. A correlation between age and iron levels in the brain has also been established. This tendency was notably noticeable in a few areas. The greatest direct relationship between iron levels and age was seen in the caudate nucleus, putamen, and globus pallidus. When compared to non-diseased people of the same age group, the iron levels in the brain of the two AD patients were greater in the caudate nucleus. The caudate nucleus is the main brain region involved in memory and spatial navigation and the hippocampus was shown to have larger iron amounts in AD patients. In the basal ganglia (the brain regions with the highest iron levels in healthy people), the PD patient had more noticeable differences: iron levels were increased in the caudate nucleus (by a factor of 2.3) and the globus pallidus (by a factor of 2.4), both of which are associated with motor functions (Ramosa et al., 2014).

This is consistent with the findings of another research that was conducted in a group of 60 senior persons (>70 years old), in which Exley et al. found no statistical significance between brain iron levels and age, indicating that this trend disappears in the elderly (Exley et al., 2012). Additional post-mortems and in vivo studies have shown that iron levels in healthy people's subcortical and some cortical grey matter

regions rise with age. Xu et al. discovered age-related iron accumulation in the putamen in people aged 22–70, with the highest amounts in the sixth decade. The authors stated that Fe levels in the globus pallidus and caudate nucleus remained constant with age, despite other data indicating a positive relationship in both locations, as previously indicated (Xu et al., 2008).

Based on the literature reviewed, it is certain that iron contributes significantly to neurodegeneration; indeed, oxygen and fatty acids are abundant in brain tissue, hence, elevated iron levels provide the perfect environment for oxidative stress and severe tissue damage. However, no compelling evidence has been provided to attribute a causal role to iron (Ndayisaba et al., 2019). Nevertheless, cognitive dysfunction in AD and PD includes, but not limited to, memory impairment, deficits in learning, memory, language, and visuospatial abilities are caused by neuropathological alterations in the cerebral cortex and limbic system (De Lau & Breteler, 2006).

Symptoms of cognitive impairment fluctuate along with the illness severity, ranging from AD-related Lewy body dementia (LBD) and Parkinson's disease dementia (PDD), all the way to the degradation of cortical cholinergic and striatal dopaminergic neurons (Corey-Bloom, 2002). They both share cognitive decline symptoms as well as some pathological aspects.

Several investigations have demonstrated that executive dysfunction is more common than memory difficulties in PD patients (De Lau & Breteler, 2006). This presents a more catastrophic cognitive impairment, which has been described as a late manifestation of PD with high prevalence, disability rate, and poor responsiveness to therapy (De Lau & Breteler, 2006). As covered earlier, the substantia nigra is the major brain area for dopamine synthesis, and this neurochemical influences numerous central nervous system systems, including movement control, cognitive executive functions, and emotional limbic activity. Therefore, the imbalance in iron (build up in this case) is critically contributing to the disturbance of the cognitive functions in AD and PD by affecting the limbic systems and the synthesis of the neurotransmitter in the substania nigra in particular as well as in other regions. The substantia nigra is located in the midbrain, posterior to the crus cerebri fibers of the cerebral peduncle. It is divided into two regions: the pars compacta (SNpc), which contains dopaminergic neurons, and the pars reticulata (SNpr), which contains inhibitor gamma-aminobutyric acid-containing (or GABAergic) neurons (Chen et al., 2019; Ma et al., 2021). The striatum, putamen, and caudate nuclei all receive dopaminergic projections from the SNpc (Fang et al., 2020; Ma et al., 2021; Sonne et al., 2022). In fact, a number of different neurological disorders cause parkinsonian-like symptoms by disrupting dopaminergic neurons in the substantia nigra. Balance, mobility, and gait issues are common in people with progressive supranuclear palsy, for instance. Dementia with Lewy bodies is a kind of Parkinsonism characterized by increasing cognitive deterioration and variations in alertness and concentration. All these neurological and cognitive disorders are affected by iron imbalance in substantia nigra (Fang et al., 2020; Thomas et al., 2020; Sonne et al., 2022).

To this end, the connection between iron overload in the brain and neurological disorders has been highlighted. However, the widespread occurrence of iron deficiency has been also shown a function in behavioral and mental health. Iron deficiency has been reported to cause developmental problems in young children in many research papers. Children that are iron deficient exhibit increased anxiety and/or sadness, as well as social and attention issues. A growing amount of research suggests that iron deficiency is connected to abnormal brain homeostasis in both myelination and neurotransmission, particularly the metabolism of monoamines. Behavioral problems and altered dopamine levels have been linked in studies utilizing rat models of iron insufficiency. The activities of the brain's basal ganglia are extremely sensitive to variations in iron status since iron is particularly abundant in the brain's basal ganglia, a region heavily regulated by dopamine and the glutamatergic system and energy metabolism (Berthou et al., 2022; Chen et al., 2019).

4 Brain Running Short on Iron

Minor to severe symptoms might develop from peripheral iron insufficiency; anemia, which is the most common and most severe form of iron deficiency caused by a variety of reasons. Poor- iron diet, blood loss, or metabolic abnormalities could cause anemia. Anemia is characterized by a reduction in hemoglobin's ability to carry oxygen. This may lead to tightness in breath, weak muscles, angina pain, and increased cardiac rate to compensate for reduced oxygen in the blood (Johnson-Wimbley & Graham, 2011).

While anemia symptoms can appear over weeks to months, iron in the brain is more resistant to dietary changes, and the brain may have critical periods that determine the level of iron in the brain throughout life (Wang et al., 2019). During the weaning stage, for example, the brain accumulates iron, establishing an iron-set point for the brain. When newborn children are fed an iron-poor diet, supplemented iron intake does not improve brain iron levels later in life. A post-weaned mammal's brain is thought to be immune to peripheral iron, which could explain why brain iron levels are difficult to change with food. Even though, supplementing mice with isotopically enriched iron showed that dietary iron reaches the brain and other organs at the same rate. Peripheral iron may enter the brain via Tf patterning and then cross the BBB via receptor-mediated transcytosis (White et al., 2015).

Iron in the brain is believed to be in continual flux with iron in peripheral pools. It has been reported that, despite dietary changes, brain iron levels are carefully regulated by the iron homeostatic system, and the typical level of iron in the brain for an adult individual is most likely decided during the mammal's key weaning phase. Accordingly, brain iron levels do not substantially or easily deviate from the norm. This weaning period can have a long-term impact on an individual's iron biochemistry in the brain, emphasizing that chronic brain iron deficiency disrupts

essential brain processes, affecting neurochemistry and eventually leading to illness (White et al., 2015).

4.1 *Iron Deficiency and Neurotransmitters Synthesis, Signaling, and Energy Demand*

Iron involvement in oxidative metabolism and the creation of neurotransmitters (as a co-factor) and myelin, makes it a core player in brain-appropriate functioning. Because iron is a powerful inducer of reactive oxygen species, it has been also linked to neurodegenerative processes. A shortage of iron in the diet has been associated with diminished brain iron levels and changes in brain chemistry in neonates and children. Iron-mediated oxidative damage is a major contributor to cell death in many diseases, as per published research studies. For example, multiple sclerosis (a demyelinating disorder), needs specific attention in terms of iron availability. Because myelin formation and maintenance need a lot of iron, oligodendrocytes must contain iron in large amounts (Piñero & Connor, 2000).

Iron is involved in the synthesis of neurotransmitters such as noradrenaline, dopamine, and 5-hydroxytryptamine, as well as adrenaline, all of which are involved in the movement, emotion, attention, and a range of other functions. These neurotransmitters are produced by a number of iron-dependent enzymes such as tyrosine hydroxylase, phenylalanine hydroxylase, as well as tryptophan hydroxylase (White et al., 2015; Youdim & Green, 1978). However, brain iron deficiency (BID) seldom causes a reduction in the production or activity of these enzymes. The fact that iron is restricted in these enzymes under BID may suggest the crucial those enzymes play for brain function (Beard et al., 2009).

Furthermore, iron modulates a number of critical processes in neurotransmitter signaling, which are particularly susceptible to changes in iron levels. For example, reduced neuronal uptake of catecholaminergic neurotransmitters has been observed in several BID models, and neurotransmitter extracellular concentration is increased in BID rats (Nagatsu, 2006). Dopaminergic signaling is further disturbed in iron deficiency due to reduced affinity and expression of D2 neurotransmitters (Youdim & Green, 1978).

The brain has a high energy need, accounting for 20% of baseline oxygen consumption, necessitating high iron levels in the mitochondria to produce ATP via the electron transport chain (Hare et al., 2013; Watts et al., 2018). Iron is used as a co-factor by a number of mitochondrial enzymes, including mitochondrial ferredoxins, cytochromes, and aconitase. Unsurprisingly, iron deficiency alters the mitochondrial shape, inhibits function, and destroys mitochondrial DNA. Despite the loss of pro-oxidant iron, reduced mitochondrial efficiency may explain why iron shortage causes an increase in oxidative stress indicators (Bastian et al., 2020; Daugherty & Raz, 2015; Hare et al., 2013).

4.2 Neurons Insulation (Myelination)

Myelin is the fatty white matter that shields axons and preserves their impulses. Slower neuronal conduction is caused by a lack of myelination, as indicated by the slowing of reflexes. Iron has different but noticeable impacts on the timing of oligodendrocyte formation (Cheli et al., 2020).

BID inhibits glial precursor cell proliferation and differentiation into oligodendrocytes in a rat model, as well as myelin components such as myelin basic protein, myelin proteolipid protein, galactolipids, phospholipids, and cholesterol. Basically, oligodendrocytes have more iron in their baseline state than other brain cells. Furthermore, iron deficiency has been associated with defective neonatal reflexes as well as abnormalities in auditory brain stem potentials and visual evoked potentials in iron-deficient children (Algarín et al., 2003; Georgieff, 2011).

4.3 Developmental Delays

The link between the BID and developmental delays in a variety of brain skills in children is now undeniable. Anemia has been linked to global IQ, lower motor skills (fine as well as gross), integration of visual-motor, as well as social and attention problems along with higher anxiety and depression scores. Some symptoms persist 10 years after treatment. Worthy here to mention that even though, the casual relationship is multifactorial since it involves socioeconomic factors such as poor nutrition, or maternal depression, the role of iron in neurodevelopment, necessitated the investigation of iron-deficient in animal models. Since observational human studies have been insufficient to determine the complete actual role of BID in neurodevelopment (Booth & Aukett, 1997; Saloojee & Pettifor, 2001). The combination of human and animal research supports iron's crucial function in neurodevelopment, and because symptoms are not easily corrected after the critical time, monitoring and early dietary intervention are also critical (Hare et al., 2013).

BID is linked to poor psychomotor performance as well as behavioral problems such as diminished response to people and situations, negative impact on cognition, behavior, and motor skills, as well as irritability. Intriguingly, previously anemic preschool children were found to be less enthusiastic, and more cautious than their counterparts, indicating that iron deficiency has the potential to have long-term effects on behavior and development. Follow-up studies have revealed worse long-term cognitive scores on measures of mental and cognitive functioning. Unsurprisingly, BID seemed to affect areas such as the hippocampus and mitochondrial damage which is probably inducing cognitive impairment. Changes in dopamine metabolism in the brain, and serotonergic function, are also predicted since an iron-deficient brain was found to produce considerable changes in dopamine levels in key brain areas. These changes will be further discussed in the last section of this chapter (Jáuregui-Lobera, 2014).

As per many studies, children with BID demonstrated worse motor sequencing and bimanual coordination, as well as a lower spontaneous eye blink rate, which is consistent with nigrostriatal circuit dysfunction. Changes in the mesolimbic pathway, positive affect, and intrinsic reward have recently been shown to help explain the altered socioemotional behavior reported in children with BID. Interestingly, iron and omega-3 fatty acids were found to alter the brain's macrostructure (e.g., the hippocampus), microstructure (e.g., neuron myelination), and amount and operation of neurotransmitters (e.g., serotonin and dopamine levels) all of which might have an impact on cognitive development and affect frontal brain function differently (Jáuregui-Lobera, 2014).

4.4 ADHD

ADHD (attention deficit hyperactivity disorder) is a developmental disease distinguished by impulsivity, hyperactivity, and inattention. ADHD is highly heritable, and neurotransmission of dopamine is implicated in multiple putative disease-causing genes (DAT1, DRD4, DRD5) (Hare et al., 2013). As a result, iron deficiency in the substantia nigra and putamen may change dopamine levels and contribute to the development of ADHD. Through a similar mechanism, iron deficiency can also contribute to restless leg syndrome (RLS), which can develop into ADHD (Jung, 2015; Rubia, 2018).

Because iron interacts with numerous phases in dopamine neurotransmission, it's plausible that idiopathic ADHD can be caused by the BID. While multiple researchers found that ADHD kids have lower ferritin levels, a study that included 194 kids found no differences in blood ferritin profile between healthy and ADHD kids. Iron profile, as mentioned earlier, in children is typically linked to a variety of socioeconomic factors, which might throw this finding off. Furthermore, because peripheral iron indicators may not often represent the iron profile in the brain, the blood iron profile is unlikely to be changed in ADHD. However, recent research on 36 people found lower levels of brain iron in the thalamic area in ADHD patients as evaluated by magnetic resonance imaging (MRI), suggesting that BID may have a role in the disease's development (Bener et al., 2014; Tohidi et al., 2021; Villagomez & Ramtekkar, 2014).

In addition, a case study found that a 3-year-old with low blood ferritin (13 ng mL^{-1}) and ADHD who was given ferrous sulfate (80 mg day-1) showed a variety of behavioral improvements after eight months. This prompted a 12-week clinical trial of iron supplementation in ADHD, through which they discovered that the therapy group improved on the ADHD rating scale. These findings need further investigation into iron as a potential treatment; however, as previously stated, iron supplementation after a critical period is insufficient to reverse cognitive symptoms of early BID in rats, which may limit its applicability in ADHD (Tohidi et al., 2021).

Nevertheless, ADHD patients show deficiencies in higher-level cognitive skills required for mature adult goal-directed activities, which are mediated by late-

developing fronto-striato-parietal and fronto-cerebellar networks. The most common cognitive deficits are sustained attention, motor response inhibition, response variability, working memory, and cognitive switching. As well as temporal processing such as motor timing, time estimation, and temporal foresight, with the most consistent deficits in time discrimination and estimation tasks (Jung, 2015; Rubia, 2018). On the other hand, children with ADHD have more consistent evidence of cognitive abnormalities than adolescents or adults with ADHD with the following domains mainly affected: educational difficulty, social exclusion, school dropout, and criminality. Indeed, there is significant variation in cognitive impairments, with some individuals displaying no impairments others showing impairments only in some cognitive areas, which may be explained by distinct pathophysiological pathways. However, all cognitive impairments are linked in one way or another to the dopaminergic pathway which is severely affected by iron deficiency in substantia nigra (Jung, 2015; Rubia, 2018).

4.5 RLS

Restless legs syndrome (RLS) is a neurological condition distinguished by unpleasant or strange feelings in the body (mostly the legs) that cause an irresistible urge that result in moving the leg. RLS affects between 3.9% and 15% of the population. RLS is far more frequent in Western countries as compared to other countries (Innes et al., 2011; Ohayon & Roth, 2002). Reduced dopamine uptake and D2 receptor density are linked to the condition, and dopamine-based medications are frequently used to treat it. Cerebrospinal fluid CSF of RLS patients has been shown to have low ferritin and high Tf levels. Direct studies of iron in the substantia nigra (SN) of afflicted individuals using post-mortem histological staining and MRI show lower levels of iron (Allen et al., 2020).

RLS can cause cognitive impairment as a result of sleep disruption, emotional issues, and attention deficiency. All these elements can have an impact on cognitive performance. Iron deficiency in individuals with RLS has been thoroughly established by brain autopsies, magnetic resonance imaging, and cerebrospinal fluid research. RLS may develop from brain iron insufficiency in the substantia nigra, even when peripheral iron is adequate. Again it is the iron's lower levels in substantia nigra which are affecting the dopaminergic system. The notion that RLS is caused by dopaminergic dysfunction induced by brain iron deficiency is supported by evidence; dopaminergic medications, the first-line adult treatment, promote augmentation (symptom worsening) with decreased ferritin levels. Frontal executive and mental flexibility as well as a decline in attention were also noticed in RLS patients. Verbal and visuospatial memory, working memory, and language functions were also impaired to various degrees (Dosman et al., 2012; Jung, 2015).

A research team used an RLS iron biology pattern animal model (Allen et al., 2020). Genetic investigations of BXD inbred strains have shown that the ones that exhibit the experimentally produced RLS pattern of ventral midbrain iron deficiency

without peripheral iron deficiency. After weaning at postnatal day 21–22, recombinant BXD strains and their parental strains (C57BL/6 J and DBA/2 J) were put on the same pellet diets for the following 100 days, except these were either iron adequate (240 ppm) or iron deficient (3–5 ppm) pellets. The amount of ventral midbrain iron in mice on adequate vs. insufficient diets differed between strains (by 35%). Furthermore, there was no link between the ventral midbrain and any of the 22 strains (Dauvilliers & Winkelmann, 2013; Ohayon & Roth, 2002). The loss of peripheral iron with an iron deficiency diet indicates that peripheral and brain iron levels are regulated differently genetically (Allen et al., 2020).

Furthermore, a recent study discovered that iron deficiency in the brain was related to the function of the blood-brain interface, as BBB endothelial cells acted as an iron reserve for the brain. Interactions between poor neuronal iron absorption and neuromelanin-containing and dopamine-producing cell activity are important in the pathophysiology of RLS. Extracellular dopamine, DAT, D1, and D2 receptors diminish iron deficiency. This is suggesting that iron influences brain dopaminergic transmission in RLS in a variety of ways (Allen et al., 2020; Dauvilliers & Winkelmann, 2013; Ohayon & Roth, 2002).

4.6 Effect of Iron on the Dopaminergic and Serotonergic System

An intriguing association between iron, the dopaminergic system, and anxiety-related behaviors was revealed in a correlation study. Although prefrontal cortex iron concentrations are linked to habituation rate, spontaneous behaviors such as locomotion and repetitive motions are due to a link in the ventral midbrain between the abundance of dopamine receptors and iron levels. Iron levels in the ventral midbrain and prefrontal cortex were also determined to be crucial for anxiety-like behaviors. Other neurotransmitters may also be involved in similar effects. For instance, a low iron level inhibits serotonin and GABA activity. It's also possible that these effects are caused by factors other than iron, such as metal interactions. The iron shortage affects erythropoiesis that causes anemia, however, the high iron buildup is seen in the substantia nigra in PD patients (Berthou et al., 2022; Hong et al., 2016; Kim & Wessling-Resnick, 2014).

Furthermore, elevated blood iron levels are related to a lower risk of PD, and high dietary iron consumption lowers the risk of PD. Iron maldistribution might explain the iron buildup in the substantia nigra and iron shortage in the erythropoietic system. Additionally, iron influences the uptake and production of dopamine; sine dopamine synthesis enzyme tyrosine hydroxylase is iron-dependent. Accordingly, the reuptake of dopamine in an animal model was inhibited in iron deficits (Exley et al., 2012).

The brain-derived neurotrophic factor (BDNF) is essential for hippocampus function. It has been postulated that BDNF activity-dependent secretion may enable synapse-specific production of proteins essential and synaptic plasticity in the

hippocampus. This is thought to be the key cellular process driving long-term spatial memory and long-term potentiation as well as long-term depression (Berthou et al., 2022; Kim & Wessling-Resnick, 2014).

Several studies examining synaptic plasticity in hippocampal slice preparations show that BDNF signaling modifications or genetic knockdown of BDNF result in severe deficits of and long-term potentiation as well as long-term depression. Depression is characterized by reduced synaptic connection in the hippocampus and prefrontal cortex which might be combined with neuronal atrophy (Berthou et al., 2022; Kim & Wessling-Resnick, 2014).

The dopaminergic system and neurotransmission are also affected by iron metabolism. The substantia nigra may be especially prone to iron deficiency, which causes decreased tyrosine hydroxylase activity, resulting in altered dopamine production, which can induce psychiatric and motor issues in adulthood. By modulating intracerebral iron homeostasis, serotonin bioactivity impacts dopaminergic signaling. The serotonin-dependent drop in intracerebral iron content affects dopaminergic (and noradrenergic) neurotransmission via dopamine production and a decrease (reversible) in the number of dopaminergic D2 receptors. This ensures dopamine recycling in the presynaptic gap (Hong et al., 2016; Kim & Wessling-Resnick, 2014).

One type of anxiety that was associated with greater plasma corticosterone levels and decreased levels of serotonin, norepinephrine, and BDNF was determined in Ceruloplasmin (Cp) deficient mice. Cp is a ferroxidase that converts Fe2+ to Fe3+ and contributes to iron outflow in the cell. Shortage in Cp had increased iron deposition in the liver and spleen but decreased iron deposition in the brain, notably in the hippocampus, which is linked to greater anxiety behaviors but no changes in motor function, learning, or memory.

On the other hand, anxiety and depression that are associated with irregular serotonin levels were linked to the iron shortage as well. Serotonin levels were found to raise in adults with iron insufficiency, perhaps due to a down-regulation of serotonin metabolism. The number of serotonin transporters is said to be decreased in the striatum of iron-deficient mice. Needless to mention, serotonin deficiency and deregulation of metabolism reduce synaptic connection at the hippocampus and prefrontal cortical levels, which may result in neuro-behavioral symptoms, neuropsychological problems, and depression. Interestingly, extracellular norepinephrine (stress hormone and neurotransmitter concentrations) was found to increase in iron-deficient situations, although tissue levels remain constant as compared to controls (Berthou et al., 2022; Exley et al., 2012; Hong et al., 2016; Kim & Wessling-Resnick, 2014).

5 Brain Iron Research Has a Way to Go

Up to our understanding, most of the research was conducted on BID in neurodevelopment or iron buildup in neurodegeneration, but no clear cases of BID in a neurodegenerative illness have been reported so far (Hare et al., 2013).

However, hypomyelination as well as reduced mitochondrial activity, and neurodegeneration were observed in a genetic mouse model of motor neuron iron shortage (IRP2: Iron Responsive Element Binding Protein 2, is a protein-coding gene). Worthy also to mention here that patients with dementia (associated with Lewy bodies) had a threefold greater rate of history of ADHD symptoms. However, because the status of iron in ADHD patients is only beginning to emerge, and the state of iron in dementia (associated with Lewy bodies) is equally unknown, it is premature to mechanistically link the two conditions (Bener et al., 2014; Booth & Aukett, 1997; Mohamed & Yamashita, 2022).

Low iron levels affect mitochondrial function and raise oxidative stress indicators, potentially by reducing the action of catalase, an iron-dependent antioxidant. Longer-term investigations of BID in rodent models will reveal the neuroanatomical and neurobiochemical alterations caused by decreased iron bioavailability.

6 Conclusion

Iron is a vital element that must be present in a precise proportion in the brain since its imbalance is related to poorer cognitive functions and altered social behavior. Luckily, the brain is extremely protected and selective in terms of micronutrient permeability via iron hemostasis. Transferrin, the iron-mobilizing protein, and transferrin receptor are widely expressed on blood vessels, major neurons in the striatum, cortex, and hippocampus, as well as oligodendrocytes and astrocytes. Iron is stored intracellularly on iron storage protein ferritin. Furthermore, Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders were found to be strongly affected by alterations in the cellular distribution of iron and its related regulatory proteins. Iron deficiency, on the other hand, increased the risk of psychiatric disorders, like anxiety, depression, and attention deficit hyperactivity disorder. This suggests that further research on micronutrients and neuropsychological function will lead to a better understanding of the role of iron in maintaining the functional integrity of the young and aging brain.

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Chapter 2
The Interplay between Iron and Oxidative Stress in Brain Neurodegenerative Diseases

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1 Iron as an Essential Micronutrient

1.1 Introduction

Iron is an essential micromineral needed by most living organisms, including humans (Bao et al., 2012; Abbaspour et al., 2014; Wang & Babitt, 2019). Despite being found in small quantities in the human body and hence required in amounts less than100 mg/day in the adult diet, iron is a vital key player involved in a wide range of fundamental cellular and organismal metabolic processes that take place continuously in the body (Sizer & Whitney, 2013). These dynamic metabolic processes include oxygen transportation, cellular proliferation, energy production, host defense, neurotransmitter synthesis and function, and other oxidation-reduction reactions (Gupta, 2014; Samaniego-Vaesken et al., 2017; Gao et al., 2019). Therefore, decreased quantities or absence of iron in the body or its intakes from diet/supplements hampers the proper function(s) of these vital processes resulting in the onset of various health symptoms and diseases. Indeed, iron deficiency and in it severe states; iron deficiency anemia is to date, a worldwide health concern recognized and highlighted by the World Health Organization in both developed and developing nations (WHO, 2004; Abbaspour et al., 2014; Samaniego-Vaesken et al., 2017). Excess iron, on the other hand, is also implicated with the manifestation of many other ailments; resulted from the destructive damage occurring to the body's

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lipids, proteins, and DNA upon the elevation in the production of iron-induced free radicals (Kohgo et al., 2008; Wang & Babitt, 2019). Taking the above-mentioned notes which delineate the importance of iron and its precise homeostasis for the wellbeing of the human body; this chapter tackles important issues related to the mineral iron in the human body from iron's dietary sources, its various forms present in the diet, the daily recommended intakes, to the overall ingestion to excretion pathway(s) of iron, iron function(s) in various parts of the body particularly in the brain, the body mechanisms for iron homeostasis and their crosstalk with oxidative stress, and finally the consequences of impaired iron homeostasis and brain diseases.

1.2 Dietary Sources, Forms and Requirements of Iron

1.2.1 Iron Dietary Sources

Being essential for proper body functioning and, at the same time, the incapability of the body to synthesize it for daily's requirements, iron must be provided continuously by the diet/ supplements in considerable amounts (Sizer & Whitney, 2013). Meat, poultry, eggs, seafood/ fish, nuts, cereals, and vegetables are considered iron's richest food sources. The major iron form in foods of animal origin is found centered in the hemoglobin and myoglobin molecules, while the common iron forms present exclusively in plant sources are low molecular weight compounds (e.g., ferric citrate) and high molecular weight compounds (e.g., ferritin). Moreover, iron is found in certain fortified foods and is available as pharmaceutical and dietary supplements. Iron as lactoferrin is found in infant formula, while fortified food and supplements of iron generally contain various forms of iron such as ferrous sulfate, ferric chloride, and ferrous gluconate, among others (Shayeghi et al., 2005; Vandevijvere et al., 2013; Zielińska-Dawidziak, 2015; Skolmowska & Głąbska, 2019).

1.2.2 Iron Forms

Absorbable iron found in the diet can be categorized into two main distinctive forms: heme iron (ferrous protoporphyrin IX) and non-heme iron (organic and inorganic freely metal). These two forms differ in their chemical structures, absorption and uptake processes, bioavailability, and food sources (Abbaspour et al., 2014; Ems & Huecker, 2020).

Heme iron is found as iron (II)-centered porphyrin (ferrous ion, Fe^{+2}) that forms the prosthetic group within many proteins and is mainly derived from the diet upon the breakdown of the two major abundant proteins found only in animal sources: hemoglobin and myoglobin (West & Oates, 2008; De Carli et al., 2018). Due to its unique chemical structure being incorporated and protected by the protein structure carrying it and the presence of specific heme transporters (e.g., heme carrier protein

1, HCP1) that facilitate its movement across the cell membranes and into the bloodstream, heme iron is highly bioavailable and can reach up to 40% being absorbed from the diet during an iron deficiency state (Abbaspour et al., 2014; Shubham et al., 2020). Moreover, dietary components such as phytates, oxalates, and polyphenols, have no effect on the absorption of this form of iron. High pH in the small intestine renders the solubility of certain inorganic iron forms, which in turn reduces their absorption, but has minimal effect on the heme iron uptake and absorption (Pizarro et al., 2003; Wang & Babitt, 2019).

Non-heme iron, on the other hand, is found purely in plant-based, fortified food products, and as a mixer alongside the heme iron in animal products. This form is commonly found as freely iron metal in the oxidized or reduced forms, with the inorganic ferric ion (Fe^{+3}) as the main non-heme iron form present in plants (Abbaspour et al., 2014; Moris et al., 2021). Owing to their chemical structures, the absorption of the non-heme iron, excluding plant ferritin, is usually less uniform, and certain limiting factors (e.g., quantities in the diet, duodenal pH, presence or absence of enhancers /inhibitors factors) reduces their bioavailability, reaching to merely an average of 1–15% being absorbed from the diet (Young et al., 2018; Ems & Huecker, 2020). Nonetheless, non-heme iron quantities in the diet are greater by folds than that of the heme iron, making it the chief contributor for dietary iron (West & Oates, 2008; Samaniego-Vaesken et al., 2017).

1.2.3 Human Requirements of Iron

Human daily requirements for iron differ according to age, gender, health status, food source, and body's iron status (Samaniego-Vaesken et al., 2017; Ems & Huecker, 2020). Any disruption in the iron's homeostats in the body can cause either iron deficiency or iron excess, which in turn can cause serious adverse health effects and concerns. Hence, specific requirement values were set for iron alongside other vital nutrients to support the body's needs to accommodate the various demographic variance among individuals and establish proper iron homeostasis. As a result, the Food and Nutritional Board (FNB) of the National Academies (NASEM), US, developed a term known as "Dietary References Intakes" (DRI), in which it sets reference values for nutrient intakes used in planning and assessing diets of healthy individuals (National Institutes of Health, 2016).

In general, infants in their early stages get their iron requirements fully from their mothers' milk. However, after 4–6 months of birth, mother's milk becomes insufficient, and the demand for iron increases drastically. As age increases, the DRI of iron increases reaching approximately 8 mg/day at 13 years old. During the adolescent's period, iron requirements again increase due to the rapid body growth and puberty spurt, with females requiring a DRI of 15 mg/day with an additional 2.9 mg/day over that value and males requiring an additional 1.1 mg/day with their regular DRI value of 11 mg/day. The significant increment of iron DRI value for adolescent females compared to adolescent males compensates for the iron loss via blood during menstruation. As for the adulthood period, the DRI for adult men and

postmenopausal women is set at 8 mg/day, whereas fertile adult women who require more are set with DRI of 18 mg/day. Pregnant women also require higher iron intake for the rapid growth of the placenta, fetus, and maternal red blood cells requiring almost 27 mg/ day of iron intake (Samaniego-Vaesken et al., 2017; National Institutes of Health, 2016).

Gastrointestinal (GI) disorders such as inflammatory bowel disease, celiac disease, Heliobacter infections, and other malabsorption-related diseases reduce iron uptake by the body, causing iron deficiency. Therefore, patients with these conditions require extra iron DRI values than those required by healthy individuals (Usman et al., 2019; Montoro-Huguet et al., 2021).

As discussed earlier, plant-based foods contain only the non-heme form of iron which is generally characterized by low bioavailability due to its chemical structure that is greatly affected by the body's pH and the presence of other plant components that interfere with its absorption (Samaniego-Vaesken et al., 2017; Young et al., 2018). Thus, logically, vegetarians, especially vegan individuals who rely strictly on plants for their diet, require higher iron DRI requirements than those who consume significant amounts of animal products. Indeed, the iron needs for vegetarians particularly vegan, may reach up to 1.8 times more than those required by non-vegetarians (Pawlak & Bell, 2017; National Institutes of Health, 2016).

It is well-known that regardless of the type of iron (heme or non-heme) and the dietary factors that promote or hamper iron absorption, the determinant factor that regulates the uptake and absorption rate of this essential mineral relies on the concept of the systematic iron need of the body. This means that regardless of the richness of the diet with iron, the absorption rate increases or decreases based on the iron status of the body. A significant increment in the absorption rate of iron is noticed upon the onset of iron deficiency state, whereas reduced absorption rate takes place when iron depots in the body are replenished and filled up (Samaniego-Vaesken et al., 2017). This mechanism, alongside other body pathways, helps maintain the homeostasis of iron inside the body, compensating for any iron losses as well as preventing toxicity and iron overloading in vital body organs (Kohgo et al., 2008; Loncar et al., 2021).

1.3 Iron Bioavailability

Generally, the onset of micronutrient deficiencies is due to the low dietary intake represented by taking diets with low to null micronutrient composition. Logically, increasing their intakes by consuming diets rich in these nutrients or the ingestion of their purified pharmaceutical supplementation should replenish the shortage and subside their deficiency's symptoms. However, this is not the case in iron deficiency, indicating the presence of other determinantal factors (West & Oates, 2008; Abbaspour et al., 2014). Bioavailability, defined as the amount of ingested nutrient being absorbed and available for body's utilization, is one undeniable factor influencing the dietary availability of many vital micronutrients including iron. Indeed, dietary enhancer and inhibitory factors profoundly influence the availability

of iron for absorption. These diet-related factors exert different action according to the type of iron found in the diet (De Carli et al., 2018; Young et al., 2018; Ems & Huecker, 2020). Due to its chemical structures (soluble Fe^{+2} and predominantly the insoluble Fe^{+3}), dietary non-heme iron show low bioavailability that is profoundly influenced by the dietary components (promoters or inhibitors), pH, and oxidation activity. Phytates, phenolic compounds, and calcium, among others, are major inhibitors of iron absorption that function as either: (1) chelator agents converting non-heme iron into insoluble complexes, (2) binding agents affecting iron's uptake and transport, or (3) competitors binding with iron's absorption sites. The alkaline pH present in the lumen and the oxidation capacity also renders the non-heme iron bioavailability. High pH readily oxidizes the soluble Fe^{+2} to insoluble Fe^{+3} increasing by that the percentage of unavailable non-heme iron for absorption. Meanwhile, dietary enhancers such as ascorbic acid and meat proteins promote acidity condition, the ideal environment for non-heme iron solubility and absorption, maximizing by that the bioavailability of non-heme iron. Dietary heme iron, on the other hand, being in a protective chemical structure is unaffected by the above-mentioned factors (both inhibitors or promoter factors), and therefore show high bioavailability rates (Hunt, 2005; West & Oates, 2008; Abbaspour et al., 2014; Dasa & Abera, 2018).

1.4 Iron Metabolism

The human body contains around 3–5 g of iron on average (around 55 mg and 44 mg/kg of body weight for men and women, respectively). Due to its vast utility and necessity and if overload, toxicity in the body, these quantities of iron in the body must be kept within an optimal physiological range (Gkouvatsos et al., 2012; Abbaspour et al., 2014; Ems & Huecker, 2020). The body maintains such balanced iron quantities via strict and tight iron metabolism pathways, which controls the mechanisms of absorption, transport, storage, utilization, excretion, and the systematic regulations of iron in the body (Frazer & Anderson, 2014; Gao et al., 2019; Wang & Babitt, 2019).

1.4.1 Iron Uptake, Absorption, and Transportation

The absorption of iron (heme or non-heme) predominantly occurs in the duodenum and the upper jejunum. For heme iron, Wyllie and Kaufman (1982) and Gräsbeck et al. (1982) described two possible mechanisms for its uptake by the enterocyte: (1) Pinocytosis-like uptake mechanism (Wyllie & Kaufman, 1982) or (2) Binding with a specific heme transporter; the HCP1 (Gräsbeck et al., 1982). Recent evidence has shown that HCP1 is also coupled with another protein carrier know as proton-coupled folate transporter (PCFT) (Qiu et al., 2006; Antileo et al., 2013). Despite being primarily allocated for folate transportation, PCFT/HCP1 also has a notable role in heme iron transportation. Once inside the enterocyte, heme containing

proteins are catabolized by both heme oxygenase and biliverdin reductase enzymes, releasing inorganic iron and bilirubin, respectively. The form of released inorganic iron from these heme proteins is the non-heme iron, Fe^{+2} (Pizarro et al., 2003; Moris et al., 2021).

Non-heme iron, on the contrary, requires more elaborated absorption mechanisms than that of the heme iron (Pizarro et al., 2003; Moris et al., 2021). Typically, non-heme iron absorption occurs mainly in the apical membrane of the enterocyte with the aid of a specific transporter called the divalent-metal transporter-1 (DMT-1). This protein transporter selectively transports the soluble iron Fe^{+2} rapidly than the insoluble form of iron, Fe^{+3}. Since the predominantly non-heme iron form found in the diet is the Fe^{+3}, and the rapid oxidization of available plant's Fe^{+2} to the Fe^{+3} at the body's physiological pH, the bioavailability of these non-heme iron forms is significantly influenced by the pH co-existing in the duodenum and the presence of other dietary constituents (Abbaspour et al., 2014; Moris et al., 2021). The pH dilemma is somehow overcomed by the action of the body's gastric acid, which lowers the pH of the proximal duodenum allowing for a ferric reductase enzyme, duodenal cytochrome B (Dcytb), to reduce Fe^{+3} to Fe^{+2}, facilitating DMT-1 function to readily uptake and transport the soluble iron Fe^{+2} into the enterocyte. Hence, impairment in the gastric acid production can substantially reduce the non-heme iron absorption percentage by the body (Kohgo et al., 2008; Frazer & Anderson, 2014). Similar to body's pH condition, the presence of dietary enhancers/ inhibitors that either augment the solubility or hinder the absorption process profoundly affects the absorption of these non-heme iron forms from the diet (Ems & Huecker, 2020). These dietary enhancers/ inhibitors of iron will be further explained later in the bioavailability section.

An independent mechanism has also been reported by Theil et al. (2012) regarding a second possible absorption pathway for the non-heme, yet high bioavailable iron form; the plant ferritin. The clathrin-dependent endocytic mechanism, which is still under investigation; hypothesizes that intact plant ferritin that escapes the digestive enzymes binds to the surface of the enterocytes, and then is internalized within the enterocytic cells. The fate of ferritin inside the enterocytic cells remains unclear (Kalgaonkar & Lönnerdal, 2009; Theil et al., 2012). Regardless the presence or absence of this unique absorption mechanism, it is crucial to highlight the fact that the bulk of plant ferritins seem to be subjected to degradation upon food preparation/ processing and digestion, thereby freeing the iron within it as inorganic non-heme iron, which in turn is absorbed through the normal DMT-1 pathway (Abbaspour et al., 2014; Gao et al., 2019).

The absorption of iron in the duodenum and the upper jejunum is the first and, by most, the key step in iron metabolism and homeostasis. This means, that even with adequate and sufficient intakes of iron via diet or supplements, the efficiency of iron absorption is governed mainly by the status of iron's stores in the body. An inverse association is found between iron absorption and the body's iron stores which is directly correlated with the erythropoiesis rate. This explains the wide observed variations in iron absorption among healthy individuals ingesting almost the same quantities of dietary/ supplements of iron (Frazer & Anderson, 2014; Moris et al.,

2021). Nevertheless, factors such as food types, food-food interactions, food-drug interactions, the timing of food consumption, and gastrointestinal tract's pH can also solely or jointly modulate the extraction of the iron from the diet, and therefore should not be neglected (Pizarro et al., 2003; De Carli et al., 2018).

As mentioned above, the fate of iron inside the enterocytes depends on the iron status in the body. When the body cells are saturated with iron, the excess iron released by the enterocytes binds to apoferritin forming ferritin molecules, cellular storage form of iron. At the end of enterocytes' lifecycle, these cells are shed into the intestinal lumen (exfoliation of intestinal epithelium), and the unused stored iron in ferritin is lost (Abbaspour et al., 2014; Frazer & Anderson, 2014). On the other hand, when there is a demand on iron, free internalized Fe^{+2} in enterocytes (the converted absorbable form of heme and non-heme iron coming from diet) is transported across the basolateral membrane and into blood circulation via iron efflux protein ferroportin 1 (FPN1). Excreted freely Fe^{+2} is then re-oxidized into Fe^{+3} by either a membrane-bound copper dependent ferroxidase hephaestin or circulating caeruloplasmin, before actively binding with the serum glycoprotein transferrin (Tf), which serves as the major delivery vehicle for iron to the body's utilization/ storage sites (Petrak & Vyoral, 2005; Gao et al., 2019; Thirupathi & Chang, 2019).

1.4.2 Iron Utilization, Circulation, Reutilization, and Storage

The approximately 3–5 g of iron found in the human body are mainly incorporated in the red blood cells' (RBCs) pigment (2.5 g), the hemoglobin, while around 3–4 mg of body's iron exist as a circulating pool of Fe- transferrin (Fe-Tf). The remaining portion is stored as ferritin complexes in all cells and major storage organs (Garrick & Garrick, 2009; Thirupathi & Chang, 2019). Iron enters body's cells by binding with the transferrin receptor 1 (TfR1) found on cells' surface, undergoes endocytosis releasing the iron as Fe^{+3} from Tf. Ferrireductase six-transmembrane epithelial antigen of prostate 3 (STEAP3) reduces Fe^{+3} to Fe^{+2}, which is then easily transported to cell's cytoplasm via DMT1. Intracellular iron can be either transported to the cell's mitochondria via mitoferrin 1 and/or 2,5-dihydroxybenzoic acid for vital metabolic utilization. Cells can either use iron for the synthesis of hemoglobin, non-hemoglobin hemoproteins (e.g. myoglobin, cytochromes, catalases), and iron sulfur clusters (Fe-S), store it as cytosolic ferritin, or export iron from cells via FPN1 when exceeding cell's needs. Minute and tightly regulated amounts of Fe^{+2} are kept as liable ions in cells, participating in the oxidation-reduction reactions, promoting cell proliferation, and facilitating cell signaling (Abbaspour et al., 2014; Anderson & Frazer, 2017; Galaris et al., 2019; Gao et al., 2019).

Normally and under physiological condition, merely 1 mg of dietary iron is being absorbed by the human intestine daily, which also accounts for the same amount of iron lost from the body on a daily basis. Hence, the body's iron requirements rely momentously on the recycling process of the intracellular iron, and to a lesser extent on the iron provided by diet/ supplements (Abbaspour et al., 2014; Gao et al., 2019). The bulk of the body's iron content found in RBCs is reutilized with the help of the

reticuloendothelial macrophages. Effete RBCs (normally after 120 days) are scavenged and subjected to phagocytosis by the resident macrophages present in bone marrow, spleen, and liver. Inside the macrophages, senescent RBCs are dismantled, and the resulted heme is further catabolized by the action of heme oxygenase-1 (HO-1) releasing the iron (Fe^{+2}) within. Free Fe^{+2} goes through the normal route of being circulated via FPN1, re-oxidized to Fe^{+3} by either hephaestin or circulating caeruloplasmin, loaded to Tf, and finally is reutilized for erythropoiesis and/ or other cellular processes, or stored in many body's organs, mainly the liver, spleen, and bone marrow (Kohgo et al., 2008; Garrick & Garrick, 2009). The exact molecular mechanisms of iron reutilization in the body to date have many unknowns, but it is crystal clear that these mechanisms are considered the major suppliers of the essential iron for the body.

Excess iron in the body is bonded and stored in two major storage proteins namely: ferritin and hemosiderin (Anderson & Frazer, 2017; Galaris et al., 2019). Ferritin is the major body's iron-storage protein characterized with a high binding capacity (holding up to approximately 4500 atoms of iron) and an easily and readily releasing ability of iron for all body cells when needed. Under steady conditions, serum ferritin concentrations reflect the total body's iron stores, commonly used as a laboratory indicator for the body's iron content. Hemosiderin, on the other hand, is a complex iron storage protein that results from the degradation of iron-overloaded ferritin molecules via lysosomes. This storage form is prominent in macrophages upon the degradation of erythrocytes and in patients with iron-load diseases. Unlike ferritin, hemosiderin is poorly available to supply iron for body's needs. Despite the differences between two iron storage proteins, ferritin and hemosiderin play an important role in iron homeostasis, for both don't merely serve as vital iron reservoir needed to sustain body's various metabolic pathways, but also act as protective mechanisms by which the body sequesters toxic iron ions (Fe^{+2} and Fe^{+3}) in a nontoxic insoluble forms. Moreover, both proteins reflect the body's iron concentrations in physiological and pathological conditions (Abbaspour et al., 2014; Gao et al., 2019).

1.4.3 Iron Excretion and Regulation

Minute losses of iron of around 1 mg/day are resulted from the physiological exfoliation of cells from the epithelial surfaces. Substantial losses of iron from the body can be due to hemorrhage, menstruation, or pregnancy. Apart from that, there are no active or regulated iron elimination and excretion mechanisms from the body (Petrak & Vyoral, 2005; Abbaspour et al., 2014).

Maintaining iron homeostasis in the body is vital for both iron deficiency and iron excess are equally detrimental to the body's cells. Therefore, body's iron homeostasis is controlled by tight regulatory mechanisms at both cellular and systemic levels (Petrak & Vyoral, 2005; Carocci et al., 2018; Katsarou & Pantopoulos, 2020). At the cellular level, iron homeostasis is governed by iron regulatory proteins 1 and 2 (IRP1 and IRP2) which modulate the expression of

proteins involved in iron uptake, traffic, utilization, and storage. IRPs regulate the expressions of iron proteins namely, DMT1, FPN1, TfR1, and ferritin on the mRNAs level via binding to their iron responsive elements (IRE). Combined, IRP-IRE system responds to cellular iron deficiency by increasing iron import via the enhancement of DMT1 mRNA expression, while obstructing the iron storage proteins' uptake, storage, and export through decreasing the stability of TfR1, ferritin, and FPN1 mRNAs. The opposite occurs when an excess in cellular iron is detected, DMT1 mRNA expression is reduced and TfR1, ferritin, and FPN1 mRNAs expressions are stimulated (Gao et al., 2019; Hermann et al., 2021). At the systemic level, iron homeostasis is maintained by keeping a strict balance between iron intake and iron utilization and egress. As body lacks an active excretion mechanism for iron, this regulation is mainly controlled on the absorption sites. A peptide hormone known as hepcidin plays a central role in the iron homeostasis at the systemic level. Synthesized mainly by the liver, and to a lower level expressed in macrophages, adipocytes, and brain, hepcidin negatively regulates body's iron, inhibiting both intestinal absorption and reticuloendothelial release of iron (Kohgo et al., 2008; Abbaspour et al., 2014; Frazer & Anderson, 2014; Wang & Babitt, 2019). When iron levels are elevated beyond cellular needs under normal physiological conditions or in pathological cases such as inflammation, hepcidin kicks in and binds to FPN1 found on intestinal duodenum cells and other targeted cells, causing FPN1 internalization and degradation in lysosomes. The loss of FPN1 from targeted cells prevents iron absorption and its entry into the body's plasma. This in turn lowers Tf saturation of iron and hence lessen cellular uptake of iron. In addition to the degradation action of FPN1, hepcidin blocks iron efflux from this protein, minimizing by that the release of unwanted iron. Conversely, the release of hepcidin from liver is reduced upon physiological condition of normal cellular iron deficiency or under pathological conditions such as the genetic disorder of erythropoietic protoporphyria. The absence of the inhibitory activity of hepcidin maximizes the absorption of dietary iron by the intestinal duodenum cells to replenish the body's iron content (Galaris et al., 2019; Nemeth & Ganz, 2009). Aside the individual's internal iron status controlled by tight cellular and systemic mechanisms, it is important to remember that iron's absorption is also influenced by external factors such as dietary composition, pH, iron form, and oxidation activity that affect the bioavailability of iron at the absorption sites (West & Oates, 2008; Dasa & Abera, 2018; Gao et al., 2019).

1.5 Brain Iron

The amount of iron in the brain accounts for merely 2% or less of that of the total body iron content, yet the homeostasis of this minute quantity is vital for the brain's normal physiological functions (Gupta, 2014; Carocci et al., 2018; Ems & Huecker, 2020). Like its fundamental functions in other body cells, iron acts as a prosthetic group in various key enzymes crucial in oxygen transportation, high mitochondrial respiration, and vital redox signalling in brain cells. In addition, iron present in brain

is involved in the neurotransmitters, myelin sheets, and DNA synthesis. Iron, particularly the non-heme iron tyrosine hydroxylase, is also needed for the myelination formation and the synthesis of the dopamine, norepinephrine, and serotonin neurotransmitters (Singh, 2014; Carocci et al., 2018; Ferreira et al., 2019). Disruption of the iron homeostasis (deficiency or excess) in the brain results in severe defects of brain's motor, cognitive, and behavioral functions. Due to the high vulnerability of brain cells and their life determining roles, brain rests behind a physical barrier known as the blood-brain barrier (BBB) that regulates the exchange of materials with the circulating blood. BBB acts as a selective fence that protects brain from harmful molecules found in the circulating blood and maintains the optimal microenvironment ions content including iron needed for neurological signaling (Benarroch, 2009; Ferreira et al., 2019). Plasma Fe-Tf selectively enters brain cells across BBB's apical (blood side) membrane that resides between brain vascular endothelial cells (BVECs). There, BVECs uptake iron via two main mechanisms: (1) Tf/ TfR1 pathway and (2) non-transferrin bound iron (NTBI). The BVECs' Tf/ TfR1 pathway follows the same process used in most body cells, starting with the binding of Fe-Tf with TfR1, Fe-Tf-TfR1complex endocytosis, acidification and release of Fe^{+3}, reduction of Fe^{+3} to Fe^{+2}, movement of Fe^{+2} across endosomal membrane, and lastly into various brain cells (Singh, 2014; McCarthy & Kosman, 2015; Duck et al., 2017; Qian & Ke, 2019). Alternatively, the NTBI pathway allows iron uptake directly by brain cells through apical DMT1, H-ferritin (iron storage protein with high capacity), lactoferrin, melanotransferrin (p97), transcytosis of Tf/ TfR1 complexes pathways, and others. The exact mechanisms of these pathways are still poorly understood and heavily investigated to date (Mills et al., 2010; McCarthy & Kosman, 2015). After being released into brain's interstitial fluid, iron is distributed and absorbed unevenly by various brain cells in different brain regions. Thus, different brain regions/ structures have different iron concentrations, with substantia nigra, dentate gyrus, and red nucleus containing the highest iron levels. Such variance supports the hypothesis of the high susceptibility to oxidative damage and speedy denaturation rates exhibited by certain brain regions/ structures compared to others (McCarthy & Kosman, 2015; Carocci et al., 2018; Yu & Chang, 2019). Neuroglia (non-neurons) and neurons (nerve cells), the two type cells found in brain, possess different iron uptake mechanisms. Each of neuroglia's three cell types, astrocytes, microglia, and oligodendrocytes, possesses a unique iron uptake mechanism. Astrocytes acquire iron via NTBI different pathways such as DMT1, citrate, and ATP. Microglia, on the other hand, acquire iron via either Tf/ TfR1 pathway or NTBI pathways, based on the presence of certain stimuli such as inflammation. Meanwhile, mature oligodendrocytes which are the brain cells with the highest iron content due to their active metabolic needs for myelination, acquire iron via Tf/ TfR1 pathway and/ or the NTBI pathway; H-ferritin. Classical Tf/ TfR1 pathway or NTBI pathway (DMT1) are the mechanisms by which brain neurons acquire iron (West & Oates, 2008; Antileo et al., 2013; Yu & Chang, 2019). Iron fate, depending on brain-iron status, can be either mobilized for various neuroglia and neurons' metabolism, stored as cytosolic ferritin and/ or as labile iron pool if found in excess, or when overloaded, it is released by FPN1 and is effluxed to

the interstitial fluid, where iron is sent back to the blood circulation via Tf/ TfR1 pathway and/ or the NTBI pathways (Duck et al., 2017; Carocci et al., 2018; Qian & Ke, 2019; Yu & Chang, 2019). Iron homeostasis in the brain is tightly controlled by regulators both at the cellular level via IRP-IRE system and at the systemic level via hepcidin (Abbaspour et al., 2014; Gao et al., 2019; Thirupathi & Chang, 2019).

Observing the significant role(s) of iron for normal brain activities and the tight regulation systems aimed to maintain its homeostasis within brain cells, brain neuropathies are expected upon the diminish or excess of this essential iron in brain cells (Mills et al., 2010; Duck et al., 2017). Iron deficiency at early life stages hampers brain cells division, growth, and development. In addition, the absence of iron causes defects in the functional properties of brain cells. Iron anemia and progressive mental retardation are the early and late manifestations of iron deficiency. Iron overload, on the other hand, has been detected in various neurodegenerative conditions and is considered one major culprit in the onset and progression of these diseases via the initiation of the detrimental oxidative stress (Carocci et al., 2018; Galaris et al., 2019). Moreover, defects of several iron regulatory proteins found in brain were further detected in brain cells of individuals with neurodegenerative disorders. Hence, the basic understanding of the concept of oxidative stress, iron homeostasis and redox signalling, and the crosstalk between iron imbalance and the initiation of oxidative stress are of vital clinical relevance for degenerative diseases affecting the brain (Benarroch, 2009; Liguori et al., 2018; Galaris et al., 2019).

2 Oxidative Stress, Iron Overload, and Brain Degenerative Diseases

2.1 The Concept of Oxidative Stress and Redox Signaling

Oxidative stress, coined by Helmut Sies in 1985, is best defined as the balance disturbance occurring between the formation levels of the so-called reactive species (free radicals) and their cellular clearance levels from cells via defense mechanisms (antioxidants) (Pizzino et al., 2017; Sharma et al., 2018). Reactive species/ free radicals namely; reactive oxygen (ROS) and reactive nitrogen species (RNS); are the normal by-products of various bodily metabolic processes. Mitochondria, being the core of most metabolic pathways (e.g. TCA cycle, B-oxidation, urea cycle, oxidative phosphorylation), continuously generates these reactive species/free radicals as by-products, as well as molecules needed for other various body functions. Differentiation, apoptosis, immunity, protein phosphorylation, activation and expression of transcriptional factors, among others, require certain levels of cellular ROS and RNS for proper functioning (Gutteridge & Halliwell, 2018; Ifeanyi, 2018; Alkadi, 2020). Meanwhile, inflammation, cancer, stress, overload of heavy metals, and neurogenerative disorders are the pathological endogenous sources of these

notorious ROS and RNS. The physiological or pathological nature of ROS/RNS; is profoundly governed by the so-called "redox homeostatic balance". Specific body sensors detect variations in the redox balance, resulting in the initiation of a cascade signalling ending with the activation of antioxidant defensive system. Comprising of enzymatic and non-enzymatic components, this antioxidant system via various mechanisms maintains the levels of ROS/RNS within the normal safe threshold (Collins et al., 2012; Liguori et al., 2018). However, dysfunctional of the defensive antioxidant systems and/ or other bodily metabolic processes that disturb the balance between ROS/RNS and the antioxidant system favouring the former, result in the onset of damaging cascade oxidative events that ends with the oxidation and denaturation of body's proteins, lipids, and DNA. Exogenous sources of ROS/RNS such as cigarettes, pollutants, certain dietary components, drugs, cooking methods, and radiation can also trigger the overproduction of ROS/RNS in the body, promoting harmful oxidative stress status and its deleterious consequences (Galaris et al., 2019; Ferreira et al., 2019; Mahmoud et al., 2020).

2.2 *The Crosstalk Between Iron and Redox Signaling and the Consequences of Iron Homeostasis Impairment*

The exact chemical properties that contribute to iron's essentiality to the human body are also implicated to the onset of various oxidative-induced diseases (Anderson & Frazer, 2017; Pizzino et al., 2017; Thirupathi & Chang, 2019). The iron's ability to donate electrons is needed for the functioning of various bodily redox cycles. However, once iron levels exceed normal physiological levels, this essential ability of exchanging electrons dramatically shift to the negative activity of ROS/RNS overproduction, initiating the damaging oxidative stress condition (Grubman et al., 2014; Carocci et al., 2018; Gutteridge & Halliwell, 2018). It is important to note that iron overload itself is not always toxic per se. Some clinical cases detected the occurrence of iron overload in body organs, yet these organs did not show any injury (Carocci et al., 2018). Furthermore, the onset of iron-overload diseases such as neurodegenerative diseases do not occur instantly upon iron accumulation but rather require longer periods, indicating the involvement of other possible factors. However, it is important to note that one important factor influencing iron overload toxicity it's the ability to produce the damaging oxidative condition within cells. Based on this notion, the extent to which iron overload can reach to a toxicity level variers partially or totally with the: (1) biochemical form of cellular iron, (2) localization of the iron deposits, and (3) presence/ absence of cellular defensive mechanisms (Carocci et al., 2018; Mahmoud et al., 2020). Iron in living organisms is mostly found in sequestered forms, incorporated within vital cellular components such as haemoglobin, myoglobin, and ferritin. Being in such forms deter their interaction with cellular reactive species such as superoxide anion ($O_2^{-\cdot}$) and hydrogen peroxidase (H_2O_2) and further reduce iron's presence for harmful

microorganisms (Carocci et al., 2018; Gutteridge & Halliwell, 2018). However, minute quantities of iron can be also found as reduced (Fe^{+2}) and oxidized (Fe^{+3}) liable forms. Being able to interchangeably transform between these two forms and denote electrons to oxygen molecules, Fe^{+2} and Fe^{+3} are potential endogenic producers of ROS (directly) and RNS (indirectly), the species involved in numerous oxidative-induced diseases (Chiueh, 2001; Thirupathi & Chang, 2019; Alkadi, 2020). Fe^{+2} including Fe^{+2}-citrate complexes interact with cellular oxygen, generating a continuous flux of the reactive species O_2^{-} ˙, H_2O_2, and hydroxyl radicals (OH ˙) via Fenton reaction or Haber-Weiss reaction. Moreover, the reaction between Fe^{+2} and the reactive specie O_2^{-} ˙ convert this iron form to a more prooxidative state, Fe^{+3}. Fe^{+3}, in turn, reacts with H_2O_2 to produce the highly reactive OH ˙ via Fenton reaction. Nitric oxide (NO ˙) radicals (most common cellular RNS) are also produced by the oxidation of specific protein's amino acid by iron generated ROS. These radicals, in turn reacts with O_2^{-} ˙ generating other harmful reactive species (e.g. peroxynitrite anions; $ONOO^{-}$). Highly reactive peroxyl (ROO ˙) and alkoxyl (RO ˙) radicals are too generated by the interaction of excess iron with oxidized lipid via Fe^{+2}-dependent lipid peroxidation. These lipid's by-products possess longer half-lives than O_2^{-} ˙, H_2O_2, and OH ˙ radicals, hence, causing chronic toxicity and severe DNA damage (Gutteridge & Halliwell, 2018; Ifeanyi, 2018; Mahmoud et al., 2020). Non-enzymatic oxidation of dopamine facilitated by iron redox-reaction generates the reactive species of semiquinones and H_2O_2 at the electron transport chain within the mitochondria. This mitochondrial insult further initiates and propagates the iron release as Fe^{+2} and Fe^{+3} ions from non-toxic cellular iron forms (e.g. iron-sulphur clusters, myoglobin). Collectively, these iron-induced reactive species attack the vital cellular macromolecules, the lipids, proteins, and DNA. In addition to their denaturation and loss of function, the oxidation of these cellular macromolecules forms another positive loop of generated reactive species that exacerbates the detrimental oxidative stress effect which ultimately ends with cell's demise (Benarroch, 2009; Mills et al., 2010). The toxicity of iron overload also depends on its subcellular localization (cytosolic, lysosomal, and mitochondrial) within the body cells, including brain cells. The pH co-existing within these organelles and their cellular functions may deter or enhance the prooxidant activity of iron. Most iron transport proteins are designed for the soluble, less prooxidant iron form, Fe^{+2} which is maintained in that form in acidic environment. While high pH oxidizes Fe^{+2} to the lesser soluble, more prooxidant iron form, Fe^{+3}. Despite the ability of both iron forms, Fe^{+2} and Fe^{+3} in forming harmful ROS/RNS, the different pH found in the lysosomes (acidic pH), cytoplasm (near to neutral pH), and mitochondria (neutral to alkaline pH) may further aggravate or render this prooxidant activity (Kohgo et al., 2008; Ferreira et al., 2019). Lysosome acidity keeps circulated iron as Fe^{+2} to be sequestered via binding with other cellular components, reducing its ability to participate in harmful oxidation processes. Mitochondria, on the other hand, keeps circulated iron as prooxidant Fe^{+3} required for respiration and oxidative phosphorylation. Moreover, being the metabolic central of the cell and a site for endogenous generation of ROS, mitochondria with excess iron deposit, may result in the fast and severe adverse iron toxicity compared to the

iron accumulation in either lysosome or cytoplasm (Galaris et al., 2019). Hence, the localization of the iron overload determines the toxicity of this metal and should not be overlooked.

Normally, both free prooxidative iron forms, Fe^{+2} and Fe^{+3}, are sequestered in the body into inert unactive forms, unavailable for redox-inducing activities. In addition to the different body processes designed to maintain Fe^{+2} and Fe^{+3} as inert unactive forms (e.g. ferritin), body's defensive/ antioxidant systems kick in once levels of ROS/ RNS induced by iron overload, are beyond the physiological threshold. Indeed, the presence or absence of a precise antioxidant system(s) determine the level of iron overload toxicity imposed on the cells. The presence of BBB is considered the first brain defensive mechanism against excess levels of iron. BBB acts as a selective barrier that regulates the uptake of circulated iron from plasma to brain cells. On another level, within different brain cells, an integrated antioxidant system made of the major antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (Gpx); low molecular weight reductants ascorbate (vitamin C), α-tocopherol (vitamin E), and glutathione (GSH); and metal chelators ceruloplasmin and metallothionein co-exists (Wilson, 1997; Grubman et al., 2014; Berndt & Lillig, 2017; Golko-Perez et al., 2017; Ifeanyi, 2018). The antioxidant enzyme copper/zinc SOD and magnesium SOD react with $O_2^{-}\cdot$ and change it to H_2O_2, which in turn, is converted by the antioxidant enzymes CAT and Gpx to nontoxic water molecules. Vitamin C and E act as direct radical scavengers, interacting with $O_2^{-}\cdot$, H_2O_2, and other lipid peroxidases, stopping further oxidation of vital cellular components (especially membrane lipids) and thus, terminating the cycle of reactive species generation. Meanwhile, GSH protects brain cells from the oxidative stress via multiple modes. Similar to vitamin C and E, GSH coupled with its generator by-product glutathione disulfide (GSSG) act as a direct reactive species' scavenger. GSH is also important for iron homeostasis with its role in the biosynthesis of Fe-S clusters (Devos et al., 2014; Berndt & Lillig, 2017; Carocci et al., 2018; Galaris et al., 2019; Alkadi, 2020; Dwivedi et al., 2020). Metal chelators; ceruloplasmin and metallothionein; protect brain cells form oxidative stress by reducing the iron overload. On one hand, ceruloplasmin, a multicopper enzyme with ferroxidase activity, regulates iron egress from brain cells by oxidizing Fe^{+2} and loading it on Tf (Musci et al., 2014). On the other hand, metallothionein is a cysteine-rich metal chelator that binds with various metals including iron, preventing iron overload and the consequence of iron-induced oxidative status (Ullio et al., 2015). Together, these defensive systems protect brain cells from iron-induced oxidative stress. Nevertheless, the increased permeability of BBB or/and the defect/ alteration of the antioxidant systems in brain cells upon aging process, genetic disorders (e.g. hemochromatosis), and/ or introduction of exogenous iron (e.g. heavy metal pollutants) may lead to imbalance in the iron homeostasis favouring iron accumulation, triggering the onset of the damaging oxidative stress in brain, and occurrence of iron-induce brain neuropathies (Wilson, 1997; Duck et al., 2017).

2.3 *Iron Overload, Oxidative Stress, and Brain Degenerative Diseases (Selective Cases)*

Pathological conditions describing brain iron overload coupled with the onset of oxidative stress are well-recognized and are designated as iron-induced neurodegenerative diseases. They are characterized by the overproduction of various reactive species, oxidation and dysfunction of vital cellular macromolecules, neurological toxicity, and brain cells' death (Benarroch, 2009; Mills et al., 2010; Grubman et al., 2014; Pizzino et al., 2017; Carocci et al., 2018). Overproduced ROS/RNS promotes the oxidative stress situation characterized by glutathione consumption and depletion, protein denaturation and aggregation, phospholipids remodelling and destabilization, and DNA alteration and destruction (Carocci et al., 2018; Dwivedi et al., 2020). Classically, iron-overload diseases can be either primary (genetic) or secondary iron-overload diseases. Primary iron-overload diseases are the result of genetic defects in iron transport or regulation mechanisms. Hemochromatosis, a primary (genetic) iron-overload disease, is characterised by reduced to null expression of hepcidin, making the body unable to limit dietary iron intake at the absorption sites in the intestine, hence creating the iron-overload condition. The iron-overload toxicity associated with this genetic disease produces severe clinical manifestations throughout multiple body's organs including the brain (Carocci et al., 2018; Ferreira et al., 2019). On the contrary, secondary iron-overload diseases are mainly due to long-term blood transfusion treatment used for severe anaemia condition (e.g. thalassemia). Iron overload here occurs from the excess exogenous iron from blood transfusion treatment coupled with the ineffective body usage of iron for the synthesis of RBCs (erythropoiesis). Again, this secondary iron-overload disease promotes the dysfunction and death of multiple body organs' cells including brain cells (Kohgo et al., 2008; Anderson & Frazer, 2017). In addition, normal ageing process or inflammation may result in the uncontrollable accumulation of iron,-producing age-related or inflammation-related neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Piperno, 1998; Grubman et al., 2014; Thirupathi & Chang, 2019). To date, the exact role of iron-overloading in neurodegenerative diseases as either the primary etiology causing these diseases or as a secondary consequence resulted upon the occurrence of neurodegenerative diseases remains unclear. Nevertheless, it is evident that AD, PD, Amyotrophic lateral sclerosis (ALS), and other destructive neuropathies, all have one prevailing hallmark; the iron-overload and its induced oxidative stress impact (Mills et al., 2010; Grubman et al., 2014). It also important to note that the brain's unique structure with specific features, makes it more prone to oxidative stress than other organs. Brain is highly vulnerable to oxidative stress, due to being a highly oxygen consumer organ with rich unsaturated fatty acids content, the main component of the neurons' myelin sheets and the mediator for impulse transmission. Furthermore, the high levels of prooxidants (iron and vitamin C) concomitant with the lower repair capacity of brain cells, cause the damage by the oxidative stress fuelled by iron-

overload calamitous and irreversible (Walker et al., 2016; Salim, 2017; Carocci et al., 2018).

AD is the most frequent type of the neurodegenerative disease with an early symptom of lost memory with a decline in cognitive and motor functions, that ends with dementia (Pratico, 2008; Pizzino et al., 2017; Ferreira et al., 2019). Despite the obfuscate etiology causing AD, oxidative stress by high ROS flux in brain cells mediated by iron has been implicated as one major culprit in its pathophysiology. Supporting such notion was the numerous reports of (1) high iron content detected in amyloid β plaques (as iron-amyloid complex), neurofibrillary tangles, and even injured neurons of post-mortem brains from AD's patients, (2) amplified oxidative stress observed in AD brain cells by iron-amyloid complexes through the production of H_2O_2 radicals, (3) presence of $OH^{\cdot}$ radicals produced by the help of iron via Fenton reaction that causes the aggregation of amyloid β in AD patients, (4) altered expressions of iron proteins responsible for iron's storage, transport, and regulation found in AD patients, and finally (5) iron accumulation reduction in various brain regions of AD patients by drugs acting as iron chelator (e.g. deferiprone) alleviating some AD symptoms. These observations indicate the implication of iron overload in the pathogenesis of AD; however, iron-induce oxidation in AD mechanism(s) bears many uncertainties and requires more investigations (Zecca et al., 2004; Jiang et al., 2009; Telling et al., 2017; Carocci et al., 2018).

PD, on the other hand, is the second most frequent type of neurodegenerative diseases after AD, with early symptoms of tremor, loss of posture, bradykinesia, changes in writing and speech skills, with late stages symptoms of insomnia, depression, and progressive cognitive and motor abnormalities. Again, neurological studies have pointed out the undeniable impact of iron overload coupled with oxidative stress in the pathogenesis of PD (Mills et al., 2010; Grubman et al., 2014; Hernandez-Baltazar et al., 2018). Confirming the implication of iron overload in PD was through the following observations: (1) Elevated iron levels were recorded in the examined substantia nigra of PD patients, (2) α-synuclein aggregates (high in iron deposits) were found to alter brain's mitochondria activity, triggering overproduction of ROS and RNS, and severe depletion of cellular antioxidant reductant GSH, (3) iron auto-oxidation of dopamine and production of lethal ROS were documented in PD patients, (4) accumulation of ferritin in the macrophage microglial cells forming ferritin-reactive microglia was also observed in the degenerative PD brain cells, and lastly (5) administration of pharmacological or genetic iron chelation increased the survival rate of dopaminergic neurons, thus delaying the PD progression (Carocci et al., 2018; Kausar et al., 2018; Varešlija et al., 2020). Jointly, these observations indicate the implication of iron overload in PD. However, the exact mechanism(s) by which iron overload affect the brain and its role in PD still needs further illustration.

ALS, known also as Charcot's disease, is a fatal sporadic or familial neurodegenerative disease with pronounced deterioration and death of the motor neurons of the spinal cord and brain (Grubman et al., 2014; Zhang et al., 2020). Iron overload has been also implicated with ALS pathogenesis evident by: (1) irregulates of

various mitochondrial iron proteins discerned in both *in vitro* and *in vivo* ALS studies, (2) prevalence of mutated hemochromatosis gene (act as an intracellular iron sensor when binding to Tf) leading to iron homeostasis disturbance and consequence oxidative damage, and lastly (3) usage of iron chelator prolonged the life span of ALS animal models. Similar to AD and PD, the primary or secondary iron overload mechanisms in ALS is still unclear and warrants additional studies (Grubman et al., 2014; Golko-Perez et al., 2017; Carocci et al., 2018; Gao et al., 2019; Zhang et al., 2020).

Other neurodegenerative diseases such as Friedrich's ataxia (FRDA), Huntington's disease (HD), and neurodegeneration with brain iron accumulation (NBIA), demonstrated a strong association between their onsets and/or progression with iron accumulation in various brain regions. Despite the unclarity in which initiates the other, iron accumulation or the destructive oxidation condition detected in these neurodegeneration disorders, one thing is confirmed; the initiation of both iron overload and the oxidative stress are bidirectional and their uncontrolled presences in brain cells have profound degenerative impacts (Grubman et al., 2014; Galaris et al., 2019; Gao et al., 2019).

3 Conclusion

The cruciality of the micronutrient iron to the lives of all living organisms is undeniable and is evident by multitudinous research and scientific investigations. Hence, the need to identify and understand all biochemical aspects related to this mineral deemed logical and necessary. Iron is found in various food items at different concentrations and in various chemical forms, causing diversity in its bioavailability for bodily usage and consequently the fluctuating needs for this mineral. Besides its bioavailability differences, iron's quantity also differs throughout the human life cycle, imposing distinct iron daily requirements based on age and gender. The delineated overall metabolic pathways of iron starting from ingestion to excretion and its functions in various parts of the body particularly in the brain, further enforces the essentiality of this mineral for maintaining a healthy body. Nevertheless, the tight regulation governing iron's cellular concentrations indicates the presence of a harmful and destructive side of iron. Indeed, mounted evidence has shown significant correlation between iron overload and various neurodegenerative diseases including brain degenerative diseases. This iron-induced degenerative activity is concomitant with the onset of the destructive oxidative stress status, affecting vital cellular biomolecules including brain's cells. Together, these notes show that iron behaves as a two-edged sword, where both iron's deficiency and excess are equally harmful to the body, hence, delicate regulations of iron concentrations in the body are absolutely needed.

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Chapter 3
Specific Nutritional Therapeutic Approaches Targeting Iron Overload and Other Hallmarks of Brain Degenerative Diseases

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1 Therapeutic Opportunities from Nutritional Point of View

1.1 Introduction

The detailed pathogenesis of any disease helps underpin the preventive/ therapeutic strategies that may prevent and/ or reverse, to some extent, the damaging outcomes of various diseases, including the neurodegenerative diseases. Many brain degenerative diseases appear to be the complex outcomes of multiple and interactional factors, yet the oxidative stress initiation concomitant with the brain's iron dyshomeostasis favouring iron overload, seem to be one prominent feature observed in these various brain degenerative ailments (Chiueh, 2001; Carocci et al., 2018; Kausar et al., 2018; Galaris et al., 2019). Hence, employing therapies that reduce/ prevent unhealthy iron accumulation and/ or attenuate the damaging oxidative stress condition in brain, deem logical and promising. Indeed, interesting data from

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numerous research showed that administrating iron chelators or antioxidants or both improved the symptoms of Alzheimer's disease (AD), Parkinson's disease (PD), and other neurodegenerative diseases (Anderson & Frazer, 2017; Soo et al., 2020; Sheikh et al., 2021; Rai et al., 2021). Thus, aside conventional genetic therapies (correcting mutated genes related to iron dyshomeostasis in brain), synthetic chelator's drugs (removing excess toxic iron and preventing unhealthy iron accumulation), and antioxidant analogues (enforcing brain's defense system and lessening the oxidative stress condition), nutritional interventions (e.g. food items, specific diets) with antioxidant, chelating, and/or other enhancing capacities have been under great scientific scrutinization and were examined as desirable and promising alternative neurodegenerative therapies (Carocci et al., 2018; Renaud & Martinoli, 2019; Soo et al., 2020; Rai et al., 2021). Nonetheless, it is important to note that for any potential candidate agent (natural or synthetic) to be used for preventing/ treating brain degenerative diseases, certain criteria should be fulfilled to achieve the optimal desirable outcomes. Among these required criteria is the ability of the potential agent to cross the blood-brain barrier (BBB) reaching different target brain cells, to impose minimum cytotoxicity, to have specific cleansing activity of cellular prooxidant iron forms, to execute minimum effect on vital brain iron-containing cellular structures, and to possess antioxidant, chelating and/ or neurogenerative properties (Anderson & Frazer, 2017; Carocci et al., 2018; Pohl & Kong Thoo Lin, 2018; Renaud & Martinoli, 2019). Again, substantial evidence has demonstrated that numerous natural dietary agents exhibited a wide range of health benefits such as antioxidant and/ or iron chelating capacities, fulfilling by that some of the above-mentioned criteria (e.g. minimum cytotoxicity) and making them, to some extent, the optimum preventive/ treatment candidates for iron induced brain neurodegenerative diseases (Anderson & Frazer, 2017; Carocci et al., 2018; Rai et al., 2021). Therefore, and based on the above notions; this chapter reviews some important and possible nutritional therapeutic strategies that may aid in the prevention and/ or treatment of the iron-induced oxidative damage hallmark present in various brain's degenerative diseases.

1.2 Nutritional Therapeutic Opportunities

1.2.1 Nutritional Treatment of Iron Overload

Iron Chelators

Metal chelators, including iron chelators, are agents that can bind to toxic ions of metals, forming stable soluble complexes that are easily excreted from the body. The general mechanism by which chelators function is based on the presence of donor atoms such as oxygen, sulfur, or nitrogen within their structures, which can readily bind with different free ion forms, including iron ions (Mills et al., 2010; Anderson & Frazer, 2017; Sheikh et al., 2021). Based on their chemical composition and

affinity to iron, iron chelators can bind to different iron forms (soluble Fe^{+2} or insoluble Fe^{+3}) and/or different iron molecule numbers (ratio of chelator's molecules to iron molecules). Chelators with oxygen donor atoms favourably bind with the iron insoluble form; ferric ion (Fe^{+3}). In contrast, those with either nitrogen or sulfur donor atoms, bind readily with the iron soluble form; ferrous ion (Fe^{+2}) and other divalent dication metals such as copper ions (Cu^{+2}) and zinc ions (Zn^{+2}). On the other hand, deferiprone (DFP), deferasirox (DFS), and deferoxamine (DFO), three well-known iron chelating agents, bind to the insoluble iron ions; Fe^{+3}; on the base of their affinity to these iron molecules. Three molecules of DFP are required to bind with 1 molecule Fe^{+3} (3:1 ratio), while 2 molecules of DFS (2:1 ratio) and 1 molecule of DFO (1:1 ratio) are required to bind with 1 molecule Fe^{+3}. Iron chelators can be also classified based on their origin sources to either synthetic (e.g. DFS and DFP) or natural (e.g. DFO and lactoferrin; Carocci et al., 2018; Bulbake et al., 2019; Sheikh et al., 2021). Lactoferrin (LF) is a natural iron-binding glycoprotein found in milk, with high iron affinity that can reach up to three hundred times greater than transferrin; the main protein transporter of iron found in the body (Alhaj, 2020; Dhennin-Duthille et al., 2000).

Compelling evidence has demonstrated the neuroprotective actions of these iron chelators and in some cases, their neuro-reverse activities against numerous neurodegenerative diseases (Grubman et al., 2014; Sripetchwandee et al., 2014). Administration of the natural iron-chelating drug DFO, showed significant improvement of PD symptoms in animal studies and promising outcomes in human clinical trials (Devos et al., 2014; Guo et al., 2016). LF has been also reported to exhibit a protective role against neurodegenerative diseases (Guo et al., 2017). Exogenous administration of LF was found to reduce β-amyloid (Aβ) peptide deposition and improved cognitive decline in mice with AD through improved nonamyloidogenic processing of amyloid precursor proteins (APP) and α -secretase production and activity via the extracellular signal regulated kinases ½ cAMP response element bonding protein (ERK ½-CREB) and the hypoxia inducible factor-1 (HIF-1a) pathways. Moreover, a recent pilot study of fifty AD patients given LF for 3 months reported significant improvements in the antioxidant and anti-inflammatory biomarkers in patients' blood, as well as a reduction in $A\beta_{42}$, phosphorylated tau, interleukin-6, and caspase-3 concomitant with better progress in the cognitive function (Mohamed et al., 2019). PBT2 (Prana Biotechnology); a metal chaperone derived from clioquinol that acts as an iron, copper, and zinc chelator, has been also reported to enhance cognition function, as well as lowering the Aβ plasma levels in a phase II study for AD patients (Ritchie et al., 2003) and in preclinical AD mice. On the other hand, Zhang and coauthors reported myelinopathy damage and toxicity detected in a transgenic AD animal model upon clioquinol treatment (Zhang et al., 2013). Polyphenolic compounds found in various foods have shown to have strong protective effects on tissue metabolism, especially in the brain (Bianchi et al., 2021). Furthermore, polyphenolic derivatives such as curcumin, resveratrol, and catechins were reported to have significant neuroprotection functions through their chelating properties in AD and other neurogenerative disorders (Carocci et al., 2018; Sheikh et al., 2021). These natural polyphenolic compounds also showed potent antioxidant

properties that reduced the oxidative stress condition directly (scavenging the reactive species) or indirectly (strengthening the brain's antioxidant systems), hence hindering the oxidation process and the death of neurons and glia cells of the brain (Matteo & Esposito, 2003; Mills et al., 2010; Ifeanyi, 2018).

Natural Antioxidants

Unlike iron chelator therapies, the mechanisms of the antioxidant therapies rely mainly on trapping, interacting, and reducing reactive species (iron originated or others), stopping by that the continuous destructive cascade oxidation events, which in turn protect other unaffected cellular structures in the brain (Soo et al., 2020; Rai et al., 2021). In many brain's degenerative diseases, the protective endogenous antioxidant systems/ molecules co-existing in brain cells, are either altered or extensively depleted, resulting in the cellular failure in neutralizing the destructive reactive species and reducing the lethal oxidation stress status. Hence deploying exogenous antioxidants may help correct such imbalance, protecting brain cells from further degeneration (Gutteridge & Halliwell, 2018; Ifeanyi, 2018). Both natural and synthetic compounds were used as exogenous antioxidants in many neurodegenerative models and showed neuroprotective functions and neurodegenerative delaying activities (Mandel & Youdim, 2004; Carocci et al., 2018; Soo et al., 2020). The well-known antioxidant medication, N-acetyl cysteine was reported to exhibit neuroprotective actions in both animal and human AD, PD, and Huntington's disease (HD) models (Shahidi et al., 2017; Crinelli et al., 2019; Monti et al., 2019; Soo et al., 2020). N-acetyl cysteine has been shown to propose dual antioxidant actions including scavenging capacity of reactive species and being the precursor of the non-essential amino acid, cysteine, essential for the synthesis of cellular antioxidant reductant glutathione (GSH; Soo et al., 2020). Classes of polyphenols were also investigated in numerous neurodegenerative models due to their well-established antioxidant activities (Anderson & Frazer, 2017; Carocci et al., 2018; Maiti & Dunbar, 2018; Pohl & Kong Thoo Lin, 2018). Catechin, curcumin, resveratrol, apigenin, among other natural polyphenols have demonstrated potent neuroprotective activities against brain's degenerative diseases (Mandel & Youdim, 2004; Maiti & Dunbar, 2018; Yammine et al., 2020). The possible mechanisms by which these polyphenols exhibited their neuroprotective activities via their antioxidant capacities were either the direct uptake and binding to the free radicals (scavenging mode) or the modulation of oxidant/antioxidant status favouring lesser oxidative stress status (enhancing antioxidant molecules/ enzymes and/ or inhibiting stress related enzymes). Together, these two mechanisms help reduce the oxidative stress condition, thus attenuating one major hallmark aggravating the neurodegenerative process in the brain; the oxidative stress status (Pérez-Hernández et al., 2016; Gutteridge & Halliwell, 2018). Studies have also revealed that lipid-soluble antioxidants, vitamins A and E; exhibited their neuroprotective activities through the prevention of the aggregation of Aβ plaques and lipid peroxidases in brain cells (Soo et al., 2020; Rai et al., 2021). Furthermore, participants consuming diets rich in

antioxidant vitamins showed lower AD and PD risks, indicating the undeniable neuroprotective activities possessed by these antioxidant vitamins (Logroscino et al., 2008). Blueberries; rich in their polyphenol contents; were also reported to have significant antioxidative advantages, that maintained proper mitochondrial functions and delayed the neurodegenerative processes of PD and AD by reducing amyloid aggregation (Knaze et al., 2018; Bianchi et al., 2021). While oleocanthal, a natural phenolic compound extracted from olive oil, given to mice prevented AD development through enhancing Aβ clearance from brain cells (Abuznait et al., 2013). These results support the regulation properties of the antioxidant system and its association to the improvement of cognitive function in neurodegenerative diseases (Van der Zwaluw et al., 2014). Moreover, olive oil rich in polyunsaturated omega-3 fatty acids inhibited Aβ and tau aggregation and enhanced their clearance in the brain, lowering by that the incidence of AD (Hubbard & Sinclair, 2014).

Despite the importance of both iron chelators and exogenous antioxidants therapies in the prevention/ treatment of neurodegenerative diseases, their complete successes are hampered by pitfalls. Iron chelators are typically of large weight molecules that are difficult to penetrate the BBB, making their reach and access to target brain cells difficult and limited (Mandel & Youdim, 2004; Carocci et al., 2018; Pohl & Kong Thoo Lin, 2018). They may also exhibit other undesirable side effects, shifting their wanted neuroprotective functions into harmful neurotoxic actions (Mandel & Youdim, 2004; Carocci et al., 2018). Moreover, the regional and subcellular characteristics of iron overload in brain cells, require specific treatment that target excess iron in specific brain regions without affecting the vital iron-containing proteins elsewhere, in this case, a feature that is absent in most iron chelators (Mills et al., 2010; Anderson & Frazer, 2017; Carocci et al., 2018). Meanwhile, exogenous antioxidants therapies alone showed little efficacy in readjusting the imbalanced redox status in patients with neurodegenerative disorders. This may be due to the presence of oxidative stress inducers, such as the excess prooxidant iron ions, that continuously produce various reactive species that are beyond the capacity of these exogenous antioxidants (Mills et al., 2010; Carocci et al., 2018). Moreover, literature has shown that the positive neuroprotective actions of selected exogenous antioxidants found *in vitro* and *in vivo* animal models were not produced in human clinical trials (Pohl & Kong Thoo Lin, 2018). This may be due to the complex antioxidant systems co-existing in the human brain and the presence of other factors hindering the postulated actions of the exogenous antioxidants (Renaud & Martinoli, 2019). Furthermore, the exogenous antioxidants' dosage commonly used in human clinical trials were below the effective concentrations seen in the *in vitro* and *in vivo* animal models (Pohl & Kong Thoo Lin, 2018). Difficulty in administering high concentrations of these antioxidants, possible undesirable side effects, and the fact that many of these exogenous antioxidants tend to switch to harmful prooxidant activities at higher concentrations, may explain the low concentrations used and the absence translation of the positive outcomes detected in the *in vitro* and *in vivo* animal models in human clinical trials (Pohl & Kong Thoo Lin, 2018; Renaud & Martinoli, 2019).

Therefore, combing these two therapies (chelators and antioxidants) or finding compounds that possess both properties and other neuro-enhancing molecules, as well as having minimum cytotoxic effects, are warranted. Recently, the direction of neuroprotective and neurogenerative therapies have shifted from the pharmaceutical, synthetic or natural, single iron chelator and/ or exogenous antioxidants drugs/ supplements, to focusing on whole diet modifications, rich in compounds with iron chelating, antioxidants, and other neurogenerative enhancing capacities (Sripetchwandee et al., 2014; Carocci et al., 2018; Ferreira et al., 2019; Soo et al., 2020; Rai et al., 2021).

1.2.2 Diet Modification

AD, PD, and other neurodegenerative disorders until now have no successful complete cure but rather preventive strategies or symptoms alleviating treatments (Lange et al., 2019). Lifestyle changes including diet habits and modifications, have been reported to show significant positive associations with delayed age-related disorders, especially the neurodegenerative diseases (Gardener & Caunca, 2018; Medina-Remón et al., 2018). Moreover, the neurodegenerative impact of the essential micronutrient iron, the neuroprotective importance of antioxidants, and the high susceptibility of brain lipids to oxidation, indicate the possible usage of diets in delaying or preventing various neurodegenerative disorders (Logroscino et al., 2008; Carocci et al., 2018; Gardener & Caunca, 2018; Mezzaroba et al., 2019; Popa-Wagner et al., 2020). Studies have shown that diets fortified with omega-3 fatty acids, vitamin D, B vitamins, and coenzyme Q may be beneficial in improving PD (Scarmeas et al., 2006; Marder et al., 2013; Lange et al., 2019). Furthermore, certain diet approaches, such as ketogenic diets and food restrictions, demonstrated significant impacts on the brain and peripheral metabolisms, immunology, and gut microbiota biology, all which can potentially help in the management of neurodegenerative disorders (Lange et al., 2019; Fontana et al., 2021). During normal brain aging and/or pathogenic central nervous system diseases such as AD, PD, amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS), interactions between calorie intake, meal frequency, diet quality, and gut microbiome resulted in the modulation of specific metabolic and molecular pathways that regulate cellular, tissue, and organ iron homeostasis, as well as inflammation pathways, two well-known hallmarks of many neurodegenerative diseases (Fontana et al., 2021).

Diets Rich in Iron Chelators, Antioxidants, and Neurogenerative Molecules

Numerous studies have shown a link between the consumption of foods rich in non-heme iron and neurodegenerative disorders (Kozlowski et al., 2009; Mezzaroba et al., 2019). Despite the low bioavailability of non-heme iron, its abundance and the presence of dietary enhancers compensate for such bioavailability. In a study

conducted by Logroscino et al. (2008), a higher risk of PD was detected in participants who consumed large quantities of non-heme products, mainly fortified grains and cereals, while consuming foods with high bioavailable heme iron did not show any correlation. Similar to non-heme iron, iron supplementations showed higher PD risk especially among men. Concomitant to large quantities of non-heme products consumption, lower dietary vitamin C intake was also monitored in participants with higher PD risk (Logroscino et al., 2008). Although vitamin C is one important dietary component that enhances the bioavailability of non-heme iron and hence, increase the possible harmful iron overload, yet its well-known antioxidant function may have lessened the iron-induced oxidation action, thus explaining the higher risk of PD with its low intakes (Grosso et al., 2013; Kocot et al., 2017). Several studies have also demonstrated that diets rich in nutritional antioxidants (e.g. polyphenols and vitamin E) delayed and, in some cases, blocked neuronal degeneration and death in both *in vitro* and *in vivo* models (Gilgun-Sherki et al., 2001; Coupland et al., 2014; Niki, 2014; Icer et al., 2021). For example, vegetables and fruits rich in various classes of polyphenols, especially flavonoids, were reported to exhibit neuroprotective activity via the actions of iron cheating, antioxidant, and anti-inflammation (Sofi & Dinu, 2016; Carocci et al., 2018; Di Renzo et al., 2021). Quercetin, resveratrol, and apigenin; three well-known polyphenols, showed neuroprotective activities against cell death inducer; 7-ketocholesterol (cholesterol oxidation product in age-related diseases) injected in mouse neuronal N2a cells. Among the three tested polyphenols, apigenin was considered the optimum neuroprotective candidate due to its minimum cytotoxicity, especially when used at higher concentrations (Yammine et al., 2020). In a review by Maiti and Dunbar (2018), the natural polyphenol curcumin was reported to show manifold actions on nervous cells, including antioxidant, anti-inflammatory, and anti-amyloid properties, as well as having low toxicity effects, high efficiency, and the ability to penetrate BBB. The review also highlighted the treatment potentials of curcumin for AD, PD, HD, and other neurodegenerative diseases (Maiti & Dunbar, 2018).

Due to the high susceptibility of brain lipids to oxidation and thus destruction, diets strengthening and providing essential raw materials for replacing these degenerated lipids are of highly importance (Walker et al., 2016; Salim, 2017; Carocci et al., 2018). Epidemiological studies investigating the presence of essential polyunsaturated fatty acids (PUFA) in individual diets revealed the positive association between the quantities of PUFA and the neuroprotective actions and the delay of neurodegenerative diseases (Ferreira et al., 2019; Bianchi et al., 2021). A study conducted by Serini et al. (2012) demonstrated that the addition of n-3 PUFA; eicosapentaenoic (EPA), reduced the proinflammatory markers release; the cytokines (IL-1β/IL-10 ratio and IL-6/IL-10 ratio) in AD patients. The n-3 PUFA docosahexaenoic acid (DHA), on the other hand, reverted the inflammatory profile of AD patients' cells similar to that observed in healthy patients and in a much more efficient manner than EPA (Serini et al., 2012). Various DHA supplements also showed protective properties against PD symptoms in mice injected with the dopaminergic toxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; Wang et al., 2018). The protective mechanism of these DHA supplements was hypothesized

based on the apoptosis inhibition through mitogen-activated protein kinase (MARK) and mitochondria-mediated pathways, which in turn resulted in the overall protection of the dopaminergic neurons against MPTP toxin (Wang et al., 2018). Ample studies have also demonstrated the effectiveness of ketogenic diet in the neuroprotection of brain cells (Rusek et al., 2019; Włodarek, 2019; Jensen et al., 2020; Bianchi et al., 2021). Ketogenic diet, composing mainly of high fat quantities and merely 10% of its daily calories were carbohydrates, promoted ketones bodies formation which improved neurons activities, reduced apoptosis and inflammation, and triggered autophagy, all which reduced the progression of the neurodegenerative diseases affecting brain cells (Włodarek, 2019; Jensen et al., 2020; Popa-Wagner et al., 2020). Despite the neuroprotective and neurogenerative effects of the ketogenic diet, the harmful side effects imposed by the high intake of fats, limits its potential usage as a preventive/ therapeutic agent for neurodegenerative diseases (Rusek et al., 2019; Bianchi et al., 2021).

Caloric Restriction Diets

Studies have shown that employing dietary restriction (DR) method improved the life span of AD and PD patients and, to some extent, alleviated the diseases' symptoms (Carocci et al., 2018; Bianchi et al., 2021; Fontana et al., 2021). Caloric restriction diet can be defined as the reduction in calories/ energy intake to less than 40% of *ad libitum* (diet available at all times), while maintaining the nutritional adequacy of all essential macro- and micronutrients (Ntsapi & Loos, 2016; Carocci et al., 2018). The possible protective activity of the brain's cells imposed by this type of diet may be explained via 3 possible mechanisms (Carocci et al., 2018; Fontana et al., 2021). The reduction in calories may cause medium intense stress on body's cells including brains cells, putting these cells in continuous stress environment, hence making them more adaptive and less prone to oxidative damage. The second possible mechanism of DR is that the cut-off of calories may reduce the intake of high caloric foods that are often rich in oxidative stress molecules and compounds, which in turn minimize/ eliminate any possible exogenous reactive species' molecules and/ or inducers (Ntsapi & Loos, 2016; Bianchi et al., 2021). The third possible mechanism of DR relies on the notion that low calories may trigger the autophagy process which is necessary for the recycling of abnormal protein aggregation and damaged brain cells/ organelles produced in brain's degenerative cells, eliminating endogenous sources of reactive species molecule and/or inducers (Carocci et al., 2018; Bianchi et al., 2021). The effect of DR on the gut microbiota (via gut-brain axis) is another hypothesized mechanism by which this type of diet may reduce the progression of various neurodegenerative diseases (Cox et al., 2019). Tg2576 mouse model of AD fed with DR showed altered gut microbes, reducing certain microbes (mainly *Bacteroides*) that are related to age-related diseases. These gram-negative bacteria exacerbated the deposition of Aβ plaques in brain cells, aggravating by that the AD progression (Cox et al., 2019). Another study demonstrated that DR alleviated age-related methylation changes at sites of specific CG methylation and

hippocampal CH methylation (Hadad et al., 2018). Attenuation the changes of these methylation sites contributed to the neuroprotective effects of DR in neurological disorders via epigenetic mechanism (Hadad et al., 2018). Regardless of the mechanism(s) by which DR exhibits its neuroprotective and neurogenerative activities, studies have shown its potential role(s) in neurodegenerative diseases, but warrants further investigations to validate such beneficial effects.

Mediterranean Diet

Epidemiological data has shown a strong association between Mediterranean diet (MD) and various health benefits (Scarmeas et al., 2006; Sofi & Dinu, 2016; Gardener & Caunca, 2018; Medina-Remón et al., 2018; Bianchi et al., 2021). MD is characterized by high intakes of fruits, vegetables, legumes, cereals, and unsaturated fatty acids (mainly olive oil). Moreover, its dietary composition is made of moderate intakes of dairy products and fish, while the intake of meat, poultry, and food products high in saturated fat are low (Scarmeas et al., 2006; Marder et al., 2013; Gardener & Caunca, 2018). This unique dietary composition attributes to the well-established and documented health benefits of the MD, which include antioxidant activities, anti-inflammatory capacities, neuroprotective actions, reduction of weight, improving sleeping quality, reduction risks of cardiovascular diseases, among many others (Sofi & Dinu, 2016; Rosato et al., 2019; Zaidalkilani et al., 2022). Recent cross-sectional research conducted on Arabic-speaking women revealed that following MD, as a good source of olive oil, was linked to improved sleep patterns and less insomnia symptoms (Zaidalkilani et al., 2022). A systematic review and meta-analysis of observational studies also showed an inverse association between MD and various cardiovascular diseases including coronary heart disease and ischemic stroke, but not with hemorrhagic stroke (Rosato et al., 2019). A study aimed on assessing the adherence to MD among adults and adolescents and its association with the inflammatory markers, showed an inverse relation between the degree of adherence to MD and the proinflammatory profile with differences regarding gender and age (Sureda et al., 2018). Higher adherence to MD was correlated with lower plasmatic high-sensitivity C-reactive protein (marker of low-grade inflammation) in male adults, lower levels of leptin (hormone secreted by adipose tissue), tumor necrosis factor alpha, and plasminogen activator inhibitor 1 (vital molecule linked to pathogenesis and progression of stroke) in both adult and adolescent males. While in females, higher MD adherence was correlated with lower levels of leptin (adolescents), plasminogen activator inhibitor 1 (adults), and plasmatic high-sensitivity C-reactive protein (adults and adolescents; Sureda et al., 2018). For neurodegenerative diseases, MD has been associated with reduced risk of AD (Scarmeas et al., 2006; Singh et al., 2014), PD (Alcalay et al., 2012; Paknahad et al., 2020), ALS (Gardener & Caunca, 2018; Caplliure-Llopis et al., 2020), and HD (Marder et al., 2013; Rivadeneyra et al., 2016; Gardener & Caunca, 2018). The proposed mechanisms by which MD exerts its neuroprotective action and, to a lesser degree its neurogenerative property, are the antioxidant properties, the

anti-inflammatory activities, the beneficial effects against cardiodiabesity/ cardiometabolic syndrome, and the favorable effects on gut microbiota possessed by its dietary composition (Sofi & Dinu, 2016; Gardener & Caunca, 2018; Paknahad et al., 2020). High intake of plant-based foods provides various bioactive components exhibiting antioxidant and/ or anti-inflammatory activities, while low intake of animal-based foods reduces the molecules/ components known to trigger oxidative stress and inflammatory reactions (Marder et al., 2013; Paknahad et al., 2020; Bianchi et al., 2021). A study conducted by Valls-Pedret et al. (2012) showed a strong association between MD components and improvements in the cognitive function present in age-related neurodegenerative diseases such as AD. The specific items examined in the MD that contributed to the observed neuroprotection activities were mainly virgin olive oil, coffee, and walnuts. These food items were rich in various polyphenol classes that exhibited strong antioxidant and anti-inflammatory activities, contributing to a better cognitive performance especially in elderly subjects with AD and high-risk cardiovascular diseases (Valls-Pedret et al., 2012). In PD patients, the high adherence to MD caused remarkable improvements in the parts of language, attention, concentration, active memory, and the total score of the cognitive function (Paknahad et al., 2020). Modified diets that directly or indirectly reduce iron overload and/ or oxidative stress, improve anti-inflammatory actions, reduce well-established risk factors, as well as improve gut microflora ameliorating the gut-brain axis, have shown promising results in the neurodegenerative diseases including those of the brain (Thursby & Juge, 2017; Sureda et al., 2018; Paknahad et al., 2020; Bianchi et al., 2021). Nevertheless, the inconsistency of the results obtained from the clinical trials, the complexity of the neuroprotective/ neurogenerative mechanisms, and the delicate brain inner systems including oxidant/ antioxidant system, demand further investigations of these diet modifications, along other nutritional interventions, to confirm their role(s) in the neurodegenerative diseases and to illustrate their exact neuroprotective/ neurogenerative pathways.

Gut Microbiota

Gut microbiota is a term that collectively refers to the microbial organisms, such as bacteria, fungus, and viruses, that are found in the gastrointestinal tracts of humans and animals (Tsai et al., 2018). Gut microbiota offers many benefits to its host including strengthening of gut mucosal and epithelial integrity (Macia et al., 2012), harvesting energy (Blaut, 2015), production of essential components (e.g. vitamins and short-chain fatty acids (SCFAs); LeBlanc et al., 2013; Blaut, 2015), protection against pathogens (Thursby & Juge, 2017), and regulation of the host immunity system via gut-brain axis (Macia et al., 2012; Blaut, 2015; Thursby & Juge, 2017). The gut-brain axis, which has been implicated in the course of many neurodegenerative illnesses, can be severely impacted by brain problems (Sharon et al., 2016). Numerous germs existing in the gut are mainly: Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia, and their profiles were found to be altered in many pathological conditions such as metabolic syndrome (Petra

et al., 2015), neurodegenerative diseases including AD and PD (Grasset et al., 2017), and irritable bowel syndrome (Wu et al., 2017). An enhanced inflammatory state in the gut has been also linked to an excess of Firmicutes in relation to Bacteroidetes, which in turn has been linked to severe amyloid expression (Minter et al., 2016). SCFAs synthesis and release were found to be reduced in the guts of PD patients, linking it to the disease's development and progression (Brandscheid et al., 2017). Orally administrated probiotics (*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus reuteri*, and *Lactobacillus fermentum*) significantly reduced the Movement Disorder Society-Sponsored-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), caused positive impacts on PD symptoms and metabolic profiles, and may had a significant impact on the gut microbiota in the study patients (Tamtaji et al., 2019). Intake of probiotics also resulted in a considerable reduction in insulin levels and insulin resistance, as well as an increase in insulin sensitivity (Tamtaji et al., 2019). The normalization of insulin metabolism could potentially lower the risk of diabetes and its consequences in PD patients (Lange et al., 2019). Two mechanisms were proposed for the crosstalk between the gut microbiota and the central nervous system (CNS) influencing the delaying or progression of various neurodegenerative diseases (Spielman et al., 2018). This vital crosstalk can be accomplished via the vagus nerve and/ or signaling molecules transmitted through the circulatory system and across the BBB. Vagus nerve emanates from the medulla oblongata of the brain and extends to numerous nerves supplying various signals to multiple body organs including the gut (Spielman et al., 2018). Certain bacterial strains were reported to utilize vagus nerve signalling system, causing alteration in brain functions and behavior (Cox et al., 2019; Fülling et al., 2019). Increasing *bifidobacterium* and *lactobacillus* bacteria counts in gut via probiotic injections led to the reduction of Aβ plaques and oxidative stress markers, hence improving brain functions (Spielman et al., 2018). Meanwhile, vital signaling molecules/metabolites produced by the gut microbiota can cross BBB and reach brain cells, affecting brain functions. Evidence has shown that SCFAs (e.g. butyric acid, acetic acid) released via gut microbial fermentation attenuate the pathological features of many neurodegenerative diseases (Fülling et al., 2019; Huang et al., 2021). SCFAs provided alternative energy source compensating the hypometabolism condition in brain with progressed neurodegenerative conditions. While specific SCFAs possessing neuroinflammation modulation activities alleviated the inflammatory conditions found significantly in AD, PD, HD, and other neurodegenerative diseases (Fülling et al., 2019; Huang et al., 2021). Despite the profound association between gut microbial dysbiosis and the risk of developing neurodegenerative diseases, the exact mechanism(s) by which this microbiota affect brain functions and consequently the onset and progression of brain neurodegenerative diseases remain complex and unclear justifying the need for further studies and investigation.

2 Iron Between Deficiency and Overload

Iron is without a doubt a vital mineral needed for the various physiological processes in the human body (Abbaspour et al., 2014; Gupta, 2014; MacQueen et al., 2017). It exists predominantly in the human body in two forms; soluble iron form (Fe^{+2}) and insoluble iron form (Fe^{+3}; Anderson & Frazer, 2017; Cerami, 2017; Bi et al., 2021). These two distinct iron forms can be obtained from a wide range of food sources such as meat, poultry, eggs, seafood/ fish, nuts, cereals, vegetables as well as fortified foods and dietary supplements (Trumbo et al., 2001; MacQueen et al., 2017). The precise iron concentrations are well kept in the human body via tight regulatory processes of the whole iron metabolism (Anderson & Frazer, 2017; Gao et al., 2019). Therefore, deranged iron metabolism eventually will result in the onset of either iron deficiency or iron overload conditions, that are equally detrimental for health (Wawer et al., 2018; Bi et al., 2021).

Iron deficiency, manifested as iron deficiency anemia, is a world health issue affecting nearly 2 billion people worldwide (McLean et al., 2009; Wawer et al., 2018). Mainly, iron deficiency anemia results from the high iron requirements that normal iron intake can't cover and/or the intake of diets low in bioavailable iron (Vandevijvere et al., 2013; Wawer et al., 2018; Bi et al., 2021). Infections, blood loss, other micronutrient deficiencies (e.g. vitamin B12, folate, Cu), as well as blood genetic disorders affecting specific population groups, are other causes for the onset of iron deficiency anemia (Johnson et al., 1994; Guralnik et al., 2004; Fairweather-Tait et al., 2014). Due to the high prevalence of iron deficiency anemia worldwide, international documents were established to indicate the daily iron requirements, dietary sources of iron, and iron supplementation recommended for different population groups, as shown in Table 3.1. These figures and numbers ensure the right amounts needed for each age group preventing the possible occurrence of iron deficiency anemia.

Meanwhile, iron overload, due to excess iron stores in the body, may lead to excessive production of reactive oxygen species, oxidation of vital biomolecules (lipids, proteins, and DNA), and subsequently organ damage (Wawer et al., 2018; Bi et al., 2021). Iron overload can be classified based on the etiology into primary iron overload (genetic defects in iron transport or regulation mechanisms) and secondary iron overload (pre-existing pathological conditions such as long-term blood transfusion treatment; Ferreira et al., 2019; Carocci et al., 2018). The prevalence and distribution of iron overload, detected mainly as liver and myocardial iron loading, differ significantly across geographical regions (Lok et al., 2009; Aydinok et al., 2015). Subjects from West region showed highest myocardial iron loading and lowest liver iron loading and serum ferritin levels compared to those of the Middle East and the Far East regions (Aydinok et al., 2015). Such variations may be due to differences in the subject's age, transfusion procedure, diseases' management practices, inherent population genes, and the prevalence of iron deficiency anemia which overshadow the reports regarding iron overload occurrence and prevalence (Lok et al., 2009; Aydinok et al., 2015).

Table 3.1 Daily iron requirements, dietary sources, and iron supplementation recommended for different population groups

Population group	Recommended daily iron intakes	Recommended dietary sources of iron	Iron supplementation
Pregnancy	27.0	**Iron-rich complementary food during pregnancy** (Milman, 2011): • Fish, poultry, seafood, eggs, red meat (beef, lamb). • Green vegetables (e.g. spinach). • Dried beans (e.g. lentils and chickpeas). • Nuts. • Iron fortified low sugar breakfast cereals. **Food affecting iron absorption** (Cerami, 2017): • Food rich in vitamin C (tomatoes, oranges, grapefruit, broccoli), enhance iron absorption. • Phytate (bran, oats, and rye fiber), dietary calcium (milk), polyphenols (cocoa, tea, and coffee), and soy proteins, decrease iron absorption.	**Indications** (CDC, 1998; World Health Organization, 2016): Haemoglobin concentrations are within normal levels: • Iron supplementation (30–60 mg/day) after approximately 12 weeks of gestation. Laboratory evidence of anemia during any pregnancy stage: • Iron supplementation (60–120 mg/day), preferably in divided doses. **Iron supplementation beneficial effects** (Peña-Rosas & Viteri, 2009; Stevens et al., 2013; Cerami, 2017): • Reduction of maternal iron deficiency anemia risk at birth. • No consistent benefits on maternal or infant outcomes for nonanemic pregnant women.
Lactation	10.0	**Same recommendations as those for the pregnancy stage** (Milman, 2011)	**Indications** (Milman, 2011; Jorgensen et al., 2017)**:** Iron supplementation is not required for healthy lactating women due to two main reasons: 1. No losses of iron as menstrual losses during the first 6 months of postpartum. 2. Lactating women can use the recycled iron accumulated during prenatal formation of maternal red blood cells (RBCs). **Iron supplementation beneficial effects** (Milman, 2011)**:**

(continued)

Table 3.1 (continued)

Population group	Recommended daily iron intakes	Recommended dietary sources of iron	Iron supplementation
			• For lactating women who suffered iron deficiency during pregnancy and/or a substantial blood loss during childbirth: Iron supplementation could be beneficial. • For women with adequate iron reserves after childbirth: Iron supplementation may pose some risk.
Infants and Children (Becker et al., 2004; Capra, 2006; Department of Health, 1991; World Health Organization, 2004; Trumbo et al., 2001)			
0–6 months; premature	2.0–4.0 mg/kg	**Premature infants** (Agostoni et al., 2008; Martin et al., 2016; Gupta et al., 2017; MacQueen et al., 2017): • Breast-fed, iron supplementation recommended from 2 weeks to 1 year of age. • Complementary food should be taken at age of 6 months. **Full-term infants (**Mohr & Huguelet, 2004; Agostoni et al., 2008; Mahoney, 2014; Schanler, 2016; Gupta et al., 2017): • Exclusive breastfeeding for 6 months. • Iron supplementation recommended to be given at the age of 4 months for breast-fed infants (elemental iron 1 mg/kg daily, maximum 15 mg/kg) until they can take enough quantities of iron-rich complementary foods). • For formula-fed infants, iron-fortified formulas should be used. • Complementary foods should be taken by 6 months of age. **Iron-rich complementary**	**Iron supplementation beneficial effects** (Domellöf et al., 2014): Breast-fed infants • Iron supplements do not reduce iron deficiency anemia in infants with already low iron levels. Formula-fed infants: • Iron-fortified formula prevents iron deficiency anemia and possibly improves neurodevelopment.
0–6 months; full-term	1.0 mg/kg		

(continued)

Table 3.1 (continued)

Population group	Recommended daily iron intakes	Recommended dietary sources of iron	Iron supplementation
		foods during the Neonatal Period and Early Childhood (Walter et al., 1993; Agostoni et al., 2008)**:** • Baby cereals (including fortified rice). • Meat (beef, chicken, and lamb). • Vegetables (peas, spinach, and green beans)	
6–12 months	5.8–9.0	**Recommended sources of iron** (Becker et al., 2004): • At least three servings of iron-rich foods/day are recommended. **Iron-rich complementary foods during Childhood** (Cerami, 2017)**:** There are two major dietary sources of iron: • Heme iron: Fish, meat, and poultry. • Nonheme iron: Fortified cereals, vegetables (lentils, spinach, and pumpkin seeds), nuts, and beans (lima, kidney, and navy beans).	**Indication** (Cerami, 2017; Mahoney, 2014): • Hemoglobin levels that are too low. • Being unable to obtain 3–4 servings of iron-rich meals each day. • Living in a region where iron deficiency is prevalent. **Iron supplementation beneficial effects** (Domellöf et al., 2014): • Possible improvement of neurodevelopment in infants and children populations with high prevalence of iron deficiency anemia.
1–3 years	6.1–10.0		
4–8 years	8.0–11.0		
9–13 years	11.0		
14–18 years (boys)	15.0		
14–18 years (girls)	5.8–9.0		
Adults (postmenopausal women)	8.0	**Recommended sources of iron (**Fairweather-Tait et al., 2014)**:** • Iron requirements are same as those for menopausal women. • Dietary sources for iron are also the same as those for adult and elderly men and women.	**Indications** (Trumbo et al., 2001): • Upon hormonal replacement therapy (commonly prescribed for postmenopausal women), uterine bleeding may occur which justify the need for higher iron requirements via diet or iron supplementations. **Iron supplementation beneficial effects** (Trumbo et al., 2001): • No beneficial effects of additional iron supplementation due to the absence of menstrual losses in postmenopausal women.

(continued)

Table 3.1 (continued)

Population group	Recommended daily iron intakes	Recommended dietary sources of iron	Iron supplementation
Adults older than 65 years	8.0	**Elderly** (Fairweather-Tait et al., 2014): • Older adults might find it challenging to obtain adequate supplies of iron due to reduced food intake, lower physical activity, and impaired absorption. **Recommended sources of iron** (Fleming et al., 2001, 2002): • Food rich in heme iron (e.g. fish, liver, lean meat), and nonheme iron (e.g. cocoa, spinach, thyme, fortified cereals) are recommended. • High intakes of red meat and vitamin C have been shown to be potential factors determinant for iron status in this population group.	**Indications** (Johnson et al., 1994; Guralnik et al., 2004; Fairweather-Tait et al., 2014): • Impaired iron metabolism is detected in old age, where iron reserves may greatly increase especially in age-related degenerative diseases. • Iron deficiency anemia is also prevalent in older adults (corrected via diet or iron therapy). • **Iron supplementation beneficial effects** (Fairweather-Tait et al., 2014):Might prevent health problems associated with iron deficiency anemia but may also lead to detrimental effects related to iron overload. • Due to the delicate balance of iron in older adults, personalized approaches in marinating correct iron range in older adults are needed to avoid both iron deficiency and/ or iron overload.

Similar to other age groups, the elderly group requires significant iron intake for proper body metabolism and functions (Fleming et al., 2001; Guralnik et al., 2004; Fairweather-Tait et al., 2014). However, this vulnerable age group faces a dilemma regarding the iron levels present in their body. Studies have shown that iron metabolism is adversely altered with age, whereby the delicate and precise mechanisms governing the bodily iron metabolism are being compromised resulting in iron dyshomeostasis (Wawer et al., 2018; Bi et al., 2021). On one hand, the elderly are prone to iron deficiency due to the main causes faced by other age groups and to additional deficiency causes coexisting primary in this age group. Loss of appetite, lower physical activity, higher prevalence of chronic diseases and inflammation, regular intake of medication, impaired bodily organs' functions especially those related to iron absorption, and the occurrence of occult blood loss, among other causes, are predominantly present in the elderly group that contribute to the onset of

iron deficiency anemia (Johnson et al., 1994; Guralnik et al., 2004; Wawer et al., 2018). On the other hand, increased bodily iron stores has been also reported in the elderly group and is more pronounced in older women than older men, possibly due to onset of menopause (no iron loss related to menstruation, pregnancy, or lactation; Fairweather-Tait et al., 2014; Wawer et al., 2018; Bi et al., 2021). The other possible explanation for such elevated iron stores in the elderly age group was associated with the fluctuation intake of various dietary factors. Higher risk of increased bodily iron stores were directly related to intakes of >3 servings of fruits/ fruit juices/day, >4 servings of red meat/ week, ≥ 30 mg/day of iron supplements. While intakes of >7 servings/week of wholegrain were inversely related with higher risk of elevated iron stores (Fleming et al., 2001; Fairweather-Tait et al., 2014). The iron overload whether primary, secondary, or even moderately elevated, has been implicated with several chronic diseases, such as heart diseases, diabetes, cancer, and various brain neurodegenerative diseases (Fleming et al., 2001; Wawer et al., 2018; Galaris et al., 2019; Bi et al., 2021). Iron overload, as mentioned at the beginning of this chapter, is one undeniable feature seen in various brain degenerative ailments (Chiueh, 2001; Carocci et al., 2018; Kausar et al., 2018). The usage of iron chelators and antioxidants (neutralize /eliminate free radicals induced by excess iron ions) as potential therapeutic strategies for brain degenerative ailments further supports the strong association between iron overload and these neurodegenerative diseases (Matteo & Esposito, 2003; Bulbake et al., 2019; Icer et al., 2021; Sheikh et al., 2021). Thus, based on the sufficient evidence linking iron overload, especially in elderly population, and adverse health effects on the brain, justify the need for dietary management, lifestyle changes, and/or iron therapy (Fleming et al., 2001; Wawer et al., 2018; Bi et al., 2021). Nevertheless, knowing that the elderly population is also prone to iron deficiency anemia, it is vital to ensure that this vulnerable age group receives the optimum iron intakes that prevent the occurrence of iron deficiency as well as iron overload. Established data (Table 3.1) detailing the iron requirements (either from dietary sources or supplements) and the constant analysis of blood/ bodily iron levels can be helpful tools used to maintain iron levels (particularly in the elderly age group) within the normal range without the fear of the onset of the iron deficiency anemia and /or iron overload and their subsequent diseases.

3 Conclusion

In conclusion, nutrition interventions represent an essential and an undeniable strategy in preventing or combating neurodegenerative diseases caused by iron overload, oxidative stress status, and/ or inflammation conditions. These therapeutic nutritional interventions include, but not limited to, exogenous antioxidants, nutritional iron chelators supplements, and diet modifications that reduce iron overload directly (e.g. low iron diets) or indirectly (iron chelators, exogenous antioxidants), alleviate oxidative stress status (e.g. iron chelators, dietary antioxidants, enhanced

endogenous antioxidants), eliminate the oxidative and inflammation biomarkers (e.g. autophagy), and/ or modulate the gut microbiota that influences the gut-brain axis signalling. Despite the promising outcomes observed in the *in vitro*, *in vivo*, and some human clinical trials of these therapeutic nutritional interventions, caution should be taken when interpreting these results. Conflicting results have been reported, absence of positive outcomes has been observed, especially in human clinical trials, and the underline mechanism(s) postulated for the neuroprotective/ neurogenerative actions are still to date ambiguous and unclear. Furthermore, it is important to highlight the fact that the elderly population, who are at a higher risk of developing various brain neurodegenerative diseases, may also face the onset of iron deficiency anemia concomitant with the preexisting iron overload state. Hence, more studies and investigations are warranted to overcome the pitfalls counteracting the potentials of the therapeutic nutritional interventions in preventing/ treating neurodegenerative diseases, especially in the high-risk population groups.

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Chapter 4
Mediterranean Diet and Neuro-Cognition: Focus on Alzheimer Disease

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1 Introduction

Lately, the importance of the Mediterranean diet (MD) and its benefits have received special attention. The MD notion was developed in the 1950s by Keys referring to the eating nature observed in all countries in the Mediterranean basin. The traditional MD is the patrimony of millennia of exchange of cultures, people, and foods from Mediterranean region (Serra-Majem et al., 2019). The MD is characterized by an elevated intake of plant-based foods; legumes, fruits, seeds and nuts, bread and other forms of cereals. In addition, the MD also contains moderate proportion of dairy products, medium amounts of poultry and fish, and lastly, small quantities of wine (consumed moderately with meals) and red meat (Kafatos et al., 2000).

Different factors have interacted to modify the MD such as: development of retail trade, reduction of household size and number of generations living together, urbanization, globalization and integration of women into the labor market) by introducing remarkable change in the distribution and sale of food, in crop selection, in animal husbandry techniques and in lifestyles. This changes implies on the one hand the socio and economic aspects including food waste is elevating throughout the food chain due to mediocre processes and techniques harvesting, climatic conditions, reduction in number of small farmers and problems in logistic and storage procedures, and on the other hand, the loss of practices and knowledge that have historically play a part to the identity of Mediterranean regions persons and build a rich food universe in this region. Moreover, socio-economic changes have exceedingly affected the Mediterranean people lifestyle, conducting to the westernization of food intake patterns in the Mediterranean basin. (Serra-Majem, 2012; Bach-Faig et al., 2011; Serra-Majem, 2008).

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The role of the MD in the prevention of some chronic illness had stimulated the appetite of many researchers to study this diet in the last two decades. Several randomized trials and eventual studies have contributed consistent proofs on the beneficial effect of embracing a MD on the risk of type 2 diabetes (Abiemo et al., 2013; Itsiopoulos et al., 2011; Esposito et al., 2009; Martínez-González et al., 2008). In addition, a previous meta-synthesis associated high adherence to the MD with a decreased risk of some disorders including metabolic disorder and its resolution (Kastorini et al., 2011).

As in for the elderly, studies have previously confirmed its role in reducing mortality, preventing age-related diseases, and achieving longevity (Trichopoulou et al., 2015; Knoops et al., 2004; Lasheras et al., 2000). Cognitively, according to two meta-analyses, high adherence to the MD was associated with significant cognitive function, lower rates of cognitive impairment, and increased risk of dementia and Alzheimer's disease (AD) (Cao et al., 2016; Lourida et al., 2013). Since the earliest writings on the persons with a chronic cognitive impairment, a transactional association has been described between the MD and cognitive abilities. Hence, the goal of this chapter is to highlight recent evidence that advance the preventive effect of MD on the cognitive abilities among both the patients with or without AD.

2 Mediterranean Diet and Cognitive Health

Cognitive abilities viz. memory, thinking, learning, writing, speech, drawing, receptive and expressive capacities are all brain activities that permit us to learn, remember and recognize to transitional environmental situations (Klimova et al., 2021). A failure in these functions results in a neurodegenerative disturbance known as dementia, related with a dropping of cognitive functions (Klimova et al., 2021). Dementia is a progressive disturbance, which progressively restraints self-sufficiency and autonomy of individuals in first stages, and it is can promote their disability in later stages (Klimova et al., 2016). Consequently, it is important to try to stop the evolution of brain structure degeneration. Till now, there is no permanent cure for dementia, but it might be at most delayed by both non-pharmacological and pharmacological approaches (Szeto & Lewis, 2016). The non-pharmacological approach, have been proven to protect significantly the progression of cognitive decline in elderly persons (Klimova et al., 2017). In parallel, the pharmacological treatments may only delayed the pathological process and ameliorate temporarily the mental health of the affected person. There exist generally four main medicaments, such as rivastigmine, donepezil, galantamine (acetylcholinesterase inhibitors) and an N-methyl-Daspartate antagonist (memantine) (Klimova et al., 2015).

Several observational researches have evaluated the relation between cognitive capacity and the MD. in this context, numerous systematic reviews revealed that the MD is linked with a decreased risk of dementia and cognitive deficient (Hardman et al., 2016; Cooper et al., 2015; Van de Rest et al., 2015; Singh et al., 2014; Lourida

et al., 2013; Sofi et al., 2010a), and a decreased decline in cognitive ability, including executive function and episodic memory (Hardman et al., 2016; Petersson & Philippou, 2016; Knight et al., 2017; Van de Rest et al., 2015; Lourida et al., 2013). Nevertheless, results regarding the impact of the MD on the cognitive functions of elderly persons without cognitive deterioration remain uncertain in several reviews, which can be attributable to many reasons. Since 2010, three meta-analyses that demonstrated the relation between MD and the risk of cognitive impairment especially in AD patients. (Singh et al., 2014; Psaltopoulou et al., 2013; Sofi et al., 2010a), till now, there is no meta-analysis that investigated quantitative measures of the relation between the specific cognitive capacities and MD of elderly persons. Numerous cohort studies, grouped analysis resulted in remarkable relation between cognitive functions and MD, although investigations of individual studies revealed a relation between MD and cognitive functions especially reasoning and processing speed. This result is surprising at some degree, considering the conclusions of many published systematic reviews in this field (Hardman et al., 2016; Van de Rest et al., 2015; Lourida et al., 2013). This can, nevertheless, be elucidated by the addition of cross-sectional results in all other systemic reviews, except one (Hardman et al., 2016). For instance, one included investigation didn't reveal any relation between the change in global cognitive and the MD, however, a second analysis of the relation between the global cognitive capacity mean score and MD resulted in a highly significant cross-sectional relation ($p < 0.01$) (Samieri et al., 2013). Additionally, three recent cohort studies investigated the relation between MD and cognitive functions. The first one included 279 Italian subjects aged 65+ years, revealed that MD is linked with a significant decreased risk of cognitive deficient, The second included 2092 Greece elderly persons divided into two groups cognitive healthy group and unhealthy group, there results showed that better cognitive functions is significantly associated with Higher MD adherence (Mantzorou et al., 2021; De Amicis et al., 2018). The last cohort study-cross-sectional in The United States of America conducted by Karstens et al. (2019) included 82 healthy elderly persons aged 68+ years, divided into two groups (low adherence group to MD and high adherence group to MD), the main findings revealed that the high adherence group to MD was significantly better than low adherence group to MD at memory and learning performance ($p < 0.01$).

Likewise, previous randomized controlled trial has evaluated the relation between cognitive functions and diet adherence. The first randomized controlled trial included 44 Spanish persons with AD aged 65+ years, divided into two groups: the first group followed a MD (control group; $n = 22$), while the second group followed a coconut oil enriched MD (experimental group; $n = 22$), the adherence to MD lasted 21 days, and the results obtained showed that temporal, episodic orientation, and semantic memory have been improved in the experimental group (de la Rubia Ortí et al., 2018). Another randomized controlled trial conducted by Mazza et al. (2018) on 80 elderly Italian patients divided into two groups control group ($n = 40$) and experimental ($n = 40$) group followed MD enriched with extra virgin olive oil (EVO-O), the exposition to this Diet lasted 10 weeks and the findings revealed that after 1 year, a remarkable reductions of AD Assessment Scale

Cognitive scores in the group exposed to MD enriched with EVO-O than the control group exposed only to MD (−3.0 vs. −1.6 respectively). Another randomized clinical controlled trial involved 80 Iranian patients with Parkinson disease (aged more than 60 years) demonstrated that the mean score of the dimensions of some cognitive functions including concentration, language, flexible thinking, attention, active memory and and self-control were significantly elevated in the experimental group adhered to MD ($p < 0.05$) (Paknahad et al., 2020). A recent randomized controlled trial included 1279 elderly (aged between 65 and 79 years) reparted on 5 European centers, this patients were divided into two groups intervention group (adhered to habitual diet; $n = 641$) and control group (adhered to MD; $n = 638$), while the results obtained revealed that persons with higher adherence to the new dietary strategies in Europe experienced after 12 months a significant amelioration in episodic memory and global cognition compared to the persons with lower adherence to this diet (Marseglia et al., 2018).

3 Mediterranean Diet and Alzheimer Disease

The traditional MD is characterized by a high intake of plant-based food. Olive oil, which is considered the main source of monounsaturated fats, accompanied by a low intake of saturated fats coming from meats and poultry. Fish and dairy products are generally eaten in moderation (Willett et al., 1995). Similar to the preventive role of the MD against diabetes, cancer and cardiovascular disease, it could also have a positive effect against cognitive impairment in the elderly, as it combines divers foods and nutriments such as olive oils, antioxidants compounds, fish and vitamins B12 and B9, these elements are significantly protective against cognitive decline (Reynolds, 2006; Solfrizzi et al., 2006; Gómez-Pinilla, 2008; Luchsinger & Mayeux, 2004; Engelhart et al., 2002a; Letenneur et al., 2007).

Currently in the absence of a successful curative approach for AD, exposition to the MD may be the good strategies in the prevention of AD. In a meta-synthesis, relating to five out of 664 studies reviewed. Subjects in the highest tertile of adherence to the MD had a 33% reduced risk (Odds Ratio = 0.67; $p < 0.000$) of cognitive dysfunction or Alzheimer's versus those in the lowest tertile. In individuals with normal cognitive abilities, greater exposition to the MD was linked significantly with a decreased risk of cognitive decline (Odds Ratio = 0.73; $p < 0.05$) and AD (OR = 0.64; $p < 0.01$) (Singh et al., 2014). In a longitudinal study of 2258 individuals without dementia, the objective was to explore the relation between the risk of AD and the adherence to the MD and. After 4 years of follow-up, compared to subjects in the lowest tertile, participants in the highest tertile of adherence to the MD had a lower risk factor (Odds Ratio = 0.60; 95% CI, 0.42–0.87) of getting AD (Scarmeas et al., 2011). These results show the benefit to the elderly in adopting a balanced diet rich in plant-based food, monounsaturated fatty acid, and low in meat and animal fats to decrease the risk of developing AD.

3.1 *Fish, Dietary Fatty Acids and Risk of Cognitive Decline and Alzheimer's Disease*

The link between the consumption of unsaturated fatty acids (UFAs) and cognitive impairment has been revealed in a increasing number of longitudinal, clinical and cross-sectional studies that have investigated the association between the administration of UFAs and cognitive function (Solfrizzi et al., 2010; Cunnane et al., 2009; Berr et al., 2009; Vercambre et al., 2009; Psaltopoulou et al., 2008; Eskelinen et al., 2008; Solfrizzi et al., 2005; Morris et al., 2004; Kalmijn et al., 2004). Monounsaturated fatty acids (MUFAs) were the most important fat in the MD due to the high intake of virgin olive oil (VO-O). Cumulative proofs suggest that EVO-O can play a major role in protecting against cognitive impairment (Solfrizzi et al., 2011).

The possible connection between the risk of AD and dietary fatty acid consumption has also been assessed in previous longitudinal studies with contrasting results (Barberger-Gateau et al., 2007; Laitinen et al., 2006; Morris et al., 2003; Engelhart et al., 2002b; Luchsinger et al., 2002; Barberger-Gateau et al., 2002). Nevertheless, several evidence demonstrated that an elevation in saturated fatty acid (SFA) consumption might have negative impacts on cognitive abilities, while a marked reduction in the risk of cognitive impairement was seen in samples of population with a high consumption of fish, as well as a high consumption of UFAs, particularly omega-3 (Solfrizzi et al., 2010). in point of fact, fatty fish are the main source of polyunsaturated fatty acids (PUFAs) in MD. Recently, baseline data from OPAL (the Older People) study on long-chain PUFAs suggests that high fish intake is linked with better cognitive capacity at older ages (Dangour et al., 2009).

3.2 *Olive Oil and Risk of Cognitive Decline and Alzheimer's Disease*

Olive oil is a component of the MD composed generally of non-glycerol fraction (5%) and glycerol fraction (95%) called saponifiable fraction (Tripoli et al., 2005). The non-glycerol fraction contains mainly phenolic compounds which react against oxidative stress, while the glycerol fraction is rich in MUFAs such as Oleic acid (18:1n-9) (Cicerale et al., 2010). Moreover, the non-glycerolated fraction possess many non-fatty elements, including vitamin E, carotenes, squalene, chlorophyll and in particular, a number of phenolic compounds with remarkable biological potential including antioxidant and anti-inflammatory proprieties. The majority of phenolic compounds including complex phenols such as oleuropein, lignans and its conjugated forms and simple phenols such as tyrosol and hydroxytyrosol (derive from the hydrolysis of oleuropein) (Tripoli et al., 2005; Owen et al., 2000).

Olive oil is classified according to the criteria of quality and purity in the following order: VO-O and EVO-O, and refined olive oil (Virruso et al., 2013). The EVO-O which is most recommended for healthy aging, contains an acidity,

presented as free oleic acid, of less than 0.8% with the preserved polyphenols (Virruso et al., 2013). VO-O possesses acidity inferior to 0.2%, and like EVO-O, it conserves proportionately elevated quantities of unsaponifiable and a large quantity of phenolic compounds or tocopherols, but when refining, most polyphenols are then lost (Aiello et al., 2015). However, the two products "VO-O" and "EVO-O" constitute a real juice, and referred by the general term "virgin olive oil", because they have a similar chemical composition and that their differences are gastronomic in nature (Pérez-Jiménez et al., 2007). The total phenolic quantity in the VO-O is estimated at 500 mg/kg and includes more than 30 chemicals products belonging to various classes, such as acid and volatile compounds, and esters. (Tuck & Hayball, 2002).

Much evidence has been observed regarding the beneficial activities of the minor components which are highly bioactive elements of olive oil. As part of the MD. A particular attention has been paid to the daily intake of VO-O Previous studies have revealed that consuming VO-O improved significantly some cognitive functions including memory and learning in SAMP8 mice and reversed age-related dysfunctions in elderly mice (Farr et al., 2012; Pitozzi et al., 2012; Pitozzi et al., 2010). In addition, several experimental studies, have demonstrated that olive oil reduced significantly the 42-residue form of the amyloid β peptide (Aβ42) deposits, suppression of pE3-Aβ generation, elevate the autophagic markers expression via mTOR inhibition and decreased the oxidative stress products (Luccarini et al., 2015; Pasban-Aliabadi et al., 2013; Diomede et al., 2013). In humans, significant evidence demonstrated that VO-O can present a crucial protective effect against cognitive impairment (Solfrizzi et al., 2006). Furthermore, the exposition to the MD supplemented with EVO-O, during 10 weeks revealed a significant decrease of AD Assessment Scale Cognitive scores (Mazza et al., 2018). Furthermore, a recent review has shown that the use of EVO-O in diet has a significant effect on the delay of cognitive impairment, while a longitudinal relation between cognitive impairment and this oil intake were observed (Klimova et al., 2019).

3.3 Dairy Products and Risk of Cognitive Decline and Alzheimer's Disease

In general, little work has have been addressed to the potential role of dairy products in controlling the risk of cognitive decline or AD. In spite of recent observational, epidemiological, and intervention research providing evidence for the effect of dairy products in modeling the risk factors of cardiovascular disease and decreasing the prevalence of syndrome related-metabolic. Consumption of dairy products can decrease the risk of cognitive impairment, either directly or through mediating effects on cardio-metabolic health (Crichton et al., 2010). A cross-sectional study revealed that women with mediocre cognitive ability absorbed remarkably less the milk products when compared with normal cognitive capacity (Lee et al., 2001), and

another investigation demonstrated that higher cheese consumption was associated with a reduced probability of cognitive decline, whole milk consumption was not linked with cognitive deficient (Rahman et al., 2007). A recent review presented recent advances concerning the neuroprotective impacts of dairy products consumption against cognitive impairment and dementia (Ano & Nakayama, 2018), Oleamidein fermented dairy product induced into the M2 anti-inflammatory phenotype some microglia (enhances microglial phagocytosis) and suppresses inflammation, leading to brain protection.

3.4 *Tea, Coffee and Risk of Cognitive Decline and Alzheimer's Disease*

Observational researches indicate that tea consumption was linked with lower risks of cognitive decline (Feng et al., 2010; Ng et al., 2008), and that the preventive effect is not limited to a specific type of tea (Feng et al., 2010). Compared to placebo group, black tea has been revealed significantly improved visual and auditory attention (De Bruin et al., 2011). Green tea polyphenols may protect against cognitive deficient by attenuating oxidative stress (Xu et al., 2010; Mandel et al., 2008; Weinreb et al., 2004). Coffee consumption may also be linked with a reduced risk of AD (Eskelinen & Kivipelto, 2010). A tendency for a preventive effect of caffeine on AD has been reported (Arendash & Cao, 2010). Coffee could be the best source of caffeine to limit AD development, due to a component in coffee that works synergistically with caffeine to selectively increase plasma cytokines (GCSF levels) (Cao et al., 2011). A cumulative review of 4 investigations (two cohorts and two case-control studies) revealed that coffee intake inversely linked with the risk of AD (Barranco Quintana et al., 2007).

3.5 *Fruits, Vegetables and Risk of Cognitive Decline and Alzheimer's Disease*

Fruits and vegetables are mainly rich in vitamins and antioxidants, may also play a preventing effect against cognitive deterioration and delaying the onset of some neurodegenerative disease. Various studies have revealed that the prevalence of AD to be much greater in African people (Hendrie et al., 1995) and Japanese living in the United States (6.24 and 4.1% respectively) (White et al., 1996) than those still living in their country of origin, reporting that the prevalence of AD is influenced more by nutrition, lifestyle and environment than by genetics.

Given, the possible role of vascular factors in cognitive decline (Solfrizzi et al., 2008), high intake of vegetables and fruits appears to decrease significantly the risk of stroke and coronary artery disease (Mizrahi et al., 2009), and can, therefore,

decrease cognitive impairment. In point of fact, bioactive compounds found in vegetables and fruits, play a potential protective effect against oxidative stress products. These compounds are associated to aging and to the pathophysiology of certain age-related diseases, in particular cognitive disturbance and dementia (La Rue et al., 1997).

In a meta- synthesis of cohort studies that investigated the relation between fruit and vegetable consumption and the risk of developing cognitive deficient (AD, dementia, and cognitive decline). Pooled analysis revealed that fruit and vegetable intake is inversely linked with the risk of cognitive impairment (Wu et al, 2017).

4 Possible Mechanisms of Mediterranean Diet

The MD present a valuable source of nutraceutical products including, antioxidants, unsaturated Fatty Acids, vitamins and phenolic compounds that can control the involved biological mechanisms of cognitive disrtibunce (Feart et al., 2015; Frisardi et al., 2010; Sofi et al., 2010b). These possible mechanisms could cover a reduction of oxidative stress by enhancing the oxidative stress enzymes and reduce the Reactive oxygen species (ROS), improved inflammation and controlling metabolic factors (Frisardi et al., 2010; Scarmeas et al., 2011).

Previous clinical findings have revealed that exposition to MD result a remarkable decrease in the levels of oxidative stress and inflammatory markers, with a significant reduction of cardio-diabesity risk (Whalen et al., 2016; García-Fernández et al., 2014). A double trail study (cross-sectional study within a longitudinal population-based cohort analysis) in Northern Manhattan region included more than 1000 participants, examined the relation between the MD and the white matter hyper-intensity volume (WMHV) (Gardener et al., 2012). The main results of this study revealed that a MD was related with lower WMHV burden, which explain the protective relation between diseases related to small vessel and adherence to the MD. Nevertheless, WMV are etiologically heterogeneous and could comprise neurodegeneration. It was revealed that consuming regularly a MD reduced significantly the stroke risk in persons at high vascular risk (Estruch et al., 2013). Furthermore, another study included French older subjects ($n = 146$), reported a significant relation between the higher adherence to MD and the protected structural connectivity of white matter in multiple brain areas (including parahippocampal fornix, anterior thalamic radiations, paracingulate gyrus, cingulum and genu, body, splenium corpus) associated to ameliorate executive function, episodic memory and global cognition (Pelletier et al., 2015). A new support favoring ameliorated cognition two studies (Estruch et al., 2013; Scarmeas et al., 2011). The first one, reported an important relation between stroke prevention and MD consumption, while the second study, demonstrated that decreased cerebrovascular capacities through vascular mechanisms comes from disease was linked with adherence to the MD.

Neuroimaging study investigating components of the MD reports that lower meat intake and higher fish intake were associated with higher total brain, white and gray

matter volume (Gu et al., 2015). Moreover, limit consumption of meat products was linked to greater total brain volume and better global cognition (Titova et al., 2013). In contrast, the mains findings of a previous neuroimaging study did not reveal any significant evidence for a vascular mediation between patients with AD and MD adherence (Scarmeas et al., 2011). While, another support for brain protection (nonvascular mechanisms) by the MD comes from a randomized clinical trial, in which an increased concentration of brain derived neurotrophic factor in different areas and decreased in depression symptoms were linked with high MD consumption (Valls-Pedret et al., 2015).

5 Conclusion

Given the rising incidence of cognitive impairment in population, especially in elderly persons with Neurodegenerative diseases. Their prevention has become one the important and urgent action of public health, which conducts to the defiance of achieving optimal control and delaying its development, and their probable risk to induct other cognitive functions complications. Also, the possible unbearable costs to patient in terms of decreased quality of life. Therefore, adherence to a diet to prevent the development of cognitive disorders remains a desirable and cheaper solution. Previous studies have shown a significant relation between the adherence to MD and cognitive functions improvement in vulnerable patients especially patients with AD. Moreover, several findings from clinical and experimental studies have revealed evidences of some benefit of the MD on cognitive functions including working memory, reasoning, delayed recall, and processing speed.

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Part II
Brain Disorders Related to Iron

Chapter 5
The Critical Roleplay of Iron Neurochemistry in Progression of Parkinson's Disease

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1 Introduction

Metals such as sodium (Na), potassium (K), calcium (Ca), zinc (Zn), copper (Cu), manganese (Mn), iron (Fe), Aluminium (Al), nickel (Ni), and others played a role in human evolution. For the human body, iron is a vital trace element and a crucial component of metalloprotein. (Evstatiev & Gasche, 2012). It is also vital for normal physiological and metabolic functions of normal human functioning, such as transport of oxygen, synthesis of DNA, iron-sulphur cluster production, synthesis of neurotransmitter, and transfer of electron in the electron transport reaction, due to its specific chemical reaction features (Conway & Henderson, 2019; Lane et al., 2018; Ashraf et al., 2018). Iron is found in 3–5 g in the normal adult human being (Evstatiev & Gasche, 2012). Not only for the body, but Iron is also equally necessary for the appropriate development and activity of the brain. In body it is required for cell proliferation, DNA synthesis, the mitochondrial respiratory chain, and the generation of myelin and neurotransmitters (Connor & Menzies, 1996; Hoepken et al., 2004). Oligodendrocytes act as the storehouse for the most iron for myelin production in the neurons of the locus niger and surrounding areas (Connor & Menzies, 1996). Microglia, which operate as the brain's scavenger cells, have been found to collect iron and may contribute to neuronal cell death prevention (Oshiro et al., 2008; Toku et al., 1998). Astrocytes in comparison retain a lower physiological level of iron, have significant unutilized iron storage capacity, and might play a neuroprotective role from oxidative stress (Toku et al., 1998). When compared to astrocytes, oligodendrocytes, and microglia, research shows that

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neurons are more vulnerable to both iron shortage (Sengstock et al., 1992; LaVaute et al., 2001; Kress et al., 2002) and excess (Moos et al., 1998).

The iron spreading in the brain seem to be somewhat uneven, and those levels have been linked to age. As per histological and biochemical research, the Substantia Nigra and globus pallidus in normal human brains, as well as rats and monkeys brain, have the richest quantities of iron. A recent research that measured iron levels directly in typical human brain cells discovered that the putamen and globus pallidus had the greatest amounts, and that there was a powerful affirmative tie-up between iron levels in the basal ganglia and age.

Iron is plentiful in dopaminergic neurons of Substantia nigra as a fundamental part of tyrosine hydroxylase-dependent dopamine synthesis because it is required for tyrosine hydroxylase-dependent dopamine production as well as other enzymatic and non-enzymatic dopaminergic metabolic pathways (Hare & Double, 2016). Iron's accelerating function in the creation of harmful ROS through Fenton reaction comporising hydrogen peroxide might be explained by the discovery of significant brain labile nonheme high-spin complexes, which grow with age (Holmes-Hampton et al., 2012). This is due in part to monoamine oxidase's oxidative deamination of dopamine and the creation of smectic iron-dopamine complexes, which cause dopamine auto-oxidation and quinone generation. The Substantia nigra has a particular pigmentation due to the trapping of numerous potentially harmful compounds by neuromelanin. However, because the neuromelanin is site for toxins is eliminated in Parkinson's disease, (Hare & Double, 2016). The instable endogenous autooxidation byproducts of dopamine can severely disrupt mitochondrial complexes I and IV respiration. Due to the excessive energy requirement of independent pacemaking, the Substantia nigra may be particularly vulnerable to labile iron imbalances and ultimately resulting in ROS generation.

In recent years, an increasing number of researchers working on exploring the pathophysiology of Parkinson's disease (PD) have shown that oxidative stress caused by iron metabolism disorders, as well as the creation of reactive oxygen species (ROS), are linked to the degenerative process of the disease.

The second most reccurent neurodegenerative disease is Parkinson's disease. Older age is the sole definite prospect for development of the disease (Tanner & Goldman, 1996). In populations of European heritage, the male to female ratio appears to be more than one (de Lau & Breteler, 2006). loss of dopaminergic neurons (DA) in the Substantia nigra (SN) pars compacta (Forno, 1996), buildup of aggregates of protein synuclein known as Lewy neurites or Lewy bodies in the SN (Spillantini et al., 1997), and brain iron cumulation further on seen in non-PD brains of comparable age are all characteristic traits of Parkinson's disease (Sofic et al., 1988). Iron deposits have been seen in major brain areas, including the substantia nigra and globus pallidus, in both postmortem and imaging investigations. Noninvasive imaging investigations of PD patients verified elevated iron congregation in the SN and connected the size of the accumulated protein to the extremity of the disease (Gorell et al., 1995). Exposure to iron through food, work environment, habitation or other ways has been studied for its link to PD for these and other reasons.

This chapter summarizes the role played by iron in progressing pathology of PD, with a specific focus on the oxidative stress caused by normal iron heamostasis and its dysregulation, particularly abnormal expression of iron transporters, transferring receptors, and divalent metal transporter 1 (DMT1), as well as their relationship with PD pathological markers like Senile plaque.

2 Brain Iron Transport

2.1 Overview of Iron Movement across Brain

The blood-brain barrier and the blood-cerebrospinal barrier restrict the protein transferrin from reaching the brain under normal conditions (Jefferies et al., 1984; Crowe & Morgan, 1992). As a result, transferrin generated by oligodendrocytes and choroid plexus epithelial cells facilitates iron transport in the brain (Bloch et al., 1985; Bloch et al., 1987), with transferrin expression being prominent all through the brain. Transferrin in the bloodstream supplies iron to the brain via endothelial cells' transferrin receptor 1 at these cerebral barriers (Jefferies et al., 1984; Crowe & Morgan, 1992), and transferrin transport through these brain barriers is very slow compared to iron (Moos & Morgan, 1998). Iron absorption from transferrin in the rat brain is controlled at the entire animal level, with greater or decreased iron utilization by the tissues of the brain depending on whether the animal is iron deficient or iron loaded (Taylor et al., 1991). The modulation of transferrin receptor 1 transcription on the luminal endothelial cells of capillaries that constitute the blood-brain barrier is held responsible for this impact (Taylor et al., 1991). Iron fails to deposit in the brain under iron overload settings where non-transferrin-bound iron is present in the plasma, as revealed in a mouse hemochromatosis model (Moos & Morgan, 2000), as well as in hemochromatosis humans . Non-transferrin bound iron might bind to transferrin released by oligodendrocytes and choroid plexus epithelial cells in the outer cavity of the brain (Bloch et al., 1985, Bloch et al., 1987). Because neurons ingest diferric transferrin via receptor-mediated endocytosis, this binding is probably important. Non-neuronal cell types, such as astrocytes and oligodendrocytes, express relatively little transferrin receptor 1 in vivo, and may take up non-transferrin-bound iron by a non-transferrin receptor 1-mediated pathway. In vitro, however, enriched cultures of astrocytes, neurons, and glia were all able to absorb iron through non-transferrin-bound iron. Iron concentrations in the CSF fluid appeared to surpass transferrin's iron-binding capability, implying the existence of possibly hazardous non-transferrin-bound iron (Ma et al., 2021) . These findings were verified in rats, where anti-transferrin antibodies pretty much entirely precipitated iron in the plasma, a considerable fraction of iron was not precipitated in the cerebral fluid (Moos & Morgan, 1998). Anti-transferrin antibodies absorbed 80–93% of iron in cerebral fluid, while anti-ferritin antibodies absorbed 1–5% of it, depending on the age of the animal. When the rats were 15 days, 20 days, and 56 days old, no iron in the blood plasma went through a 30,000 molecular weight

cut-off filter, whereas the proportion of iron in the cerebrospinal fluid passed through the filter was 5%, 10%, and 15%, respectively (Ma et al., 2021). As glia (astrocytes, microglia and oligodendrocytes) have been indicated to be involved in brain iron utilization and the pathogenesis of PD, a brief overview of their roles is described below.

2.2 Astrocyte Iron Movement

Astrocytes are the most plentiful type of cells in the CNS, performing a range of biological functions such as cellular aid throughout CNS growth, ion homeostasis, neurochemical utilisation, neuromodulation, and neuroprotective effects, as well as being important stimulators of synaptic, neuronal, and cognitive function (Vasile et al., 2017). Astrocytes are thought to span 95% of the capillary surface of the blood-brain barrier, acting as an iron transport channel into the brain as well as regulating the process (Ma et al., 2021). DMT1 has been found in the end foot processes of astrocytes that come into touch with endothelial cells (Wang et al., 2001). The potential of astrocytes to receive iron through active contact with endothelial cells has been presented as a possible explanation for their apparent lack (or extremely low levels) of transferrin receptor 1 expression (Moos & Morgan, 2004; Moos et al., 2007). While DMT1 is implicated in iron uptake from non-transferrin iron substrates in working astrocytes (Pelizzoni et al., 2013), the Zn + 2 transporter ZIP14 [280] and resident transient receptor potential channels (TRPCs) in resting astrocytes (Pelizzoni et al., 2013) are two further non-transferrin-mediated iron uptake mechanisms in astrocytes. Because iron extent in the brain surpass transferrin's iron-binding capability, considerable nontransferrin-bound iron occurs (Moos & Morgan, 1998). 2 Transferrin is a protein that binds two iron atoms and distributes iron from the bloodstream to all parts of the body save sanctuary locations like the brain (Ponka et al., 1998). The blood-brain barrier and the bloodcerebrospinal barrier prevent transferrin from getting into the brain from the blood (Jefferies et al., 1984; Crowe & Morgan, 1992). Transferrin is generated locally in the brain (Richardson & Ponka, 1997). 3 The majority of iron absorption by cells is mediated through the interaction of diferric transferrin with the transferrin receptor 1, which is mediated by transferrin-bound iron uptake. While transferrin cannot pass the blood-brain barrier, DMT1 is involved in non-transferrin-bound iron absorption by astroglia in the brain. Other routes of non-transferrin-bound uptake, like via the Zn^{+2} transporter ZIP14, might potentially play a role. Iron is taken up by neuronal cells in the brain from locally produced transferrin (Bloch et al., 1985; Bloch et al., 1987). 4 Transferrin is initially generated by the liver to maintain iron homeostasis in the body. Transferrin is exclusively found in the brain since it is made by oligodendrocytes and choroid plexus epithelial cells (Bloch et al., 1985; Bloch et al., 1987). 5 Ascorbic acid levels in the blood are generally modest (approx 50 M) (Lane & Richardson, 2014. The levels of ascorbic acid in mammalian brains is believed to be up to 8 times that of plasma iron levels (200–400 M) (Covarrubias-

Pinto et al., 2015). By retaining ferrous iron, which limits redox cycling, this may reduce the toxicity associated with high non-transferrin-bound iron (Covarrubias-Pinto et al., 2015) 6 Ceruloplasmin, a ferroxidase found in the blood, is involved in systemic iron mobilisation. In the brain, a glycosylphosphatidyl inositol link connects a distinct ceruloplasmin to the plasma membrane, and it plays a role in iron efflux from astrocytes. Decreased iron release from astroglia caused by a conditional deletion of FPN1 inhibited oligodendrocyte precursor cell re-myelination. In addition, reduced iron release from astrocytes reduced the production of cytokines in microglial cells, which are implicated in re-myelination . Depending on the stimulation, astrocytes can become activated to protect or harm the body, with the chemicals produced by these cells having neurotrophic or inflammatory effects. In fact, astroglias have exhibited immunological and inflammatory functions that are comparable to those of microglia. The stimulation of astrocytes causes reactive astrogliosis, which can be common in atypical PD, and can be interfered by extracellular α-synuclein binding. Reactive astrogliosis serves to restrict disease and help repair. Astrocytes have also displayed qualities to remove and absorb extracellular α-synuclein, which may be helpful for SNpc neurons but may potentially lead to increased production of inflammatory cytokines such as interleukin-1 and tumour necrosis factor-1. High quantities of iron have been displayed to activate microglia and astrocytes, which may then act on dopaminergic neurons, causing neurodegeneration (Ma et al., 2021.

2.3 Oligodendrocytes (Transferrin Secretion)

When it comes to oligodendrocytes, it's widely known that they have an involvement in myelin production, and immunohistochemical investigations have shown that they not only express transferrin and ferritin, but they're also the major cells in the brain that stain for iron (Gerber & Connor, 1989; Todorich et al., 2009). There's additional evidence that oligodendrocytes can receive iron from ferritin in the interstitial fluid or cerebrospinal fluid via T cell immunoglobulin and mucin domain-containing protein 2 (Tim 2) (Todorich et al., 2008) however the relative relevance of this route vs transferrin is unclear. As a matter of fact, transferrin was found in oligodendrocytes, however no transferrin receptor 1 expression has been observed in these cells (Hill et al., 1985). However, reports of transferrin being discovered in oligodendrocytes in humans, rats, and chickens (Oh et al., 1986; Stagaard & Saunders, 1987; Connor & Fine, 1986; Connor & Fine, 1987) contradict this. This last result might indicate that transferrin is present within endosomes, or that these cells produce transferrin. It has been claimed that while oligodendrocytes can produce transferrin, it is not secreted, leaving only the choroid plexus to perform this job (Leitner & Connor, 2012). Transferrin, like transferrin receptor 1, is extensively distributed throughout the brain, and the distribution of transferrin receptors measured by 125Iodine-labeled transferrin and anti-transferrin receptor monoclonal antibody binding is nearly identical (Hill et al., 1985). Iron shortage causes hypo-

myelination regardless of the route of iron absorption by oligodendrocytes, suggesting that iron plays a key part in this process (Bae et al., 2020), with myelinating neurons and motor coordination improved in transferrin over-expressing transgenic mice (Saleh et al., 2003). Furthermore, it is well recognised that iron shortage throughout human development results in motor and behavioural problems that last into adult age, highlighting iron's critical role in the CNS (Kim & Wessling-Resnick, 2014). This is because of the pivotal role of iron in neuron activity, as evidenced by the existence of transferrin receptors (Moos et al., 1998).

2.4 Microglia

Microglia are macrophage-like cells that contribute to dopaminergic neuron degeneration in Parkinson's disease (PD) through inflammatory activation (Banati et al., 1998), which can occur after exposure to mutant and overexpressed α-synuclein (Su et al., 2009) or other inflammatory mediators like lipocalin 2 (Jang et al., 2013). Activated microglia, on the other hand, can play a neuroprotective role, with the two effects being reliant on distinct activation states, specifically the conventional M1 phenotype, which produces pro-inflammatory cytokines, and the M2 anti-inflammatory phenotype (Colton, 2009; Cherry et al., 2014). In rat neuron-microglia-astroglia cultures, iron has exhibited to cause particular and continuous dopaminergic neurotoxicity. Higher transcription and translation levels of the p47 and gp91 subunits of the superoxide producing enzyme, NADPH oxidase 2 (NOX2), result in increased ROS when microglia are activated by increasing iron levels. This reaction is noteworthy because iron exhaustion rather than iron loading has been playing a role up-regulate NOX2 expression in other cell types via a hypoxia-inducible factor-1 (HIF-1)-mediated mechanism (Yuan et al., 2011). Based on these findings, it's reasonable to assume that NOX2 expression is regulated differently depending on the type of cell.

3 Iron Metabolism in Brain

3.1 Absorption

Neurons and glia are the major types of cells that make up the brain. Neuromelanin is shown to retain iron ions for a extended period, and ferritin is the chief protein for iron storage in neurons. Astrocytes and microglia manufacture L-ferritin to stock iron ions in glial cells, while oligodendrocytes express L- and H-ferritin (Jiang et al., 2017). Nutrients, including iron ions, do not come into direct touch with cells in the Central Nervous System (CNS). The blood–brain barrier (BBB) and the blood–brain spinal cord barrier (BBSCB) distinguish the CNS from the systemic circulation. The BBB is a unique structure made up of ancillary foot of capillary endothelial cells,

peripheral skin cells, and astrocytes that rigorously controls what enters the CNS (Daneman & Prat, 2015; Camandola & Mattson, 2017). Holo-Transferrin (Holo-TF) is prevented from accessing the nervous system by the hydrophobic BBB. To cross the BBB, Holo-TF must get via the brain capillary endothelial cells. Holo-TF binds to the TfR1 TF receptor on the luminal surface of brain capillary endothelial cells and passes them via the bloodstream. The Fe^{2+} is transported out of the capillary endothelial cells via the FPN on the abluminal surface, where Fe^{2+} is oxidised to Fe^{3+} by ceruloplasmin (CP) (Rouault, 2013; Rouault & Cooperman, 2006). The transit of FPN-exported ferrous iron is aided by CP, which is expressed in astrocytes. TF is produced and released by glial cells in nerve cells, and plica choroidae cells drain iron ions into interstitial fluid and cerebrospinal fluid, which permeate across brain parenchymal tissue and interact to the TfR1 receptor on neuronal membranes. (Patel et al., 2002). Apo-Transferrin (Apo-TF) enters the bloodstream via arachnoid villi after releasing iron ions. Ferroportin (FPN) is managed by hepcidin in the system, though the origin of hepcidin inside the brain is unknown. It may penetrate the BBB into the brain to regulate iron metabolism (Fig. 5.1) (Daneman & Prat, 2015).

3.2 Storage

Iron Regulatory Proteins (IREBs) regulate the expression of related proteins at the cellular level to maintain brain iron homeostasis. The reduction in IRP2 expression causes an imbalance in iron levels of brain, although myelin iron remains unaffected. Brain iron balance will be disrupted by mutations in genes governing iron metabolism, which will impact myelin production. As discussed above the origin of hepcidin generation is unknown. It is unclear if it is generated in the brain or it permeates through the BBB after its production in hepatic cells. In a model of an inflammatory cell signalling cascade, inflammation stimulates microglia and increases the production of hepcidin by astrocytes; this signal obstructs the liberation of iron ions in neurons and finally making way for the neuronal cell death which further augment the discharge of different anti-inflammatory and pro-inflammatory substances at the same time, there is no activation of normal human microglia, and there is no signaling cascade between cells (Fig. 5.1) (Gerlach et al., 1994; Zecca et al., 2004; Peng et al., 2021).

3.3 Brain Iron Toxicity and Accumulation

With ageing, iron ions start to deposit in the CNS. The ferritin protein and the substantia nigra are the principal targets of iron ions. Iron ion buildup can cause

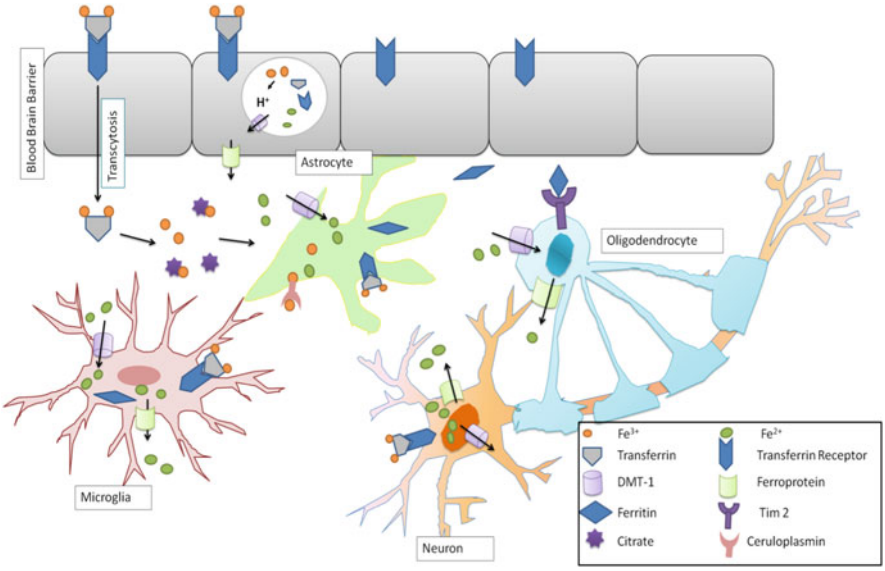

Fig. 5.1 Brain's iron metabolism. The Transferrin receptor (TfR) on the inner membrane of endothelial cells takes up transferrin (Tf) coupled to ferric iron (Fe^{3+}), and the Fe^{3+} bound Tf and TfR complex is internalised into endosomes. Duodenal cytochrome b converts Fe^{3+}-bound Tf to ferrous iron (Fe^{2+}). The divalent metal transporter l (DMT1) in the endosome membrane transports Fe^{2+} to the cytosol, and ferroportin l exports it into the extracellular matrix (FPN1). Tf is regenerated after Fe^{2+} release to bind to Fe^{3+} in the circulation. **1. Astrocytes:** Tf-TfR1 might allow astrocytes to absorb Fe^{3+}. Fe^{2+} absorption is aided by DMT1, Zip14, and TRPC. Cp may oxidise Fe^{2+} to Fe^{3+} and subsequently stimulate Fe^{2+} release via FPN1. Iron may be efficiently stored in ferritin. **2. Microglia:** DMT1-mediated iron import and FPN1-mediated iron export could transport Fe^{2+} in microglia. Microglia can also stock iron in ferritin and transfer Fe^{3+} ions to neurons via the Lf/LfR pathway. **3. Oligodendrocytes:** Oligodendrocytes store iron mostly in the form of ferritin or Tf. Oligodendrocytes have the ability to release Tf. The major mechanism for iron absorption is Tim2-induced ferritin uptake. **4. Neuron:** Tf-bound and non-Tf-bound iron (NTBI) are taken up by neurons. NTBI may also bind to citrate and ATP produced from astrocytes, allowing oligodendrocytes and astrocytes to get iron

neurotoxicity through a variety of methods. Excessive iron ion buildup will increase BBB permeability, cause inflammation, influence iron ion redistribution in the brain, and ultimately modify brain iron metabolism. When iron ions start to accumulate in the brain, they can act both as the electrophiles and neutrophiles., Fenton and Haber–Weiss chemical processes will create reactive oxygen free radicals. Protein oxidation, membrane lipid peroxidation, and nucleotide change can all be caused by free radicals. Oxidative stress occurs when ROS levels exceed the antioxidant capacity of organelles, causing damage to neurons and, in extreme situations, tissue deterioration. (Peng et al., 2021).

4 Gut Microbiota: A Bridging Stone Between Iron Metabolism and Neurodegeneration

In mammals, oxidized or reduced iron is absorbed mostly through the duodenum, which has a stringent absorption regulatory system. Remaining iron that escapes absorption in duodenum reaches the colon, which is abode to the number of gut microbiome, a collection of bacteria. Iron plays a pivotal role in the growth of intestinal microorganisms because it is a ferritin cofactor in redox processes, metabolic pathways, and respiratory chain of bacteria. As a result, the amount of iron ions in the colon cavity influences the configuration, multiplication, and living status of intestinal microorganisms, and changes in intestinal microbes have an effect on the host's health. The gut-brain axis, which includes neuronal, immunological, and metabolite-mediated pathways, has been found to interact between the digestive tract and the central nervous system in a rising number of studies. Preclinical and clinical research has revealed that the gut microbiota is important in the gut-brain interface, and that changes in gut microbiota composition are linked to the etiology of neurological illnesses, particularly neurodegenerative diseases (Peng et al., 2021). Studies have shown a correlation amongst the host microbiota (including bacteria of mouth and gut), neuroinflammation and neurodegenerative disease, which might be produced directly by invading microbes of the brain owing to barrier leakage, toxin and inflammatory factor production, or indirectly by immune responses being modulated. Furthermore, the microbiota composition influenced the deposition of α-synuclein (Mulak & Bonaz, 2015).

5 Biochemical Pathways Accelerating Iron Aggregation

5.1 Disabled Iron Discharge

Intoxication with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA) depletes ferroportin in parkinsonian models (Ward et al., 2014) tau function are depleted in the Substantia nigra in Parkinson's disease, culminating in neural iron accumulation and iron-dependent death of nigral neurons. (Ayton et al., 2013;, Lei et al., 2012) Ceruloplasmin may aid cellular iron outflow by ferroportin, and mice lacking this enzyme suffer deferiprone (DFP) rescuable age-dependent iron elevation and parkinsonism. (Ayton et al., 2013) Low ceruloplasmin activity has been seen in the Substantia nigra, cerebrospinal fluid, and serum of PD patients. (Ward et al., 2014) In Parkinson's disease, genetic variants in the ceruloplasmin gene are linked to parkinsonism (Lei et al., 2015) and SN hyperechogenicity (Ayton et al., 2013; Hochstrasser et al., 2005).

5.2 *Modified Iron Deposition*

Neuromelanin is expressed as an alternate "iron sink" to supplement neurons' restricted ability to store extra iron into ferritin molecules (Ward et al., 2014; Belaidi & Bush, 2016) However, in PD, such capabilities may be surpassed, resulting in increased ferritin immunoreactivity in Substantia nigra microglia (Belaidi & Bush, 2016 By functioning as a metastable storehouse for iron, enhanced concentrations of iron-loaded ferritin may contribute to age-related neurodegeneration. (Ward et al., 2014; Belaidi & Bush, 2016).

5.3 *Enhanced Iron Influx*

Single-nucleotide variations in Transferrin (Tf) and its receptor (TfR) discovered in PD case reports may have a protective role by altering Tf linked iron transportation into the cell. (Rhodes et al., 2014) Lactoferrin and its target might possibly be involved. (Faucheux et al., 1995a, b) Finally, elevated levels of the iron importer divalent metal transporter correlate with iron buildup in the Substantia nigra of patients and MPTP incuced model of PD mice. (Salazar et al., 2008).

6 Altered Neurobiology of Iron in PD

Many metabolic processes at cellular level are thought to be defective or disrupted in PD, including α-synuclein aggregation, Lewy body formation, ubiquitin–proteasome system malfunction, and oxidative stress, may be affected by iron.

6.1 *Abnormal Iron Homeostasis under Pathophysiological Condition of PD*

The pathophysiological mechanism of Parkinson's disease is regarded to have a significant impact on the mechanism of transport and storage of iron. A large number of data suggests that systemic metabolism of iron is aberrant in Parkinson's disease. In PD, serum markers of iron transport, such as transferrin or lactoferrin, are seen to be diminished, albeit the details of which transporter is changed vary between reports ((Logroscino et al., 1997; Grau et al., 2001). Iron culminated greater in the substantia nigra region in PD patients than in control cases in the brain (Martin et al., 1998). Because transferrin and lactoferrin are involved in iron absorption, researchers looked at their expression in Parkinson's disease. In individuals with PD, lactoferrin immunoreactivity is higher in afflicted dopamine releasing neurons in

comparison to normal controls, although transferrin levels are lower (Faucheux et al., 1995a, b). The increased immunoreactivity is only seen in locations where there is neurodegeneration, and it is not shown in cholinergic neurons in people with Parkinson's disease. The imprudent buildup of iron in dopaminergic neurons in individuals with PD might be due to enhanced levels of lactoferrin in the dopamine releasing neurons of substantia nigra. The significance of variations in systemic iron transport is unclear, although systemic abnormalities might readily indicate a core issue with iron homeostasis in PD. In Parkinson's disease, ferritin levels are also affected. The level of ferritin isoforms and their H/L ratio fluctuates depending on the pathological situation. Because of no established link between PD and changes in iron levels, the changes in PD are startling. Despite higher iron concentration in the brain region responsible for PD(substantia nigra), individuals with PD had decreased extent of both ferritin subunits (relative to similar aged control individuals) but no change in the H/L ratio in the substantia nigra was found (Connor et al., 1995). Increased iron absorption by another species in the substantia nigra in PD (such as neuromelanin or α-synuclein, as described below) or altered regulation of iron storage proteins as part of the pathophysiology of PD could define the absence of homeostatic adjustments in ferritin levels in response to changes in iron content.

6.2 *Interconnection Between Iron and Alpha Synuclein*

Lewy bodies, the hallmark characteristic of sporadic as well as familial PD, are made up mostly of alpha synuclein. Familial PD is caused by pathogenic translational mutations in the Syn gene (PARK1) and multiplication (duplications and triplications) of the Syn gene (PARK4). Syn had been discovered to have a special binding pocket for metals such as iron which are divalent in nature. Overexpression of Syn causes higher iron levels intracellular and iron redistribution from the cytoplasm to the perinuclear area within α-synuclein-rich inclusions in neuronal cells susceptible to excessive iron. Iron may bind directly to Syn in ferrous Fe^{2+} as well as ferric Fe^{3+} forms, however the ferric form has been shown to be more powerful in speeding up the rate of Syn aggregation and fibril formation (Wolozin & Golts, 2002; Ma et al., 2021).

6.3 *Ubiquitin–Proteasome System Induced Cell Death*

One of the primary pathways for the degeneration of cellular, nonmembrane-bound proteins is the ubiquitin–proteasome system (UPS), whose role is to establish adequate cellular concentrations of shortlived regulatory/functional proteins and to destroy unusual, misfolded, damaged, or toxic proteins reviewed in. Defects in, or overloading of, the UPS may result in harmful protein buildup, biological malfunction, or death. Under investigational circumstances of enhanced oxidative stress

and/or mitochondrial complex I inhibition, UPS overload or malfunction seems to develop (e.g., the rotenone rat model of PD). Furthermore, because Lewy bodies and Lewy neurites include not just α-synuclein aggregates, but also ubiquitin, parkin, and torsin A(an ATPase), there is some evidence that dysregulated UPS activity is at least a part of PD pathogenesis. The iron chelator desferrioxamine lowers the presence of ubiquitin-positive intracellular inclusions in the SN of mice, which suggests that iron may have a part in UPS dysfunction (Zhang et al., 2005). Furthermore, IREBs appear to modulate the mRNA of a 75-kDa mitochondrial complex I protein (Lin et al., 2001), which might impact function of mitochondrial complex-1, which is widely recognised for its harmful role in Parkinson's disease (Chen et al., 2019).

6.4 How Oxidative Stress Is Linked to Iron Imbalance

Dopamine oxidation produces hydrogen peroxide (H2O2). Iron is a powerful redox agent, and when it encounters H_2O_2, ferrous iron (Fe^{2+}) catalyses the Fenton reaction, which produces oxygen radicals (ROS) that raise the burden of cell's oxidative stress (Gerlach et al., 1994). In fact, when rat neuron cultures were exposed to the combination of Fe^{2+} and H_2O_2, cell survival was lower and free radical levels were higher than when the cultures were treated with a vehicle. The presence of free radicals is known to cause protein degradation, misfolding, and aggregation. Scientists have assessed the interconnection between free oxygen radicles and the human encephalon in depth, Because of its intensive usage of oxygen for different anabolic and catabolic activities and its relative lack of antioxidant and regeneration qualities compared to other organs, the brain is considered to be particularly vulnerable to free-radical buildup, particularly oxygen radicals (Andersen, 2004; Sayre et al., 2005; Mancuso et al., 2007).

ROS are produced by a variety of standard and deteriorated cellular pathways, including auto-oxidation of dopamine, disordered mitochondrial complex I, incorrect integration of extrinsic toxic substances, insufficient glutathione availability, and poorly stored or excess iron concentrations. Uncontrollable ROS manufacturing can cause damage to nuclear and mitochondrial DNA, lipid peroxidation, damaged or misfolded proteins, and aggregated proteins undetected by the UPS owing to incorrect ubiquitination. Iron may have a role in oxidative stress on several levels, including direct ROS generation, α-synuclein aggregation, interference with the UPS system's function, and other cellular processes in the brain (Carocci et al., 2018).

7 Ferroptosis —Cell Death Pathway in PD Utilizing Iron

A recently discovered iron-dependent cell death mechanism has important implications for Parkinson's disease pathophysiology. Ferroptosis appears to be caused by an iron-dependent strategy that incorporates lipid oxidation, glutathione peroxidases-4 depletion to modify glutathione defence, mitochondriopathy, and various morphological changes that are distinctive from other cell death mechanisms (e.g., apoptosis, necrosis, and autophagy) (Dixon et al., 2012) enhanced intracellular iron is related to enhanced transport of iron inside transferrin (Tf) via transferrin receptor (TfR) endocytosis, which is aided by α-synuclein, and increased import of Fe via the divalent metal transporter 1 (DMT1) (Zecca et al., 2005). Furthermore, b-amyloid precursor protein (APP) or ceruloplasmin destabilise ferroportin on the cell surface, impairing iron export (CP). The labile pool of iron is boosted when the storage proteins neuromelanin and ferritin are no longer able to securely store intracellular iron, which acts as a catalyst for the manufacture of phospholipid hydroperoxides. Glutathione biosynthesis requires cysteine absorption via the Xc antiporter (in oxidative circumstances) or the alanine, serine, cysteine–preferring (ASC) system (in reducing conditions) (GSH). Glutathione peroxidase 4 (Gpx4) reduces phospholipid hydroperoxides to their corresponding lipid-alcohols with the help of two GSH molecules, creating H2O and glutathione disulfide (GSSG) as side products. Increased intracellular iron levels combined with Gpx4 depletion, as shown in PD models, stimulate the formation of phospholipid hydroperoxides, resulting in membrane breakdown via a ferroptotic pathway. Depleting phospholipid hydroperoxides (ie, liproxstatin-1 or ferrostatin-1) or reducing the labile iron pool (ie, deferiprone) are therefore attractive strategies for suppressing ferroptosis in PD pathogenesis (Moreau et al., 2018).

8 Treatment Strategies for Parkinson's Disease Targeting Iron Homeostasis

8.1 Iron Chelators: A Promising Treatment for PD

Chelation of iron using different chelators has been proposed as a possible treatment strategy for the cure of neurodegenerative disorders with iron excess symptoms, such as Parkinson's disease. Previous studies have shown that the Fe^{3+} chelator deferoxamine (DFO) reduced the harmful effect of the iron–melanin complex in nigrostriatal co-cultures (Mochizuki et al., 1993). Therapy with DFO was also recognized to effectively cure behavioural abnormalities and enhance the survival rate of dopamine releasing neurons in the SN and striatum in mouse model of MPTP induced PD, by upregulation of the expression of proteins including HIF1, TH, vascular endothelial growth factor (VEGF), and growth associated protein 43 (GAP-43) and downregulating the expression of α-synuclein, DMT, and Tf

receptor. However, due to its poor pharmacokinetic profile orally, shorter half-life, and poor penetration in brain. Another artificial chelating agent, deferiprone (DFP), was discovered, which has been shown to be effective in an MPTP-model of PD. Developing PD patients on stable dopamine treatments were included in a 12-month single-center research using DFP in a pilot double-blind, placebo-controlled randomised clinical trial. Early-start patients reacted to therapy more sooner and more stable than late patients based on substantia nigra iron deposits and UPDRS scores, while safety preserved all through the trial. (Devos et al., 2014). Some 8-hydroxyquinoline analogues have indeed showed potential in the therapy of Parkinson's disease neurodegeneration. Clioquinol, an iron chelator with lipophilic properties, has been shown to revert iron buildup in the SN of MPTP-induced Parkinson's disease animal models (Kaur et al., 2003). Furthermore, clioquinol treatment of genetically modified mice model overexpressing A53T Syn prevents an iron–Syn interplay, Syn aggregate clustration, Syn-related neuronal loss in the SN, dendrites spine density reduction in hippocampus and caudate putamen intermediate spiny neurons, and movement and cognition decline. Another iron chelator which can penetrate brain, VK-28, was able to preserve neurons in 6-OHDA induced PD like symptoms in rats (Ben-Shachar et al., 2004). Increased iron in nigra region of brain and monoamine oxidase B (MAO-B) activity are both hallmarks of PD and hence therapeutic markers. Rasagiline has a powerful MAO-B inhibitory and neuroprotective effect due to the propargylamine moiety (Youdim et al., 2001). Because of propargylamines' neuroprotective properties, various bifunctional iron chelators with propargylamine moiety (HLA-20 and M30) were developed from the typical iron chelator, VK-28. These agents have properties to chelate iron like DFO, as well as MAO-A and B selectively inhibition and neuroprotection properties (Youdim et al., 2005; Zheng et al., 2005a, 2005b, 2005c; Gal et al., 2005, 2010). These chemicals provide neuroprotection, via dual mechanism i.e. iron chelating and MAO-B inhibitory action, might be used in treatment of Parkinson's disease. Summary of these compounds is discussed in Table 5.1.

9 Conclusions and Future Prospects

In the earth's crust, iron is a plentiful metal element. Iron's redox characteristics enable efficient electron transport, which is useful to a wide range of biological processes. However, When the adequate iron homeostasis is interrupted, such responsive qualities of iron may increase the production of reactive oxygen species (ROS), resulting in an overabundance of metal ions in the system. As an outcome, precise framework exists in organisms for iron uptake, stockpiling, and dispersion. Excessive iron buildup causes oxidative stress events, in high quantities, it can be hazardous to cellular components, especially body tissues and organs. Furthermore, iron is necessary for the creation of a myelin sheath in neurons as well as aerobic respiration in mitochondria. Whenever brain iron homeostasis is disrupted, iron is concentrated in various areas of the brain, causing oxidative stress, mediating

Table 5.1 Studies showing different iron chelators in treatment of PD

S. no	Compound	Nature	Phase of study	Conclusion	Reference
1.	Deferiprone	Synthetic	Phase-3 (NCT01539887)	Effective. Reduces iron levels but may not necessarily provide symptomatic relief.	Clinicaltrial.gov
2.	Deferoxamine	Synthetic	Pre-clinical	Efficacious against MPTP, 6-OHDA and rotenone and $FeSO_4$ induced PD like symptoms	Sangchot et al. (2002)
3.	Apomorphine	Synthetic	Completed (NCT02006121)	Effective. Reduces iron levels but may not necessarily provide symptomatic relief.	Clinicaltrial.Gov
4.	VK-28	Synthetic	Pre-clinical	Protects neuronal cells from the toxicity caused by 6-ohda. Additionally protects against lipid peroxidation caused by iron	Zheng et al. (2005a, 2005b, 2005c)
5.	Clioquinol	Synthetic	Pre-clinical	MAO inhibitory activity, in MPTP-induced Parkinson's disease, rescues iron-induced toxicity.	Kaur et al. (2003)
6.	M30	Synthetic	Pre-clinical	Protective effect due to MAO inhibition in 6-OHDopamine, MPTP and Lactacystine induced Parkinson disease	Gal et al. (2005)
7.	1-hydroxypyridin-2one	Synthetic	Pre-clinical	Neuroprotective effects due to hydroxamic acid in 6-OHDA induced Parkinson disease	Workman et al. (2015)
8.	HLA-20	Synthetic	Pre-clinical	Selective MAO-B inhibitor, neuroprotection in P-12 cell ines against 6-OHDA induced toxicity.	Zheng et al. (2005a, 2005b, 2005c)
9.	Quercitin	Natural	Pre-clinical	Neuroprotective effects in 6-OHDA	Lesjak et al., 2014,

(continued)

Table 5.1 (continued)

S. no	Compound	Nature	Phase of study	Conclusion	Reference
				induced Parkinson disease	Costa et al. (2016)
10.	Epigallocatachin gallate			Efficacious against MPTP, induced PD like symptoms	Reznichenko et al. (2010) Leaver et al. (2009)
11.	Curcumin	Natural	Pre-clinical	Neuroprotective effects in fisetin and 6-OHDA induced Parkinson disease	Singh et al. (2013)
12.	Silibinin	Natural	Pre-clinical	Efficacious against MPTP, induced PD like symptoms Inhibited alpha-synuclein oligomer toxicity in OLN-93 cell line	Lu et al. (2009)
13.	Phytic acid	Natural	Pre-clinical	Protects against MPP+ and 6-OHDA toxicity in normal and excess iron condition	Xu et al. (2008, 2011)

synuclein production via the Ubiquitin–proteasome pathway, and eventually leading to the development of Parkinson's disease. In Parkinson's disease, oxidative stress induced by iron buildup in neurons encourages the formation of Lewy body and alpha synuclein, which damages neurons and causes motor function losses, among other things. Although adopting iron-chelating techniques has shown some promise in terms of alleviating PD symptoms, further study is needed before the findings can be translated into clinical practise for the treatment of PD. Nonetheless, there has been little genetic research on iron-reduction measures in Parkinson's disease patients. There is a lot of room for more investigation into this type of treatment, given the expanding number of iron chelating drugs with potential disease-improving effects, as well as the availability of markers of iron load in MRI and CSF. Furthermore, genetic studies in model animals on the control of several critical genes in iron homeostasis have revealed the possibility of more efficient and accurate therapy. Iron's part in the pathogenesis of Parkinson's disease is generally acknowledged. Iron not only exacerbates the buildup of alpha synuclein and lewy bodies, but it also results in oxidative stress to neurons. Given the uniqueness and relevance of iron in the process of ferroptosis, future study should focus on determining how ferroptosis has a position in the molecular physiology of PD, which might lead to new insights into the illness and therapeutic suggestions. In light of the current discovery of a possible connection between iron, the host microbiota, and Parkinson's disease, it is expected that by research on the body's and brain's iron

metabolic mechanisms in greater depth, to improve or cure the condition, new and effective targeting and treatment procedures are needed. Will be discovered (Peng et al., 2021).

Conflict of Interests Authors declare no conflict of interests.

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Chapter 6
Iron-Calcium Crosstalk in Neurodegenerative Diseases

Monika Kadian, Garima Sharma, and Anil Kumar

1 Introduction

Iron and calcium are two vital minerals that can be found in food (Valdés Hernández et al., 2014) and they have the property of being necessary for regular brain function and harmful in large doses (Hidalgo & Núñez, 2007). Iron is needed for the maintenance of healthy cognitive functions and plays a vital role in physiological neuronal activity (Grantham-McGregor & Ani, 2001; Beard & Connor, 2003; Lozoff & Georgieff, 2006; Vlasova et al., 2021). Iron, on the other hand, produces neurotoxicity and substantial cognitive deficits when it is found in high concentrations. Ferroptosis, an iron-dependent cell death process, was recently discovered (Dixon et al., 2012), and it encompasses multiple molecular mechanisms previously linked to neurodegenerative disorders (Stockwell et al., 2017; Reichert et al., 2020; Weiland et al., 2019; Masaldan et al., 2019). However, just few research have looked at the involvement of Ca2 + −dependent signaling cascades in ferroptotic neuronal death, and nobody said if the redox disequilibrium seen in ferroptotic neurons alters Ca2+ equilibrium and signaling. As of Ca2+ is an ubiquitous signaling molecule that plays important operations in activity-mediated gene transcription, neuronal excitability, synaptogenesis, ageing, and neuronal loss (Hidalgo, 2004; Bezprozvanny, 2009; Bading, 2013; Brini et al., 2014; Burgoyne et al., 2019), this specific feature gains major importance for neuronal function. Furthermore, changes in cellular redox status alter the activity of various proteins involved in Ca2+ homeostasis and signalling, with some being stimulated and others being blocked by elevations in cellular oxidative tone (Görlach et al., 2015; Feno et al., 2019; Núñez & Hidalgo, 2019). Moreover, calcium is a critical mediator of activity-dependent gene

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expression and other key neural activities, while iron is required for the correct formation of intellectual skills. Certain neural stimulus, in instance, generate calcium signals that enhance the transcription of genes encoding for synapse formation via the serial activation of signalling pathways and transcription factors, a neural activity that appears to be linked to memory formation (Hidalgo & Núñez, 2007). They are, nevertheless, engaged in a number of neurodegenerative pathways, including protein and metal aggregation, the formation of reactive oxygen species, and oxidative stress (Rivera-Mancía et al., 2010). The disruption of iron (Brewer, 2010) and calcium (Yu et al., 2009) equilibrium has been associated to age-related illnesses like Alzheimer's disease (AD) (Pchitskaya et al., 2018), Parkinson's disease (PD) (Lee et al., 2013; Pchitskaya et al., 2018; Núñez & Hidalgo, 2019), Huntington's disease (HD) and Amyotrophic lateral sclerosis (ALS) (Pchitskaya et al., 2018; Núñez & Hidalgo, 2019), Friedrich's ataxia, Pantothenate kinaseassociated neurodegeneration (Swaiman, 1991), and other brain anomalies (Wiethoff & Houlden, 2017). Iron homeostasis, on the other hand, varies with age in normal, healthy people, leading to increased iron deposition in the central nervous system (Hallgren & Sourander, 1958) and perhaps contributing to cognitive impairment (Penke et al., 2012). Steady increase in the number of elderly individuals, cognitive decline is a topic of considerable concern. As a result, more research on the process of mineral buildup in the brain is required, as it may provide valuable information regarding their function in the understanding of aging process. In the chapter's upcoming sections, we'll go through the involvement of iron in neurotransmission and how ferroptosis leads to neuronal loss and destruction. We also cover the fundamentals of neuronal Ca2+ regulation and signalling, as well as its possible function in iron-related processes and ferroptosis, iron-calcium crosstalk and the Ca2 + −iron-ferroptosis interconnection as a potential contributor to neurological illnesses (Gleitze et al., 2021).

2 Iron

Metals are extensively dispersed in living organisms and are classified as "biometals" or "toxicants metals" depending on whether they provide a beneficial or harmful purpose to the host. Transition metals (described as those components that compose at least one ion with a partly filled orbit of electrons, e.g., Fe, Cu, and Zn) play a role in the regulation of basic cellular activities when existing in the right concentration. Imbalance in concentration of any metal, which results in levels beyond the usual physiological range, can cause biological harm, as it can with many other molecules (Frey & Reed, 2012; Williams, 2012; Galaris et al., 2019). Iron is used as a cofactor or structural component of proteins in all cells, from yeast to humans, for a variety of important biological processes (D'Mello & Kindy, 2020). However, disruption of the homeostatic processes that regulate iron metabolism, resulting in a decrease or excess of iron inside or out of the cell, can also have major consequences for cell and organism health (D'Mello & Kindy, 2020).

2.1 Homeostasis and Repercussion of Altered Concentration of Brain Iron

Iron, an oxidoreduction type metal, is involved and essential for the formation of proper cognitive performance in the brain. Irreparable neuronal impairments and intellectual disabilities are now the main signs of deficiency of iron in the growing brain (Grantham-McGregor & Ani, 2001; Beard & Connor, 2003; Lozoff & Georgieff, 2006; Vlasova et al., 2021; Gleitze et al., 2021). It is also required for activation of LTP within hippocampus, a synaptic plasticity mechanism considered as a basic paradigm of memory consolidation (Herring & Nicoll, 2016), according to research in male rodents. Thus, following inadequate high-frequency induced stimulation of hippocampus, iron supplementation enhances prolonged LTP generation, although iron chelation reduces baseline neurotransmission across synapse and hinders persistent LTP (Muñoz et al., 2011; Muñoz, 2012). Iron act as a cofactor for many enzymatic reactions at the cellular level, and is also required for the activity of many proteins that are involved in normal processes of mitochondria, as well as neurochemical and myelin formation (Connor & Benkovic, 1992; Mena et al., 2015; Requejo-Aguilar & Bolaños, 2016). Glia, especially oligodendrocytes implicated with iron-associated myelin production and regulation, have greater iron concentration compared to neurons (Roth & Núñez, 2016; Reinert et al., 2019), rendering them highly vulnerable to iron-associated oxidative damage. The homeostasis of iron with in brain is highly controlled at the stages of transcription and post-transcription (Burdo & Connor, 2003; Singh et al., 2014; Yu & Chang, 2019). Moreover, a very well developed structure of iron regulatory proteins (IRP) and iron-responsive elements (IRE) regulates the synthesis of iron-related proteins that are involved in metabolism, retention, and recycling of iron. IRP1 and IRP2 are the two isoforms that regulate production of proteins by connecting to IREs in respective mRNA untranslated regions (Wilkinson & Pantopoulos, 2014). IRPs connect to IREs located in the leader sequence (or 5' UTR region) of the mRNA coding for ferritin and Ferroportin 1 (FPN1) in iron-compromised cells, restricting their respective protein synthesis and limiting iron stores and release. In contrast, IRPs bind to IREs at the trailer sequence (or 3′ UTR region) of mRNAs coding for transferrin receptor 1 (TfR1) and divalent metal transporter 1 (DMT1), maintaining their mRNAs and thus boosting iron consumption and translocation. Every one of these elements work together to make sure that the intracellular labile iron pool is tightly controlled, with redox-active iron concentrations varying from 0.5 to 1.5 M, or even lower than 5% of overall internal iron status of the particular cell (Cabantchik, 2014). IRP2 is damaged in the presence of iron, and the IRP1 apoprotein will become a cytoplasmic (c)-aconitase without any transcription activity after attaching to such a '4Fe-4S-complex'. Remarkably, ROS and RNS can trigger IRP1 even in excessive iron environments via modifying the '4Fe-4S-complex' of c-aconitase (Katsarou & Pantopoulos, 2020; Urrutia et al., 2021).

The BBB is a cellular assembly comprising of rigidly cling endothelium that safeguards the open entry of substances to brain (Bradbury, 1997; Moos et al., 2007;

Yu & Chang, 2019). Systemic disseminated iron is primarily tied to transferrin (Tf) and then it is moved into the brain via a BBB. Briefly, the brain is quite vulnerable to oxidative stress or damage than that of other body tissue or organ because of its increased consumption of dynamic energy for metabolic activities, which actually creates massive volumes of ROS, reduced total antioxidant, and high proportion of oxidation-sensitive lipoproteins usually contains unsaturated fatty acids (e.g. PUFAs) (Gemma et al., 2007). As a result, keeping iron homeostasis, and consequently normal ROS concentrations, is critical for mental well-being. Thus, iron balance within brain and signaling are closely controlled at several stages and by a variety of molecular components, because any disruption might result in increased iron-mediated ROS generation, which can impede healthy brain performance.

2.2 Brain Anomalies and Iron

Various investigations have found that iron levels rise in specific areas of the brain in the aged and in several neurodegenerative illnesses, owing to altered functioning of mitochondria, excessive ROS generation, inflammatory conditions, and changes in iron balance (Ward et al., 2015; Muñoz et al., 2016; Urrutia et al., 2021). As a result, abnormally high amounts of iron are expected to induce neuronal cell death by activating a variety of cellular pathways that are now being investigated (Ndayisaba et al., 2019; Urrutia et al., 2021). Ferroptosis, an unique kind of iron-associated cell demise, could gives rise to mechanistic explanation over how neurons end up dying in neurodegenerative illnesses, which has been a long-standing mystery. Indeed, alteration in iron balance and its metabolic activities that also results in a noxious boost in the subcellular labile iron pool, plays an important part in the initiation and advancement of neurodegeneration (Ward et al., 2014), such as AD, the very prevalent neurodegenerative illness in the aged people globally, and PD (Masaldan et al., 2019). On post-mortem assessment, numerous reports from patients with AD showed substantial loss in neurons and associated synaptic activity, and also the buildup of structural proteins like amyloid plaque and tau-tangles, made up of the amyloid peptide (A-beta) and tau-hyperphosphorylation, respectively, and then these aggregates are primarily identified in the hippocampus and frontal cortex region of the brain (Selkoe, 2001). Under this perspective, a recent study shows that iron transporters such Tf receptor and DMT1 are related to elevated brain iron concentration and neurodegeneration (Yan & Zhang, 2020). Structural alterations and increased ferritin expression have been found in microglia, which may drastically change the biological capability of these glial cells by boosting an expanded pro-inflammatory setting, resulting in expedited ageing and potential threat to neurodegenerative disorders (Ashraf et al., 2018; Urrutia et al., 2021). Inflammatory mediators also influence the expression of iron-associated transporters or proteins in neurons, boosting DMT1 expression while reducing FPN1 expression, results in iron buildup (Urrutia et al., 2013). Iron dysregulation has even been considered as a key

preclinical process in the pathogenesis and evolution of Alzheimer's disease (Peters et al., 2015). Numerous investigations using MRI have found higher iron contents with in cortical and hippocampal brain regions of AD subjects, along with a deterioration in cognitive functioning (Zhu et al., 2009; Raven et al., 2013; Langkammer et al., 2014). Furthermore, the iron-associated protein ferritin concentrations may serve as a proxy for overall brain iron burden, which, when elevated, may result in neurodegeneration in certain areas of the brain (Bartzokis et al., 2004; Ayton et al., 2015). The presence of ferritin with in CSF of MCI patients, as determined by neuroimaging (MRI), has been linked to hippocampal shrinkage (Ayton et al., 2015).

Parkinson's disease (PD) is a devastating neurological condition marked by stiffening, tremors, and difficulty with walking, and even a variety of non-motor manifestations. The preferential death of dopaminergic neuronal cells in the substantia nigra pars compacta (SNpc) is a critical aspect in this neurological illness (Berg & Youdim, 2006; Muñoz et al., 2016; An et al., 2018) and the elevated iron levels inside the affected area mainly SNpc, which houses deteriorating dopaminergic neuronal cells, are a well-known characteristic of Parkinson's disease (Sofic et al., 1988; Andersen, 2004; Pietracupa et al., 2017; Cheng et al., 2020a, b). In PD, the quantity of proteins, which regulates iron concentration, is abnormally shifted, leading to greater labile iron pool, which also can cause synuclein agglomeration [1–15,91]. This is similar to what has been observed in AD. Moreover, the fact that pharmaceutical treatments with iron-chelation ability can reduce neurodegeneration in AD or PD animal studies emphasises the importance of iron as a neurodegeneration modulator in AD and PD (Nuñez & Chana-Cuevas, 2018).

Furthermore, Amyotrophic lateral sclerosis patients' spine nerves have elevated amounts of iron and calcium (Kasarskis et al., 1995). Successful therapy by iron-chelates in ALS murine model confirms iron's essential involvement in the disease's development (Jeong et al., 2009; Kupershmidt et al., 2009). Pathophysiological pathways to clarify the aberrant iron buildup presented by the neural and glial cells of ALS rodents include changes in proteins that are engaged with iron balance, suppression of anterograde synaptic transmission contributing to iron buildup in ventral motor neurons, and steadily increasing iron amount within mitochondria of both neurons as well as glial cells (Jeong et al., 2009).

Huntington's disease (HD), a neurological illness largely defined by a catastrophic increase of CAG repeats (more than 36) during first exon of huntingtin gene. HD individuals' striatum and brain cortex degenerate over time, beginning many years prior to actual commencement of clinical symptoms (Tabrizi et al., 2011). Numerous bad consequences of mutant huntingtin (mHTT) have been reported, including aberrant transcriptional activity (Chiang et al., 2007; Yamanaka et al., 2008; Hogel et al., 2012; Ahmed et al., 2015), altered cellular antioxidant levels (Paul et al., 2014), mitochondrial malfunction (Corona & Duchen, 2016), and disturbed calcium levels (Bezprozvanny, 2009). Iron accumulation may also play a role in the beginning of HD (van Bergen et al., 2016; Berggren et al., 2015, 2016).

All ageing mammals normally accumulate iron, and it is associated with cognitive and neurological deficits in the older people (Bartzokis et al., 2011). In HD, iron levels are elevated in degenerative brain brain regions, and iron balance is disturbed (Dumas et al., 2012; Chen et al., 2013; Berggren et al., 2016). Disturbance in iron regulation within brain starts earlier clinical manifestations in HD individuals (Dumas et al., 2012; Rosas et al., 2012), implying that iron is engaged in the mHTT-induced pathogenic process (Firdaus et al., 2006; Muller & Leavitt, 2014).

Furthermore, iron excessive accumulation is frequently cited as a main culprit of oxidative stress in brains (Muller & Leavitt, 2014). mHTT increases the formation of ROS in HD patients (Quintanilla et al., 2013; Paul et al., 2014; Ribeiro et al., 2014). Additionally, in HD, iron seems to have the capability to interfere with mHTT-induced oxidative damage. mHTT clusters have also been demonstrated to be iron-associated oxidative stress hotspots (Firdaus et al., 2006). Numerous research has found that iron chelators reduce mHTT neurotoxicity, implying that iron buildup may play a role in the beginning of HD. In R6/2 mice, treatment with clioquinol helps to improve HD pathogenesis and alleviates suffering (Nguyen et al., 2005). Also, R6/2 mice injected with the iron-chelator deferoxamine demonstrated a consistent progress in cognitive decline (Chen et al., 2013). In HD cell lines, deferoxamine therapy reduces the activation of oxidative stress markers (Firdaus et al., 2006).

In publications produced during 1863 to 1877, Nicholaus Friedreich, a German neuroscientist from a group of medical experts, introduced a novel ailment condition (Koeppen, 2013), which was termed later Friedreich's ataxia (FA). It is a novel illness defined by progressive degeneration associated atrophy of the posteriorly situated spinal columns, resulting to development and advancement of ataxia, loss of sensation, and extreme muscles fatigue in affected people, and was frequently linked with cardiomyopathy. Harmful mutations in the frataxin gene (FXN) produce FA (Campuzano et al., 1996). Like in most individuals, one of most prevalent type mutation is a GAA trinucleotide repetition in the starting intron of FXN that is inappropriately enlarged (typically about 600 and 900 repetitions) (Campuzano et al., 1996; Monrós et al., 1997).

Variations in the levels of iron-related markers such ferroportin, ferritin and transferrin receptor 1 in the dentate nuclei and dorsal ganglia (Koeppen et al., 2012) corroborated the occurrence of iron processing variation in the nervous system of FA individuals (Koeppen et al., 2009). Mostly in instance of dentate nuclei, researchers saw a transfer of iron from the damaged neuronal cells to the microglial cells, and in the instance of dorsal ganglia, researchers detected a transfer of iron from the neuronal cells to the satellite cells. The increase in iron status in such locations coincides with formation of ROS, implying potential changes in iron equilibrium may play a role in etiopathogenesis via ROS generation. Frataxin insufficiency is also linked to inadequate antioxidant defense system, resulting in an oxidative stress-prone phenotype in neurons (Chantrel-Groussard et al., 2001; Paupe et al., 2009).

3 Calcium

Calcium (Ca2+) governs a wide range of cellular processes, such as responsible for muscle contraction, chemical secretion, different metabolic reactions, gene expression, cell growth and function, and also for cellular damage (Berridge, 2012). These ions move into the cell primarily using ion channels, which are trans-membrane proteins. Ca2+ channels (either voltage-dependent calcium channels or receptor-based calcium channels) don't really need ATP, however Ca-pumps (ATP-ases) must need ATP for transfer of Ca2+ across it. The sarco-endoplasmic reticulum calcium pump (SERCA) transports a portion of intracellular Ca2+ to the endoplasmic reticulum (ER), where it is generated by involvement of inositol 1,4,5-triphosphate receptors (IP3R) or ryanodine receptors (RyR) (Görlach et al., 2015).

Other cellular compartments with highly specialized Ca2+ transport mechanisms include mitochondria (power house of the cell), the nucleus (brain of the cell), and the Golgi bodies (packaging unit of the cell). In case of mitochondria Ca2+ transport is mainly electrogenic (process in which the transfer of net charge across the membrane takes place by electrical activity), owing to the enormous gradient created across the mitochondrial inner-membrane by the respiratory chain's proton pumping. Ca2+ balance inside the mitochondria is critical for cell processes and pathology and its uptake by mitochondria, regulates the speed at which energy is produced, influences the intensity and spatial and temporal rhythms of cytosolic Ca2+ outputs, and plays a role in the cell demise (Görlach et al., 2015).

3.1 Homeostasis and Repercussion of Altered Concentration of Brain Calcium

Calcium, an ubiquitous signaling molecule that controls a diverse number of cell functions across period (Berridge et al., 2003). Unbound Ca2+ concentrations within nerve cells are in the 70 to 100 nm region at resting state however outside cells, Ca2+ levels are around 1.5 mM. Such huge concentration ratio, together with resting potential levels of 70 to 90 mV (negative interior of the cell), produces an electrochemical gradient that encourages Ca2+ entrance. Ca2+ homeostasis and signalling are critical for normal cell proliferation and development; as a result, neurons in the brain have strong Ca2+ homeostatic and signalling systems (Berridge, 1998; Brini et al., 2014), that govern the neurological mechanisms that underlie neuronal plasticity and complex mental cognitive processes like memory consolidation. Ca2+, also deposited in cellular organelles like the ER, where it has a free amount of 0.5 mM (Núñez & Hidalgo, 2019). The two plasma membrane calcium (PMCA) transporters, the PMCA pump, and the Na+/Ca2+ exchanger, as well as the sarcplasmic/endoplasmic reticulum Ca2+-ATPase (SERCA) pump, which regulates the appropriate concentration gradient among the endoplasmic reticulum and the cytoplasm, seem to be the key mechanisms responsible for calcium balance (Brini

et al., 2014). Such transporters use a multi-faceted approach and have a wide range of calcium binding affinity, transfer rates, and potentials to ensure that appropriate intracellular gains in unbound calcium concentration, identified as calcium signals, produced by the various sensory input received by neuronal cells are properly managed.

3.2 Brain Anomalies and Calcium

The calcium signalling is critical for appropriate functioning of neurons, as described under Sect. 3.1. Just brief surges in cytosolic calcium occur during healthy settings; however, diseased situations disrupt the cellular systems that govern calcium equilibrium and signalling, culminating in calcium imbalance that eventually contribute to neurodegenerative conditions (Brini et al., 2014; Ijomone et al., 2020). Additionally, reduced concentrations and functionality deterioration of PMCA subtypes have also been linked to neurodegenerative conditions (Hajieva et al., 2018; Strehler & Thayer, 2018). The capability to control calcium concentrations is damaged in processes linked with neuropathological ageing (Doser & Hoerndli, 2021). However, very modest changes in calcium concentration can damage neuronal cells, increased vulnerability to suicide stimulus. Similarly, a disruption in calcium balance has been observed in a variety of CNS disorders, including Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS), Multiple sclerosis (MS), and Parkinson's disease (PD), etc. (Pchitskaya et al., 2018; Franco-Iborra et al., 2018; Popugaeva et al., 2018; Post et al., 2018; Sirabella et al., 2018; Núñez & Hidalgo, 2019). Nonetheless, numerous processes have been linked to calcium imbalance, which include changes in calcium ions buffer capacity and/or distorted calcium channel processes, often including voltage-gated calcium channels (VGCCs) (Veng & Browning, 2002; Campbell et al., 1996), NMDA receptors (NMDARs), and Ryanodine receptors (RyR) channels (Bodhinathan et al., 2010), as well as elevated excitotoxicity risk and compromised endoplasmic and mitochondrial processes (Marambaud et al., 2009). Similarly, decreased endoplasmic calcium transmission has been linked to synaptic dysfunction and death in a variety of clinical situations (Okubo et al., 2018). Unusually excessive intracellular calcium activates calcium regulated enzymes such as lipases and proteases of calpain group, which cause cellular damage or demise (Nixon, 2003). Because mitochondria immediately sense calcium signals originating from subcellular organ, endoplasmic reticulum, and as both organelles have molecular connections and close proximity, functions of mitochondria is definitely altered in neurodegeneration (Area-Gomez & Schon, 2016; Popugaeva et al., 2017; Lee et al., 2018). Furthermore, in neurological disorders, the physiological equilibrium among the events of calcium/calmodulin-dependent protein kinase II (CaMKII) and calcium-regulated phosphatases, like calcineurin, is disrupted; this disruption causes cognitive deficits and promotes long-term depression, impaired learning and spatial memory leading to cell death

(Berridge, 2011; Bezprozvanny & Hiesinger, 2013; Popugaeva et al., 2017). The calcium signalling modulator's protective role in amelioration of neurodegenerative disease are not fully figured out. Alicapistat, a calpain inhibitor was investigated in a human trial after showing promising results in pre-clinical studies on animals for neurodegenerative disorders (Fà et al., 2016). These investigations, however, were discontinued because poor pharmacodynamic profile observed with alicapistat (Lon et al., 2019). Furthermore, just few new calcium-regulated pathway-targeting drugs are now being investigated in clinical testing (Plascencia-Villa & Perry, 2021). The NMDA-receptor antagonist, e.g. memantine got approval by the US FDA, has been shown to counteract calcium accumulation within neurons, which can exacerbate cell death (Lipton, 2006; Bezprozvanny & Mattson, 2008). Memantine, on the other hand, does not cure or halt neuron deterioration; it merely alleviates the manifestations of Alzheimer's patients.

Dopaminergic nerve cells presenting autonomous pace-making functioning, which generates impulses mostly in lack of synaptic input within substantia nigra, are particularly sensitive to calcium imbalance in PD patients (Guzman et al., 2009). Further, this behavior of dopaminergic neuron puts a lot of strain on them to handle impulse-generated calcium signals properly, which is apparently facilitated by the large intracellular calcium across cell membrane L-type calcium channels, which far exceeds that with other cells (Surmeier et al., 2010). The ALS and MS (Siklós et al., 1998; Grosskreutz et al., 2010; Jaiswal, 2013; Mühling et al., 2014) have both been linked to abnormal calcium signaling (Gonsette, 2008) and it observed that the loss of motor neurons is a common symptom associated with ALS patients. Moreover, it is confirmed that calcium-overload induced excitotoxicity may play a significant role in ALS pathophysiology.

Further, calcium imbalance also associated with MS patients in which synaptic damage is triggered by glial calls stimulation and driven by impaired mitochondrial functions, excitotoxicity, excessive oxidative stress, and impaired calcium levels, which subsequently leads to the generation of proteolytic enzymes and apoptotic cell death (Gonsette, 2008).

4 Calcium-Iron Crosstalk: A Strange Phenomenon

ROS production, physiological stability of mitochondria, neuroplasticity and synapses formation are all activities that calcium and iron play in neurons. Furthermore, calcium and iron communicate with one another through ROS signalling. Elevated ROS concentrations, especially ROS production due to iron overload, have been found to alter the activity of critical participants in calcium balance and its transmission in healthy as well as elderly and individuals affected by neurological diseases (Gordeeva et al., 2003; Hidalgo & Donoso, 2008; Muñoz et al., 2020; Santambrogio et al., 2020; Doser & Hoerndli, 2021). Similarly, according to Gleitze and his coauthors (Gleitze et al., 2021) under physiological settings, ROS production

specifically by iron in neuronal cells changes upstream as well as downstream signaling of calcium, which plays a significant role in synapse creation and memory consolidation (Kishida et al., 2006; Hidalgo et al., 2007; Massaad & Klann, 2011; Muñoz et al., 2011). In brief, iron imbalance raises cytosolic calcium concentrations, which activates calcineurin, a calcium-related phosphatase involved in synaptic function and cognition (Lee et al., 2016; Baumgärtel & Mansuy, 2012). In contrast, elevated intracellular calcium through the NMDAR activate the enzymatic activity of neuronal nitric oxide synthase (Ghosh & Salerno, 2003) and produce superoxide radicals in hippocampal region of the brain (Brennan et al., 2009), whereas this calcium upsurge initiates a signal transduction pathways in cortex that maximizes superoxide formation via NADPH oxidase excitation (Girouard et al., 2009). Furthermore, iron-induced ROS levels increment stimulate calcium discharge from the endoplasmic reticulum via RyR, which are very sensitive to redox changes, in developing neurons of hippocampal region, and thus the increment in cytosolic calcium concentrations connect NMDAR stimulation to ERK1/2 excitation and its translocation to nucleus (Muñoz, 2012). Numerous results (Wu et al., 2001; Lynch, 2004; Thomas & Huganir, 2004) suggests that CREB-mediated transcription of genes responsible for synaptic plasticity is accompanied by ERK1/2-regulated long-term CREB phosphorylation. As a result, these data suggests that these event-based neuronal responses are aided by iron-induced, RyR-associated calcium release.

The excessive iron concentrations causes two separate calcium-signaling processes in astroglial cells, first in which calcium move inward via the Na+/Ca2+ transporter and second calcium discharge from the subcellular site especially endoplasmic reticulum via increased inositol 1,4,5-trisphosphate receptor activity (Guan et al., 2021). Because of evidenced metabolic and nutritional interaction among neurons and glial cells, astroglia are critical participants in brain functioning (Guerra-Gomes et al., 2018; Ratan, 2020). Thus, iron-associated calcium imbalance within astrocytes impairs neuronal performance.

5 Ferroptosis: A Cell Death

In 2012, the Stockwell Laboratory at Columbia University's Department of Biological Sciences uncovered a newer approach of controlled cell demise, termed as "Ferroptosis" (Dixon et al., 2012; Cheng et al., 2020a, b). It is a non-apoptotic controlled cell death characterized by the buildup of deadly lipid peroxidation in the presence of iron (Dixon et al., 2012). Cell enlargement (oncosis), disrupted mitochondrial structure (Stockwell et al., 2017), and specific characteristics of lipid peroxidation accompanying selective oxidation of phosphatidylethanolamine (Kagan et al., 2017) are all hallmarks of ferroptosis. Cell death is prevented by inhibiting the development of oxidized lipids. Loss of membrane permeability, widening of pores and disturbance of ionic equilibrium, and production of free

radicals that inhibit the activity of membrane-embedded proteins necessary for cell survival are hypothesized as downstream mechanisms wherein lipid peroxidation results in cell death malfunction or death (Agmon et al., 2018). The capacity of chelating agents especially iron, lipophilic antioxidants, inhibition and reduction of lipid peroxidation to decrease mortality are the main criteria for identifying ferroptosis. Reduction of glutathione, intensification of intracellular ROS and oxidative stress, overabundance of extracellular glutamate, reduced cerebral GPX4, enhanced lipoxygenase (LOX) activity, safety from lipid soluble antioxidant vitamin E (especially in AD), safeguarding from iron chelators (Devos et al., 2014), and safety from pioglitazone, an Acyl-CoA synthetase 4 (ACSL4) inhibitor (Doll et al., 2017) are all common features of ferroptosis in neurodegeneration (Lei et al., 2019). Furthermore, throughout ageing and neurological disease, brain iron stores grow, which can be identified in living individuals (Martin-Bastida et al., 2017) as well as postmortem brain.

5.1 Iron Balancing in Ferroptosis

Despite having iron in the term, 'ferroptosis' involvement and regulation have only lately been discovered. Initially, it was unclear if the ferroptosis-inducing lipid peroxidation was generated by the labile iron stock combining with lipid peroxides to generate these entities within membranes, or whether iron-dependent enzymes were entirely responsible for this oxidative event (Stockwell et al., 2020). Numerous research has found that iron-dependent lipoxygenases frequently cause the development of lipid peroxides, which are then propagated by labile iron (not linked to enzymatic reactions) to promote massive lipid peroxidation (Wenzel et al., 2017; Shah et al., 2018). Other iron-dependent enzymes may play a role in lipid peroxidation in some cases; cytochrome P450 oxidoreductase was actually recognized as a trigger of lipid peroxidation following ferroptosis (Stockwell et al., 2020; Zou et al., 2020). Ferritin is a protein that stores Fe(III) in an inert state so that it does not lead to lipid peroxidation. In nutshell, ferritin richness is a critical determinant of ferroptosis responsiveness: higher ferritin means more iron(III) preservation and higher protection to ferroptosis as the labile iron pool gets sparse. Reduction of ferritin, on the other hand, causes iron to be released into the labile iron pool, increasing vulnerability to ferroptosis. Ferritin-targeted autophagy, also referred as ferritinophagy, has been used to cause enhanced vulnerability to ferroptosis by triggering lysosomal breakdown of ferritin and discharge of iron into labile iron pool (Hou et al., 2016; Gao et al., 2016). Another iron-regulating pathway has recently been discovered, wherein prominin 2 promotes the development of ferritin-containing multivesicular structures and exosomes, that carry iron out of cells (Brown et al., 2019).

5.2 Calcium and Iron Induced Cell Death: Play Collective Role in Oxytosis or Ferroptosis

Calcium-dependent cellular damage caused by glutamate was first described as oxytosis (Murphy et al., 1988). Preliminary research further into molecular underpinnings of oxytosis suggested that a decline in cytoplasmic glutathione (GSH) content, increased ROS generation in mitochondria, peroxidation of membrane phospholipids, and significant calcium inflow were all contributing factors to death (Miyamoto et al., 1989). Reduced GSH concentration causes massive increment in ROS production leading to triggering of signaling processes that lead to a massive inward flow of calcium and results in cell demise (Maher et al., 2018). However, calcium free medium do not markedly influence cells, but increased inward flow of calcium is an important modulator of the cell death mechanism.

On other hand, ferroptosis, as we described above under Sect. 5, is a controlled cell death caused by deadly membrane phospholipids-peroxidation. For instance, iron chelating agents, lipid soluble antioxidants, and certain medicament that impede phospholipids peroxidation processes, all prevent ferroptosis-induced cellular damage (Stockwell et al., 2017; Fricker et al., 2018). Mechanism behind the occurrence of ferroptosis is selective blocking of glutathione peroxidase 4 and cystine/glutamate antiporter xc system leads to ferroptosis, for example a cystine/glutamate antiporter xc inhibitor, erastin, induces ferroptosis indicated by mitochondrial structure distortion, especially shrinkage however, no observable indications of apoptosis or necrosis (Dixon et al., 2012). The prevailing opinion is that oxytosis and ferroptosis are analogous sorts of cell death since their cell death processes are so identical (Fricker et al., 2018; Lewerenz et al., 2018; Maher et al., 2018). Even though fatal excessive inward flow of calcium is an inherent component of oxytosis, the role of calcium in ferroptosis is yet unknown. Further, a study conducted by Dixon and his coworkers (Dixon et al., 2012) discovered that calcium chelators do not prevent HT-1080 cellular demise mediated by erastin.

6 Connecting Link to Neurodegeneration: Iron, Calcium, and Ferroptosis

6.1 Pantothenate Kinase-Associated Neurodegeneration (PKAN)

PKAN is associated to number of illnesses characterized by extrapyramidal motor symptoms and brain iron buildup. Mutations in PANK2, which codes for mitochondrial pantothenate kinase 2, the first enzyme in Coenzyme A production, cause PKAN (Santambrogio et al., 2020). The molecular pathways connecting iron and calcium buildup in this illness are poorly understood. Iron as well as calcium are believed to be necessary ions for maintaining brain activity, but their reciprocal

equilibrium must be properly controlled to prevent negative consequences. Elevated iron promotes oxidative stress, which leads to changes in calcium homeostasis-related proteins (Núñez & Hidalgo, 2019; Santambrogio et al., 2020). As a result, a rise in intracellular calcium promotes mitochondrial malfunction and a disruption of iron homeostasis, implying that maintaining a healthy neural activity requires a balanced interaction between the two. Any disruption of this balance can harm nerve cells, leading to neurodegeneration. In addition, different clinical events that result in aberrant intracellular calcium signalling can trigger apoptotic cascades (Marambaud et al., 2009). Numerous neurodegenerative diseases, including AD and PD, as well as ALS (Núñez & Hidalgo, 2019), have been linked to a deleterious iron-calcium relationship. Another category of inherited diseases, known as Primary Familial Brain Calcification (PFBC), is marked by calcium phosphate accumulation in the central nervous system, contributing to subsequent neuronal damage manifested by neuromuscular disorders, cognitive deficits, and psychopathological disturbances (Westenberger et al., 2019). Santambrogio et al. discovered for the very first time in iPS-derived neurons that calcium buildup is a common indication in neurotoxicity linked with panthothenate kinase insufficiency, a condition defined predominantly by iron overload (Santambrogio et al., 2020). Furthermore, PANK2 mutations are linked to an abnormal mitochondrial CoA synthesis, which may result in a range of metabolic abnormalities related to lipid metabolism, which are required for membrane remodelling, according to the highly reliable current concept. These changes have been shown to disrupt mitochondrial walls and affect their activities (Santambrogio et al., 2015; Orellana et al., 2016), implying that lipid dyshomeostasis may play a significant role in the disease's aetiology.

A study carried out by Santambrogio and his colleague also reported that PKAN iPS-derived neurons had impaired iron metabolism but not iron deposits, which led to a rise in ROS generation and a change in mitochondrial membrane potential (Orellana et al., 2016). This can lead to a rise in intracellular calcium that can further insult the mitochondria, causing synaptic dysfunction and neuronal injury. Surprisingly, calcium buildup was already visible in patients who had an Imaging tests prior at same time as an MRI (Santambrogio et al., 2020). Despite the small number of individuals studied by Santambrogio and his team, the finding shows that calcium and iron buildup occur at the same time.

6.2 Calcineurin

Unusually elevated intracellular calcium activates calcium-regulated metabolic enzymes responsible for the metabolism of proteins and lipids, like the calpain family, and causes cell damage (Nixon, 2003). Because mitochondria immediately sense endoplasmic reticulum generated calcium signals and both organelles have direct molecular linkages and lies in close proximity, thus, mitochondrial activity is definitely altered in neurological diseases (Area-Gomez & Schon, 2016; Popugaeva et al., 2017; Lee et al., 2018). Furthermore, in neurological disease, the physiological

equilibrium among the tasks of CaMKII and calcium-regulated phosphatases, like calcineurin, is disrupted; this disruption causes synapses issues and problems and promotes long-term depression, impaired memory, and neurodegeneration (Berridge, 2011; Bezprozvanny & Hiesinger, 2013; Popugaeva et al., 2017).

6.3 *Ryanodine Receptor*

There are so many studies reported by numerous researchers discovered a link among brain iron concentrations and calcium signaling pathways. One such link was discovered after researchers reported that ROS generated by iron enhances RyR-regulated calcium discharge in in-vitro neuronal cell lines studies (Muñoz et al., 2006, 2011; Hidalgo et al., 2007; Hidalgo & Núñez, 2007). The H2O2 treatment to primary neuronal cells from hippocampus region enhances oxidation-based changes of RyR-cysteine moiety and boosts RyR-regulated calcium discharge. Further, the activation of RyR-mediated Ca2+ discharge is most likely due to RyR oxidation modifications induced by iron-generated ROS (Kemmerling et al., 2007). Some researchers studied deeply about (Muñoz et al., 2011) how an elevation in intracellular unbound calcium by iron-induced RyR activation and how it contributes to the increased phosphorylation and transportation of extracellular-signal-regulated kinases (ERK1/2) to nucleus, which is required for long-term potentiation and synapses formation (Thomas & Huganir, 2004).

6.4 *Acyl-CoA Synthetase Long-Chain Family Member 4 (ACSL4)*

The ACSL4 gene encodes for fatty acid-CoA ligase 4 (FACL4), is an acyl-CoA synthetase, that is an important type of lipid metabolic enzymes. ACSL4 is characterized by its specificity for arachidonic acid and has recently been discovered to play a key function in ferroptosis (Cheng et al., 2020a, b). Cell death is caused by enzymatic abnormalities of amino acid synthesis pathway, lipid synthesis and metabolism, and iron trafficking, according to past findings (Bhutia & Ganapathy, 2016; Abeti et al., 2016; Yu et al., 2017). Furthermore, earlier research has linked ferroptosis to metabolism-related problems with amino acid and lipid biosynthesis as well as iron transportation (Cao & Dixon, 2016; Stockwell et al., 2017; Wang et al., 2017; Doll & Conrad, 2017). Three main elements that govern ferroptosis are ACSL4, an antiporter system of cysteine and glutamate, and glutathione peroxidase 4 (Doll & Conrad, 2017), in which, ACSL4 stimulates the production of phytosterol esters metabolised from arachidonic acid and epinephrine, a mechanism linked to ferroptosis, according to current data (Doll et al., 2017; Kagan et al., 2017). Increased levels of ACSL4 enhances ferroptosis and is thought to be critical modulator of ferroptosis and thus involved in pathogenesis of neurodegenerative diseases (Kagan et al., 2017).

7 Conclusion

In the brain, multiple processes and networks regulate neuronal metabolism of iron and calcium signalling, and any one of them might have a negative impact on cognition abilities. Numerous studies have found a link between impaired calcium levels, disrupted calcium signalling, iron imbalance, and ferroptosis in neurological issues, are summarized here. This chapter provides a thorough knowledge about how imbalance of calcium and iron and both in the brain impacts on brain physiology and how they contributes to neurodegenerative diseases.

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Conflict of Interests Authors declare no conflict of interests.

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Chapter 7
Iron and Alzheimer's Disease

Yi Liang Lo and Shi-Hui Cheng

Abbreviations

ACh	Acetylcholine
AD	Alzheimer's disease
APOE	Apolipoprotein-E
APP	Amyloid precursor protein
Aβ	Beta-amyloid protein
BBB	Blood-brain barrier
BMVEC	Brain microvascular endothelial cells
Ca^{2+}-ATPase	Calcium ATPase
CDC	Centers for Disease Control and Prevention
CDK5	Cyclin-dependent kinase 5
ChEI	Cholinesterase inhibitor
CNS	Central nervous system
CSF	Cerebrospinal fluid
DASH	Dietary Approaches to Stop Hypertension
DMT1	Divalent metal transporter
DNA	Deoxyribonucleic acid
EBN	Edible bird's nest
EOAD	Early-onset Alzheimer's disease
ER	Endoplasmic reticulum
ERK	Extracellular signal-regulated kinase
FDA	United States Food and Drug Administration
Fe	Iron

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Fe^{2+}	Ferrous ion
Fe^{3+}	Ferric ion
GABA	Gamma aminobutyric acid
GFAP	Glial fibrillary acidic protein
GPX4	Glutathione peroxidase 4
GPX4BIKO	GPX4 brain inducible knockout
GSK3β	Glycogen synthase kinase 3
Hb	Haemoglobin
HCP1	Haem carrier protein
HDAC	Histone deacetylase
H-ferritin	Heavy ferritin subunit
His	Histidine
HO	Haem-oxygenase
IDA	Iron-deficiency anaemia
IF	Interstitial fluid
IRE	Iron regulatory element
IREG1/Fpn1	Ferroportin
IRP	Iron regulatory protein
LOAD	Late-onset Alzheimer's disease
LOOH	Lipid hydroperoxide
MCI	Mild cognitive impairment
MedDiet	Mediterranean diet
MIND	Mediterranean-DASH Intervention for Neurodegenerative Delay
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MUFA	Mono-unsaturated fatty acid
Na^+/K^+-ATPase	Sodium-potassium ATPase pump
NBIA	Neurodegeneration with brain iron accumulation
NFT	Neurofibrillary tangles
NIH	National Institutes of Health
NMDA	N-Methyl-D-Aspartate
NMDAR	N-Methyl-D-Aspartate receptor
NTBI	Non-transferrin-bound iron
PD	Parkinson's disease
PET	Positron emission tomography
pH	Potential/Power of hydrogen
PP2A	Protein phosphatase 2
PPA	Primary progressive aphasia
PSEN	Presenilin
PUFA	Poly-unsaturated fatty acid
qPCR	Real-time/Quantitative polymerase chain reaction
RAF	Rapidly accelerated fibrosarcoma
RAS	Rat Sarcoma virus protein
RBC	Red blood cells

RDA	Recommended daily allowance
RNA	Ribonucleic acid
ROS	Reactive oxygen species
rRNA	Ribosomal ribonucleic acid
RSL3	RAS-selective lethal 3
RT	Reminiscence therapy
RT-PCR	Reverse transcription polymerase chain reaction
SDH	Succinate dehydrogenase
SPT	Simulated presence therapy
TCM	Traditional Chinese medicine
Tf	Transferrin
Tf-Fe	Transferrin-bound iron
TfR	Transferrin receptor
Tim2	T-cell immunoglobulin mucin domain protein-2
TREM2	Triggering receptor expressed on myeloid cells 2
TSA	Trichostatin A
US	United States of America
USD	United States Dollar
UTR	Untranslated region
WHO	World Health Organization
τ	Tau protein

1 Introduction

Iron (Fe) is an essential micronutrient that plays an important role in various biochemical processes. Its chemical properties as a reducing agent make it crucial for electron transfer in redox reactions, which are principal steps in cellular respiration/energy production (Abbaspour et al., 2014; Paul et al., 2017; Lane et al., 2018). Iron is also a key element responsible for producing haemoglobins (Hb) in erythrocytes/red blood cells (RBC) to transport oxygen in the body (Abbaspour et al., 2014; Paul et al., 2017; Lane et al., 2018). Other functions of iron not only act as cofactors for enzymes like succinate dehydrogenase (SDH), but also involved in the regulation of gene expression which affects cell growth and differentiation (Paul et al., 2017; Gao et al., 2019). Dietary iron in food can be categorized into two forms, haem and non-haem iron (Moustarah & Mohiuddin, 2021; National Institutes of Health, 2021). Haem iron is abundant and only found in animal sources such as red meats, poultry and seafood (Hooda et al., 2014; Moustarah & Mohiuddin, 2021; National Institutes of Health, 2021). Conversely, non-haem iron is found in plant and dairy products like fruits, vegetables, nuts, lentils, cereals and other iron-fortified crops (Hooda et al., 2014; Moustarah & Mohiuddin, 2021; National Institutes of Health, 2021; The Nutrition Source, 2021).

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that shrinks (atrophy) the brain structure, resulting in the deterioration of various cognitive abilities in learning, memory, emotions, and sensory perception (Centers for Disease Control and Prevention, 2020; Alzheimer's Association, 2021; World Health Organization, 2021a). Being classified as a type of dementia, AD is the most common type which contributes to about 60–70% of cases worldwide according to the World Health Organization (WHO) (World Health Organization, 2021a). It was also stated that there are currently more than 55 million people suffering from dementia worldwide, with approximately ten million new cases increasing every year (World Health Organization, 2021a). This disease is reported to increase inevitably if left uncontrolled. The Alzheimer's Association predicts that the prevalence of AD could escalate from 26 million in 2009 to more than 100 million worldwide by 2050 due to longer lifespans in humans, and ageing as a strongly known risk factor (Mucke, 2009; Centers for Disease Control and Prevention, 2020; World Health Organization, 2021a). Despite the fact that it is mainly found in ageing populations, it is not an inevitable consequence of ageing, for AD is developed by a myriad of factors rather than a singular cause like most chronic diseases (Centers for Disease Control and Prevention, 2020; World Health Organization, 2021a). As such, it is possible that younger people may be diagnosed with AD, but it is rare in many cases (Centers for Disease Control and Prevention, 2020). Studies have shown that AD begin for two decades or more before memory or other cognitive symptoms arise (Villemagne et al., 2013; Barthélemy et al., 2020; Alzheimer's Association, 2021). AD is also one of the most fatal diseases known to mankind, with death rates increasing unlike other chronic diseases such as heart disease and cancer on the decline (Centers for Disease Control and Prevention, 2020). Reports have shown that AD death rates increased by 39 percent in the United States (US) between 2000 and 2010, with the death proportion was found to be higher in women than men (Tejada-Vera, 2013; Centers for Disease Control and Prevention, 2020; Alzheimer's Association, 2021; World Health Organization, 2021a).

As one of the major causes of disability and dependency among the global population, AD has a detrimental impact on our society and daily lives. According to the Centres for Disease Control and Prevention (CDC), AD is the sixth leading cause of death in adults in the US (Centers for Disease Control and Prevention, 2020). Dementia itself as a whole has significant associations with economic costs invested in caregiving and medical treatment, which creates a heavy burden on communities and health care systems worldwide (World Health Organization, 2021a). It was reported that the estimated total global societal cost of dementia was USD 1.3 trillion in 2019, and these costs are likely to exceed USD 2.8 trillion by 2030 with the increasing number of people with dementia and care costs (World Health Organization, 2021a). The CDC also supports this financial pressure, as costs for treating AD were likely to increase between USD 379 and more than USD 500 billion in the US annually by 2040 (Centers for Disease Control and Prevention, 2020). While most people living with AD are being supported with caregiving by family and friends, it may become an overwhelming task to the caregivers to adapt to new challenges, with some patients requiring intensive care as the disease worsens

(Centers for Disease Control and Prevention, 2020; World Health Organization, 2021a). The WHO reported that informal caregivers (most commonly friends and family members) spent an average of 5 hours per day providing care to people suffering from dementia, with 70% of carer hours being taken responsibility by women (World Health Organization, 2021a). This results in great stress to families and caregivers, where pressures on financial, physical and emotional aspects emerge (Centers for Disease Control and Prevention, 2020; World Health Organization, 2021a). Nevertheless, caregiving provides benefits to both the caregiver as well as the patient for bringing personal fulfilment to the carer, as well as developing new skillsets and strengthening family relationships (Centers for Disease Control and Prevention, 2020). Another impact is that people with AD or dementia are often being discriminated and stripped of their basic rights and freedom available to others (World Health Organization, 2021a). This inequality is prevalent in many countries, whereby physical or chemical restraints were used considerably in patients even though regulations to protect their standard rights of freedom and choice are in place (World Health Organization, 2021a). While AD will prove to be a growing societal burden as the global population ages, there is, unfortunately, no viable cure for AD, with controlled drugs (e.g., aducanumab) and disease-modifying therapies developed to date only have limited efficacy on altering disease progression (Belaidi & Bush, 2016; World Health Organization, 2021a).

To this day, the role of iron in AD is not fully discovered yet, as research studies in iron neurochemistry and its role in neurodegenerative disorders has only received significance in almost the last three decades due to debates on iron increase as a primary or secondary event in such diseases (Belaidi & Bush, 2016). However, it was believed that iron is involved in the incidence of AD, as cumulating evidence indicates that the risk of AD surges with the association of increasing age and oxidative stress in the brain (Bonda et al., 2010; Huang et al., 2016; Lane et al., 2018). The fundamental contribution of oxidative stress is highlighted greatly, as higher concentrations of reactive oxygen species (ROS) are discovered in AD than in healthy brains (Bonda et al., 2010; Huang et al., 2016; Lane et al., 2018). In addition, with excessive redox-active degradation products, it kindles the dysregulation of redox-active metals (particularly iron and copper) within the brain, causing a pathological accumulation of metal ion levels, which collectively promote Fe-induced oxidative stress that leads to neuroinflammation and neurotoxicity (ferroptosis in worse cases) (Huang et al., 2004; Yu et al., 2009; Yang & Stockwell, 2016; Belaidi & Bush, 2016; Lane et al., 2018). Therefore, with the support from modern advancements in diagnostic and treatment options towards various neurodegenerative diseases, it is potentially suspected that iron plays a central role in neurodegeneration and oxidative stress in AD for it is a redox-active transition metal, as well as its amassment in several brain regions in healthy aging and neurodegenerative disordered patients (Ward et al., 2014; Belaidi & Bush, 2016; Lane et al., 2018). Thus, this book chapter discussed the current knowledge on the pathogenesis of AD and the relationship on how iron is involved in the major events occurring in AD development. To explain the effects of iron on AD, this book chapter emphasized the evidence on iron homeostasis in the brain and its importance of the tight

regulation of its uptake, transport and storage due to the lack of an iron-specific excretory mechanism under physiological terms (Kohgo et al., 2008; Belaidi & Bush, 2016; Ems et al., 2021).

2 Alzheimer's Disease

2.1 Pathogenesis

Many hypotheses have been proposed regarding the cause of AD (Mucke, 2009; Walker, 2018; Long & Holtzman, 2019). While the pathophysiological mechanisms of AD currently remain unclear, plenty of evidence suggested that AD and most neurodegenerative diseases were attributed to the accumulation of abnormal protein filaments in the form of neuritic/senile plaques and neurofibrillary tangles based on histopathological hallmarks (Swerdlow, 2007; Mucke, 2009; Walker, 2018; Tiwari et al., 2019; Kumar et al., 2021).

Plaques are extracellular deposits that consist of a core molecular structure made of beta-amyloid peptides (Aβ) (Long & Holtzman, 2019; Kumar et al., 2021). Aβ is a 40 to 42 amino acid long peptide that is derived from a larger transmembrane protein known as amyloid precursor protein (APP) through proteolytic cleavage (Goedert & Spillantini, 2006; Kumar et al., 2021). This catabolic process involves the actions of proteases namely α-, β-, and γ-secretase, where α-secretase plays a role in preventing Aβ formation by cleaving APP to produce precursor fragments which are soluble and non-toxic to neurons (Goedert & Spillantini, 2006; Long & Holtzman, 2019; Kumar et al., 2021). However, Aβ is produced when a sequential cleavage happens by both β-secretase and γ-secretase that binds to the N- and C-termini of the Aβ sequence located in APP respectively, resulting in the production of sequentially shorter peptides which will combine and form mainly into either a 40 [beta-amyloid 40 ($A\beta_{40}$)] or 42 [beta-amyloid 42 ($A\beta_{42}$)] amino acid long chain (Goedert & Spillantini, 2006; Tiwari et al., 2019; Long & Holtzman, 2019; Kumar et al., 2021). $A\beta_{40}$ is produced abundantly and it is the less amyloidogenic form in nature, whereas $A\beta_{42}$ is less abundant but it is highly insoluble and severely neurotoxic, which explains why $A\beta_{42}$ deposits easier in the formation of plaques (Goedert & Spillantini, 2006; Swerdlow, 2007; Tiwari et al., 2019; Long & Holtzman, 2019). Nonetheless, both Aβ polymers have a direct role in plaque formation and induced neurotoxicity due to amyloid aggregation (Tiwari et al., 2019). Usually, Aβ levels are regulated tightly, as it is quickly extracted by clearance mechanisms in the brain (Swerdlow, 2007; Mucke, 2009). But it is possible to happen due to the overproduction or dysfunction in Aβ clearance, leading to a net increase in Aβ (Mucke, 2009). When this occurs, free Aβ peptides will clump into beta-sheet conformation prions that comes in various forms ranging from oligomers to fibrils, protofibrils and amyloid plaques, in which $A\beta_{42}$ is more aggregation-prone in the Aβ assembly process (Mucke, 2009; Tiwari et al., 2019; Long & Holtzman, 2019). Therefore, elevation in both $A\beta_{40}/A\beta_{42}$ levels was found to block ion signalling

channels, disrupt calcium homeostasis, as well as increase mitochondrial oxidative stress that reduces energy metabolism and glucose regulation, which collectively and ultimately lead to neuronal apoptosis (Tiwari et al., 2019). Aβ plaques initially occur in several regions of the neocortex before spreading out to the remaining parts of the brain (e.g., hippocampus, amygdala, diencephalon, basal ganglia etc.) in later stages (Tiwari et al., 2019).

Neurofibrillary tangles (NFT) are intracellular fibrillary structures found in neurons created by hyperphosphorylated proteins named tau (τ) (Tiwari et al., 2019; Kumar et al., 2021). The primary function of τ proteins is to stabilize axonal microtubules, as it consists of a microtubule-binding domain that is purposed for creating them by the co-assembly of tubulin (Tiwari et al., 2019; Long & Holtzman, 2019; Kumar et al., 2021). Neurons in the brain contain a network of microtubules that are essential for intracellular transport (Long & Holtzman, 2019; Kumar et al., 2021). In AD, due to the build-up of extracellular Aβ plaques, hyperphosphorylation occurs in τ through the action of several kinases [mainly glycogen synthase kinase 3 (GSK3β) and cyclin-dependent kinase 5 (CDK5)], which leads to the formation of τ oligomerization and aggregation (Tiwari et al., 2019; Long & Holtzman, 2019; Kumar et al., 2021). The consequences after hyperphosphorylation are the destabilization of microtubules, which disintegrates and cause the hyperphosphorylated τ aggregates to form twisted strands/tangles (NFT) (Tiwari et al., 2019; Kumar et al., 2021). As NFTs are highly insoluble patches which are deposited within the neuronal cytoplasm, it inhibits cellular processes and obstructs nutrient intake from the microtubules that were damaged in the process due to NFT (Goedert & Spillantini, 2006; Tiwari et al., 2019; Kumar et al., 2021). All of which leads to the loss of neuronal communication and signalling processes, and eventually neuronal cell death (Tiwari et al., 2019). Tau aggregates develop first in the hippocampus before they may spread throughout the cerebral cortex (Long & Holtzman, 2019; Kumar et al., 2021). According to longitudinal and cross-sectional studies of tau- and amyloid-PET imaging and MRI scans, unlike Aβ plaques, tangles are more strongly correlated to the progression of cognitive impairment in AD (Aschenbrenner et al., 2018; Hanseeuw et al., 2019).

The destructive pairing of plaques and tangles in the development of AD can also be associated due to genetic factors. It was reported that 1–2% of total AD cases is inherited through autosomal dominant disorders, constituting early-onset AD (EOAD) with a faster rate of progression (Long & Holtzman, 2019). Mutations can occur in the APP gene located on chromosome 21 which is linked to familial AD (Swerdlow, 2007; Kumar et al., 2021). It also can occur in presenilin (PSEN) genes (PSEN1 and PSEN2 located on chromosome 14 and 1 respectively), where these PSEN isoforms are part of the total protein subunits that form the γ-secretase complex (Swerdlow, 2007; Tiwari et al., 2019; Long & Holtzman, 2019; Kumar et al., 2021). Such mutations in any of these genes will increase the production of Aβ plaques, causing a cascade of events that drive towards AD development (Swerdlow, 2007; Tiwari et al., 2019; Kumar et al., 2021). Despite the case, the high remainder of total AD cases is not genetically inherited, known as sporadic AD where environmental or genetic differences act as risk factors. Sporadic AD in the majority of

cases develops after the age of 65 years, which mostly presents with late-onset AD (LOAD) (Long & Holtzman, 2019). In LOAD/sporadic AD, the strongest genetic risk factor is the apolipoprotein-E (APOE) gene in chromosome 19 (Long & Holtzman, 2019; Bryant, 2021; Kumar et al., 2021; Sienski et al., 2021). APOE functions as a regulator in lipid metabolism to transport and deliver lipids to target sites (Swerdlow, 2007; Long & Holtzman, 2019; Kumar et al., 2021). The APOE gene consists of three alleles encoding three APOE isoforms namely APOEε2, APOEε3 and APOEε4 (Swerdlow, 2007; Long & Holtzman, 2019). The APOEε4 allele is responsible for disrupting the normal function of APOE, as a single copy increases the risk of LOAD by 3 ~ four-fold, whereas two copies increase the risk by approximately 12-fold (Long & Holtzman, 2019; Kumar et al., 2021). It is still important to note that a single APOEε4 allele does not sentence an inevitable lead to AD, as environmental effects and genetic modifiers can result in incomplete penetrance (Gureje et al., 2006; Hall et al., 2006; Blennow et al., 2006; Waring & Rosenberg, 2008; Perea et al., 2020; Kumar et al., 2021). However, 50% of people who carry one allele have AD, while 90% develop AD for having two alleles (Karch & Goate, 2015; Kumar et al., 2021). A study in 2006 also has proved that 40–80% of people with AD have at least one APOEε4 allele (Mahley et al., 2006). Moreover, the age of disease onset of AD lowers as each APOEε4 allele increases in number (Kumar et al., 2021). An increase in AD risk is also proposed in more studies to be significantly associated with variant alleles found in triggering receptor expressed on myeloid cells 2 (TREM2) gene, which is a transmembrane receptor expressed on microglia that is responsible to remove Aβ plaques and tangles (Guerreiro et al., 2013; Jonsson et al., 2013; Karch & Goate, 2015; Tiwari et al., 2019; Long & Holtzman, 2019).

Other risk factors can also come into play in the onset of AD, involving many variables like metabolic/nutritional disorders and exposure to environmental changes besides aging and genetic mutations (Sezgin & Dincer, 2014; Tiwari et al., 2019). In addition to aging, there is a decent possibility that other chronic diseases (e.g., hypertension, diabetes, obesity) and inflammatory disorders may have an effect on AD (Tiwari et al., 2019). In terms of epigenetics, these factors may induce epigenetic alterations and EOAD, as associations between aging and DNA methylation events have been reported in several regions of the brain (Hernandez et al., 2011; Balazs, 2014). Epigenetics is important to understand AD for its mechanisms involved in memory formation and conservation, while low rates of DNA methylation led to memory loss due to the degeneration of neuronal plasticity and histone modification dysregulation (Mastroeni et al., 2011; Tiwari et al., 2019). Studies on APP/PSEN1 double-mutant transgenic mice show that reduction in histone acetylation by the enzyme histone deacetylase (HDAC) was linked to impairment in associative learning ability, and HDAC inhibitors such as trichostatin A (TSA) demonstrate promising results on potentiating synaptic plasticity, memory and learning abilities (Francis et al., 2009; Delgado-Morales et al., 2017).

2.2 Symptoms and Treatments

As AD induces cognitive impairment through a progressive nature, its symptoms are dependent on the severity stage/degree of the disease. AD is classified into three stages: early/preclinical/presymptomatic, middle/mild/moderate, and late/severe/dementia stages (Kumar et al., 2021; National Institute on Aging, 2021). The origins of its pathogenesis start in the hippocampus which is responsible for forming memories, which explains why the first and most common symptom is short-term memory loss, followed by disabilities in problem-solving, judgment and critical thinking (National Institute on Aging, 2021). In the preclinical stages, individuals can appear asymptomatic with concrete laboratory evidence through neuropsychological testing (Backman et al., 2004; Kumar et al., 2021). As such, AD can be speculated by the identification of several biomarkers including amyloid, tau proteins and APOEε4 levels to suspect its existence during the asymptomatic stage (Kumar et al., 2021). Eventually, a definitive diagnosis is considered as the impairment of memory and learning worsens, with multiple neuropsychiatric symptoms like apathy, depression, apraxia, social withdrawal, disinhibition, and losses in executive functions beginning to emerge (Backman et al., 2004; Kumar et al., 2021). Primary progressive aphasia (PPA) also follows with a decrease in oral and written language as it approaches the middle stage (Förstl & Kurz, 1999; Taler & Phillips, 2008; Kumar et al., 2021). Patients start to suffer impairments in memory and/or non-memory domains in the brain, known as mild cognitive impairment (MCI) (Kumar et al., 2021). While these individuals may still be able to work, socialize and function independently, the ability to perform most daily activities through the progressive deterioration of AD will be lost inevitably (Förstl & Kurz, 1999; Kumar et al., 2021). Simultaneously, motor functions begin to be impeded in the form of apraxia, and long-term memory becomes compromised (Förstl & Kurz, 1999). During the late stage, patients suffer from severe memory impairment to the extent that they are completely dependent upon caregivers (Förstl & Kurz, 1999; Kumar et al., 2021; National Institute on Aging, 2021). Language usage is significantly reduced in AD patients, which eventually leads to a complete loss of speech (Förstl & Kurz, 1999). Delusional symptoms become more prevalent, as 20–40% of patients will experience it in this stage (Förstl & Kurz, 1999; Kumar et al., 2021). Hallucinations also become more common in terms of visuospatial, auditory and olfactory features (Förstl & Kurz, 1999; Kumar et al., 2021). Extreme apathy and exhaustion arise due to associations of restlessness and uncontrolled aggression resulting from dysregulations in the circadian rhythm (Förstl & Kurz, 1999; Kumar et al., 2021). As such, manifestations like wandering, irritability and emotional lability appear more seriously than in previous stages (Kumar et al., 2021). Muscle mass and mobility decrease significantly to the point where patients cannot perform the most basic functions like chewing and swallowing due to severe apraxia, causing most to end up bedridden and require caregiving to carry out daily activities (Förstl & Kurz, 1999; Kumar et al., 2021). The long persistence of these collective symptoms and other risk factors associated with AD (e.g., old age) eventually leads

to death as a result of a decreased life expectancy, usually due to pneumonia followed by myocardial infarction and septicaemia (Förstl & Kurz, 1999; Kumar et al., 2021).

Despite the severity of the disease, there is, however, no cure for AD. To this date, only symptomatic treatments are available to suppress the progression of the disease. One of these treatments is the usage of approved medications, which mainly focuses on either the involvement of cholinesterase inhibitors (ChEI), or partial N-Methyl D-Aspartate (NMDA) antagonists named memantine (Mucke, 2009; Long & Holtzman, 2019; Kumar et al., 2021). ChEIs act on reducing the breakdown of acetylcholine (ACh), an important neurotransmitter in the brain which is decreased in AD patients (Fullwood, 2007; Long & Holtzman, 2019; Kumar et al., 2021). Drugs that are FDA-approved for this category include donepezil, rivastigmine and galantamine which effectively increase the concentrations of ACh (Long & Holtzman, 2019; Kumar et al., 2021). There is strong evidence stating that these medications are applicable in all stages of AD depending on their pharmacological characteristics (Birks, 2006; Kumar et al., 2021). More studies also show that ChEIs have disease-modifying effects on providing neuroprotective activities in the brain, while recent findings discovered that these drugs decrease Aβ levels (Fullwood, 2007). Having said that, the overall effects of these medications are modest (Birks & Grimley Evans, 2015; Birks & Harvey, 2018; Long & Holtzman, 2019; Fink et al., 2020). Not only are they ineffective on long-term disease progression, but they also possess side effects when consumed regularly (Long & Holtzman, 2019; Kumar et al., 2021). Excess ChEIs in the body usually leads to nausea, vomiting and diarrhoea, with around 10–20% of users will experience such side effects (Alldredge et al., 2013; Kumar et al., 2021). The latest findings on ChEI usage show no effects on treating MCI, and may worsen AD conditions in the preclinical stage (Han et al., 2019; Long & Holtzman, 2019).

Memantine is another type of FDA-approved drug used to treat moderate-to-severe AD by inhibiting NMDA receptors (NMDAR), preventing excitotoxicity due to glutamate overstimulation, and decelerating intracellular calcium accumulation (Lipton, 2006; Long & Holtzman, 2019; Kumar et al., 2021). Although the exact mechanism of its effects is unclear, memantine has proved to be able to treat AD with credible efficacy and safety when used alone or in combination with ChEIs (Kishi et al., 2017; Long & Holtzman, 2019; Kumar et al., 2021). A meta-analysis on reviewing the effects of memantine in thirty studies showed its significant improvements in cognitive function and behavioural disturbances without considerable heterogeneity (Kishi et al., 2017). However, similar to ChEIs, the effects of memantine are small in treating moderate-to-severe AD, and has no effect on long-term disease progression (Apostolova, 2016; McShane et al., 2019; Long & Holtzman, 2019; Kumar et al., 2021). Adverse effects of memantine consumption are mild, which include dizziness, headaches, constipation and hypertension (Kumar et al., 2021). Although the combination of donepezil and memantine was found to be statistically significant, its effects were still marginal in terms of clinical stages (Raina et al., 2008; Long & Holtzman, 2019). Therefore, this medication is not recommended to be prescribed to patients with mild AD, and treatment should be

halted immediately if disease conditions worsen or remain unchanged after long-duration memantine dosage was given (Long & Holtzman, 2019; Kumar et al., 2021).

In more severe cases of AD where uncontrolled agitation is expressed, antipsychotics are used in modest amounts in order to reduce aggression and psychosis (Ballard et al., 2006; Schneider et al., 2006; Apostolova, 2016; Kumar et al., 2021). It is only considered as a last resort if the patient or caregiver has been fatigued in the treatment process (Kumar et al., 2021). Yet, usage of this drug class comes with heavy drawbacks compared to its limited treatment advantages (Ballard et al., 2006; Vigen et al., 2011). Research on antipsychotics was known to cause serious adverse effects like stroke, extrapyramidal symptoms and accelerated cognitive impairment (Ballard et al., 2006; Vigen et al., 2011; Apostolova, 2016). Further meta-analyses also have suggested a significant increase in mortality was associated with the chronic usage of antipsychotics (Ballard et al., 2006, 2009; Declercq et al., 2013). Withdrawal from long-term antipsychotic use may appear to be safe in some AD patients, but an increase of relapse was discovered in cases of discontinuation (Declercq et al., 2013). In addition, certain patients with severe symptoms could benefit and may heavily depend on antipsychotic medication to suppress deterioration of behaviour (Declercq et al., 2013).

Besides pharmaceutical treatment, psychosocial interventions are used as adjuncts or alternative therapies for AD. Simple approaches towards environmental and behavioural aspects such as caregiving, music therapy, reminiscence therapy (RT), simulated presence therapy (SPT) and aerobic exercise/physical activity may be very useful in managing challenging behaviours (Farina et al., 2014; Okonkwo et al., 2014; Cheng, 2016; Abraha et al., 2017a, 2017b; Kumar et al., 2021). Despite the case, no robust or adequate evidence supports the effectiveness of these therapies on behavioural issues associated with AD, as shown with the lack of high-quality research and contradictory results or limitations from randomised trials (Robinson et al., 2007; Hermans et al., 2007; Zetteler, 2008; Farina et al., 2014; Okonkwo et al., 2014; Cheng, 2016; Abraha et al., 2017a, 2017b). Moreover, these non-pharmacological interventions are not focused specifically to treat AD, but on dementia as a whole instead (Okonkwo et al., 2014; Cheng, 2016; Abraha et al., 2017a, 2017b). Other lifestyle aspects like mental challenges (e.g., received education, occupational attainment, learning a new language, chess) may reduce AD risk by postponing the onset of its syndromes due to their ability to stimulate cognitive function, which associates with an increase in cognitive reserve and plasticity (Stern, 2012; Myung et al., 2016; García-Casal et al., 2017; Wada et al., 2018; Antoniou, 2019; Lillo-Crespo et al., 2019).

Dietary factors and supplementations are only meant for providing protective effects against AD development (Canevelli et al., 2016; Cao et al., 2016). Vitamin B studies showed controversial results despite being reported to inhibit oxidative stress in AD (Aisen et al., 2008; Mendiola-Precoma et al., 2016). Intake of vitamin E (particularly α- and γ-tocopherols) was found to be associated with a slower cognitive decline in certain clinical trials, but other studies stated otherwise (Hu et al., 2013; Dysken et al., 2014; Mendiola-Precoma et al., 2016). Several experiments on

vitamin C have shown its role in reducing Aβ formation, yet data collected from cohort studies were conflicting similar to those on vitamin E (Harrison, 2012; Arlt et al., 2012; Hu et al., 2013; Monacelli et al., 2017). Vitamin D strengthens cognitive performance, and is associated with AD risk according to genetic aspects (Annweiler & Beauchet, 2011; Hu et al., 2013; Littlejohns et al., 2014; Mendiola-Precoma et al., 2016). Polyphenols like resveratrol yield various biological activities which benefit neuroprotective functions, making it a potential therapeutic agent for AD (Hu et al., 2013; Ma et al., 2014; Diaz-Gerevini et al., 2016). Several trials of polyphenols have demonstrated its inhibition on Aβ formation and attenuate homocysteine concentrations (Hu et al., 2013; Phan et al., 2019). Unsaturated fats [mono- (MUFA) and polyunsaturated fatty acids (PUFA)] may also prove beneficial to AD, in which MUFAs were reported with antioxidant and anti-inflammatory effects, whereas PUFAs influence the expression of inflammatory genes and are important in neuronal function and plasticity (Ramesh et al., 2010; Hu et al., 2013; Morris & Tangney, 2014; Mendiola-Precoma et al., 2016). Studies on the Mediterranean diet (MedDiet) which is rich in these fats, proved an association between its diet adherence and a reduced risk of MCI and AD development (Hu et al., 2013; Singh et al., 2014; Mendiola-Precoma et al., 2016). Research on Dietary Approaches to Stop Hypertension (DASH) diets exhibited similar effects on delaying cognitive decline to that of MedDiet (Hu et al., 2013; Tangney et al., 2014). The combination of both diets mentioned known as the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet also demonstrated the significant reduction in incident AD as a preventative intervention (Dominguez & Barbagallo, 2018; Omar, 2019). Despite the potential of unsaturated fats as a therapeutic option, some studies suggested its inefficacy on AD. Examples like those on PUFAs do not display any benefit to patients with mild to moderate AD (Cunnane et al., 2013; Burckhardt et al., 2016). Other alternative herbal medicines and supplements were taken into consideration as well, including Souvenaid, *Ginkgo biloba*, acetyl-L-carnitine and curcumin (Hamaguchi et al., 2010; Shah, 2013; Waite, 2015; McKeage & Lyseng-Williamson, 2018; Kandiah et al., 2019; Chainoglou & Hadjipavlou-Litina, 2020; Mota et al., 2021). Though these compounds exhibited feasible hypothetical effects on AD, confirmations on their benefits to treating AD cannot be made due to insufficient supporting data and evidence, with limited studies available (Hamaguchi et al., 2010; Shah, 2013; Waite, 2015; McKeage & Lyseng-Williamson, 2018; Kandiah et al., 2019; Chainoglou & Hadjipavlou-Litina, 2020; Mota et al., 2021). New discoveries on edible bird's nest (EBN) have suggested its neuroprotective effects against AD, with experiments reporting its ability to suppress neuroinflammation and neuronal cell death due to its sialic acid content (Loh et al., 2022; Kim et al., 2020; Ismaeil et al., 2021). Also, based on historical applications, traditional Chinese medicine (TCM) has received solid clinical support on its promising effects towards AD treatment and prevention (Sun et al., 2013; Liu et al., 2014). Such medicines provide satisfactory results from preclinical and clinical trials, which include but not limited to *Huperzia serrata*, periwinkle, *Centella asiatica*, *Polygala tenuifolia*, *Radix polygalae*, *Poria*, *Rhizoma Acori Graminei* and *Polygonum multiflorum*, which provide memory improvements, antioxidative effects and neuroprotection

(Sun et al., 2013; Liu et al., 2014). Still, further investigation is required to confirm and identify its relevance in AD therapy (Sun et al., 2013; Liu et al., 2014).

3 Brain Iron Metabolism

3.1 What Is Iron?

Iron is a mineral which is an essential micronutrient required for various metabolic processes that sustains a healthy growth and development in most organisms (Abbaspour et al., 2014; Ems et al., 2021). Despite its geological abundance and its comparatively low daily intake, iron is often a growth-limiting nutrient in the human diet (Abbaspour et al., 2014; Ems et al., 2021). Iron is an excellent redox element because of its ionic form in nature that allows it to accept and donate electrons (electron transport) easily, which gives the iron a critical role in cellular redox reactions (Abbaspour et al., 2014; Paul et al., 2017; Lane et al., 2018). Such reactions include oxygen transport, enzyme activation, DNA synthesis and energy production (Abbaspour et al., 2014; Paul et al., 2017; Lane et al., 2018; Gao et al., 2019; Thirupathi & Chang, 2019). It plays a keystone role in Hb and myoglobin production, which are special proteins that can bind to oxygen (Abbaspour et al., 2014; Paul et al., 2017; Lane et al., 2018). Iron also acts as catalysts or cofactors for enzymes involved in energy production, and as a vital component of the immune system to function normally (Ward et al., 2011; Paul et al., 2017; Gao et al., 2019).

The recommended daily allowance (RDA) for iron in adults is 8 mg for males and 18 mg for females respectively, according to the National Institutes of Health (NIH) (National Institutes of Health, 2021). Iron deficiency is the most widespread nutritional disorder in the world, mainly prevalent in young children and women regardless of pregnancy (Abbaspour et al., 2014; Ems et al., 2021; National Institutes of Health, 2021; World Health Organization, 2021b, 2021c). This deficiency consists of several stages: from mild stages where iron and ferritin concentrations start to decrease, to severe stages known as iron-deficiency anaemia (IDA) which is associated with low Hb and hematocrit levels, resulting in the shrinking of RBCs that disrupts oxygen transport in the blood (Abbaspour et al., 2014; National Institutes of Health, 2021). Examples of deficiency symptoms are fatigue, weakness, dizziness, impaired cognitive and immune function (National Institutes of Health, 2021; World Health Organization, 2021d). Hemochromatosis, known as excessive iron stores in the body can be toxic due to its contribution to oxidative stress and its ability to alter bodily pH, leading to multiple organ dysfunction (Abbaspour et al., 2014; Ems et al., 2021; National Institutes of Health, 2021; Porter & Rawla, 2021). Overdosing iron sources can cause gastric upset, nausea and vomiting, in addition to declines in zinc absorption rates and plasma zinc concentrations (National Institutes of Health, 2021). Fatal stages of iron poisoning can cascade to organ failure and death (National Institutes of Health, 2021).

Only two types of iron can be found in dietary sources: haem iron and non-haem iron (Abbaspour et al., 2014; National Institutes of Health, 2021). Haem iron has a much higher bioavailability than non-haem iron, and other dietary factors have little influence on the absorption of haem iron than non-haem iron (Abbaspour et al., 2014; National Institutes of Health, 2021). Still, non-haem iron contributes more to iron nutrition than haem-iron in most meals (Abbaspour et al., 2014; National Institutes of Health, 2021). Haem iron is mainly found in animal sources like meats, seafood and poultry; whereas non-haem iron is mainly found in plant sources like cereals, legumes, fruits and vegetables (Abbaspour et al., 2014; National Institutes of Health, 2021). Ascorbic acid/Vitamin C and haem iron sources (e.g., meat, poultry, seafood) are known to potentiate non-haem iron absorption, especially in vegetarian diets (Abbaspour et al., 2014; National Institutes of Health, 2021). Contrariwise, inhibitors like phytate/phytic acid and certain polyphenols suppress non-haem iron absorption (Abbaspour et al., 2014; National Institutes of Health, 2021). Calcium reduces the bioavailability of both haem and non-haem iron unlike other iron inhibitors (Abbaspour et al., 2014; National Institutes of Health, 2021).

3.2 Iron Absorption and Transport into the Brain

Because iron is only obtainable through dietary consumption, its absorption primarily occurs in the small intestine, particularly the duodenum and jejunum before entering blood circulation (Conrad & Umbreit, 2000, 2002; Abbaspour et al., 2014; Gao et al., 2019; Thirupathi & Chang, 2019). Ingested iron that was broken down from the digestion of food sources generally takes on either of three physical states: namely ferrous (Fe^{2+}), ferric (Fe^{3+}) and haem iron (Conrad & Umbreit, 2000, 2002; Abbaspour et al., 2014; Przybyszewska & Żekanowska, 2014). Haem iron is absorbed into intestinal mucosal cells through a transmembrane protein called haem carrier proteins (HCP1), which will then be catabolized in the enterocytes by haem-oxygenase (HO) (isoforms HO-1 and HO-2) to liberate Fe^{2+} ions (Abbaspour et al., 2014; Przybyszewska & Żekanowska, 2014). Evidence on HCP1 expression and functions has been solidly documented despite some reports on the unknown mechanism of haem iron absorption (Abbaspour et al., 2014; Przybyszewska & Żekanowska, 2014; Gao et al., 2019). The absorption of non-haem iron (Fe^{2+} and Fe^{3+}) is mediated by divalent metal transporter (DMT1) proteins expressed on the apical membrane of enterocytes, which only favours the bivalent form (Fe^{2+}) due to the insoluble form of Fe^{3+} ions (Conrad & Umbreit, 2000; Abbaspour et al., 2014; Przybyszewska & Żekanowska, 2014; Gao et al., 2019; Thirupathi & Chang, 2019). To enhance the uptake of Fe^{3+}, it is only achievable through its reduction into Fe^{2+} by ferric reductases in the intestinal lumen (Abbaspour et al., 2014; Przybyszewska & Żekanowska, 2014). The internalized Fe^{2+} in the enterocytes is then exported into the blood plasma via ferroportins (IREG1/Fpn1) located on the basolateral membrane, with excess Fe^{2+} being stored by binding to ferritin in the Fe^{3+} form (Abbaspour et al., 2014; Przybyszewska & Żekanowska, 2014; Gao et al., 2019).

Exported iron in the blood is further catalysed into the inert Fe^{3+} state via ferroxidase enzymes which includes hephaestin and ceruloplasmin before binding to transferrin (Abbaspour et al., 2014; Kohlmeier, 2015; Jiang et al., 2019; Thirupathi & Chang, 2019). Transferrin (Tf) acts as iron transporters in the bloodstream to deliver Fe^{3+} ions to various target tissues (Conrad & Umbreit, 2000; Gkouvatsos et al., 2012; Abbaspour et al., 2014; Gao et al., 2019).

The brain possesses a microvascular system of endothelial cells with unique properties that functions as a key regulatory mechanism on proper neuronal function by tightly controlling its ionic microenvironment between blood vessels, known as the blood-brain barrier (BBB) (Abbott et al., 2010; Daneman & Prat, 2015; Yu & Chang, 2019; Qian & Ke, 2019). The uptake of transferrin-bound iron (Tf-Fe) complexes which arrives at the BBB is mainly administered via the binding of Tf-Fe molecules to transferrin receptors (TfR) (Belaidi & Bush, 2016; Gao et al., 2019; Yu & Chang, 2019; Qian & Ke, 2019). The bound Tf-TfR complexes then undergo endocytosis to transport across the apical membrane of the capillary endothelium into cerebral endothelial cells (Abbaspour et al., 2014; Belaidi & Bush, 2016; Gao et al., 2019; Yu & Chang, 2019; Qian & Ke, 2019). Tf-TfR endosomes start to dissociate Fe^{3+} ions by ferric reductases to be reduced to Fe^{2+} under acidic conditions, allowing iron to be translocated into the endothelial cytoplasm via DMT1, ready to be utilised in the brain (Lane et al., 2018; Yu & Chang, 2019; Qian & Ke, 2019).

Two transport forms of iron are hypothesized for brain intracellular transport, namely Tf-Fe and non-transferrin-bound iron (NTBI) (Lane et al., 2018; Qian & Ke, 2019). Intracellular iron is likely to bind with Tf secreted from epithelial cells of the choroid plexus instead with other iron transporters (e.g., citrate-$Fe^{2+/3+}$, ascorbate-Fe^{2+}, albumin-$Fe^{2+/3+}$, lactoferrin-Fe^{3+}/Lf-Fe^{3+}) due to its higher affinity (Qian & Ke, 2019). Hence, Tf in cerebrospinal fluid (CSF) and brain interstitial fluid (IF) is completely saturated with iron, hinting the higher concentration of Tf-Fe than NTBI (Knutson, 2019; Qian & Ke, 2019). These iron complex entities are distributed unevenly to different neuroglial cells in the brain, with each cell type may have distinct mechanisms of iron uptake (Yu & Chang, 2019). Neurons and astrocytes acquire iron through TfR/DMT1-mediated pathway for Tf-Fe uptake, and DMT1-dependent pathway for NTBI uptake (Skjørringe et al., 2015; Yu & Chang, 2019; Qian & Ke, 2019). Oligodendrocytes focus on taking up H-ferritin which is controlled by corresponding receptors T-cell immunoglobulin mucin domain protein-2 (Tim2) according to studies on mice, yet the mechanism of iron release from H-ferritin into the cytosol of oligodendrocytes remains unclear (Leitner & Connor, 2012; Belaidi & Bush, 2016; Yu & Chang, 2019; Qian & Ke, 2019). Immature oligodendrocytes may also obtain iron via the TfR/DMT1 pathway (Qian & Ke, 2019). Microglia was reported to take up NTBI via a Tf-independent mechanism, in addition to its expressions of TfR and DMT1 that may imply its ability to take up Tf-Fe (Leitner & Connor, 2012; Lane et al., 2018; Qian & Ke, 2019). After iron is metabolised by or stored within the various cells in the brain, excess iron is released through IREG1 to be exported out to the IF or CSF (Yu & Chang, 2019; Qian & Ke, 2019). The excess iron is then transported back into the bloodstream to be delivered

to other bodily tissues, via binding with the choroidal epithelia on either TfR-dependent or TfR-independent pathways (Yu & Chang, 2019).

3.3 Iron Regulation in the Brain

As the body lacks an established excretory mechanism for iron, iron homeostasis is vital for all normal brain functions and metabolic activities (Kohgo et al., 2008; Abbaspour et al., 2014; Belaidi & Bush, 2016; Yu & Chang, 2019; Ems et al., 2021). Iron regulation is controlled tightly through its uptake, storage and release on cellular levels (Belaidi & Bush, 2016; Lane et al., 2018; Yu & Chang, 2019). The main regulators of iron in the brain are iron regulatory proteins (IRP) and hepcidin (Yu & Chang, 2019).

IRPs are iron-sensitive, cytosolic *trans*-proteins that regulate the expressions of iron metabolism genes post-transcriptionally via attaching to loop-structured elements in target mRNAs known as iron regulatory elements (IRE) (Benarroch, 2009; Mills et al., 2010; Zhang et al., 2014; Gao et al., 2019). IRPs come in two forms: IRP1 and IRP2 (idi; Zhang et al., 2014; Belaidi & Bush, 2016; Zhou & Tan, 2017; Gao et al., 2019; Yu & Chang, 2019). Both isoforms of IRPs are ubiquitously expressed, whereby IRP1 is highly expressed in most tissues, and IRP2 is mainly found in the CNS and small intestine (Zhang et al., 2014; Belaidi & Bush, 2016; Gao et al., 2019; Yu & Chang, 2019). Under Fe-limiting conditions, IRP2 expression in the brain is promoted, allowing it to bind to IREs either on the 5′-untranslated region (UTR) to inhibit mRNA translation such as ferritin and IREG1; or the 3'-UTR to increase mRNA stability from degradation such as TfR and DMT1 (Mills et al., 2010; Zhang et al., 2014; Belaidi & Bush, 2016; Zhou & Tan, 2017; Gao et al., 2019; Yu & Chang, 2019). The formation of IRP/IRE complexes in the collectively involved mRNA ultimately increases iron uptake while decreasing iron storage and export, thereby balancing intracellular iron levels to compensate iron deficiency (Zhang et al., 2014; Belaidi & Bush, 2016; Zhou & Tan, 2017; Yu & Chang, 2019). In short, the IRE-IRP system maintains brain iron homeostasis through responding to alterations in iron concentration on a cellular level (Yu & Chang, 2019).

Hepcidin is a 25 amino acid peptide hormone produced by the liver, which acts as a master regulator of iron homeostasis on a systemic level (Kohgo et al., 2008; Nemeth & Ganz, 2009; Ganz & Nemeth, 2012; Abbaspour et al., 2014; Przybyszewska & Żekanowska, 2014; Vela, 2018; Gao et al., 2019; Yu & Chang, 2019). As a negative feedback regulator, hepcidin controls intestinal iron absorption, iron recycling from macrophages and iron ejection from hepatocytes, thus regulating plasma iron concentrations and tissue iron distribution (Kohgo et al., 2008; Ganz & Nemeth, 2012; Abbaspour et al., 2014; Yu & Chang, 2019). Hepcidin production is mainly regulated by systemic iron deposit levels, erythropoietic activity and inflammation factors (Nemeth & Ganz, 2009; Ganz & Nemeth, 2012; Vela, 2018; Gao et al., 2019; Yu & Chang, 2019). The effects of hepcidin on the regulation of systemic iron bioavailability roots from its role in controlling IREG1 expression

post-translationally, which induces secondary iron overload within cells (Kohgo et al., 2008; Nemeth & Ganz, 2009; Przybyszewska & Żekanowska, 2014; Vela, 2018). By directly attaching to IREG1 molecules in high plasma iron environments, the resulting hepcidin-IREG1 complex undergoes internalization and degradation through lysosomal action (Nemeth & Ganz, 2009; Ganz & Nemeth, 2012; Abbaspour et al., 2014; Przybyszewska & Żekanowska, 2014; Belaidi & Bush, 2016; Gao et al., 2019; Yu & Chang, 2019). As such, IREG1 levels decreases on the cell membranes which directly reduces iron efflux from cells into plasma, thereby decreasing plasma iron levels to normal range (Ganz & Nemeth, 2012; Abbaspour et al., 2014; Przybyszewska & Żekanowska, 2014; Vela, 2018; Gao et al., 2019; Yu & Chang, 2019). Under low plasma iron environments, hepcidin production is inhibited, leading to an increase in IREG1 levels to compensate plasma iron levels via cellular iron release (Ganz & Nemeth, 2012; Abbaspour et al., 2014; Przybyszewska & Żekanowska, 2014; Gao et al., 2019).

Hepcidin has been shown to be lowly expressed non-uniformly in different brain regions based on studies involving RT-PCR, qPCR, in situ hybridization and immunohistochemistry (Zechel et al., 2006; Nemeth & Ganz, 2009; Wang et al., 2010; Vela, 2018; Yu & Chang, 2019). Hepcidin immunoreactivity was discovered in neurons and GFAP-positive glial cells according to Zechel *et al*. and Wang *et al*., which hints hepcidin may be involved in brain iron regulation (Zechel et al., 2006; Wang et al., 2010; Yu & Chang, 2019). Moreover, these studies have supported its regulatory function, with reports indicating the positive association between hepcidin mRNA levels and aging (Wang et al., 2010; Yu & Chang, 2019). In vitro studies have also proved its purpose on downregulating iron efflux via IREG1 degradation in brain microvascular endothelial cells (BMVEC), and its inhibition on TfR, DMT1 and IREG1 expressions in astroglia cultures (Du et al., 2011; McCarthy & Kosman, 2014; Song et al., 2018; Yu & Chang, 2019). However, there is no evidence to display its functions through in vivo studies.

4 Iron and Alzheimer's Disease: What Is the Interplay?

The effects of iron in the brain are pivotal for sustaining the high metabolic rates in neuronal tissues through its involvement in mitochondrial respiration, myelin and neurotransmitter syntheses (e.g., dopamine, serotonin, GABA) (Mills et al., 2010; Ward et al., 2014; Belaidi & Bush, 2016; Lane et al., 2018; Thirupathi & Chang, 2019; Yu & Chang, 2019). Studies show that prenatal or postnatal iron deficiency patients exhibit aberrations in neurodevelopment including learning and memory impairment (Radlowski & Johnson, 2013; Belaidi & Bush, 2016). However, progressive neurodegeneration with brain iron accumulation (NBIA) is associated with aging within the substantia nigra, putamen, globus pallidus, caudate nucleus and cortices (Mills et al., 2010; Ward et al., 2014; Hare et al., 2015; Belaidi & Bush, 2016; Bu et al., 2019; Levi et al., 2019; Thirupathi & Chang, 2019). Besides, dysregulations in iron homeostasis that contributes to NBIA is implicated in multiple

neurodegenerative disorders including Parkinson's disease (PD), Huntington's disease and AD (Mills et al., 2010; Ward et al., 2014; Belaidi & Bush, 2016; Lane et al., 2018; Gao et al., 2019; Yu & Chang, 2019). Increased iron concentrations in the brain were first discovered in 1953, and its association with plaques and NFTs or with ferritin in surrounding glial cells was consistently reported (Belaidi & Bush, 2016; Lane et al., 2018; Wang et al., 2019). MRI analysis demonstrated that brain iron load increases in the parietal cortex, motor cortex and hippocampus in AD patients (Langkammer et al., 2014; Tao et al., 2014; Belaidi & Bush, 2016; Wang et al., 2019). Moreover, increased iron levels are associated with Aβ plaque formation and τ entanglements (Meadowcroft et al., 2009; Belaidi & Bush, 2016; Wang et al., 2019). Additional supporting evidence also suggested that excessive brain iron deposition within diverse neuronal populations such as oligodendrocytes, enhances oxidative stress via Fenton- and Haber-Weiss reactions, as well as lipid peroxidative stress which acts as a prime contributor to the elevated state of oxidative stress in the AD brain (Kohgo et al., 2008; Yu et al., 2009; Hare et al., 2013; Ward et al., 2014; Bradley-Whitman & Lovell, 2015; Yang & Stockwell, 2016; Belaidi & Bush, 2016; Lane et al., 2018; Morris et al., 2018; Wang et al., 2019; Yu & Chang, 2019).

As mentioned, increased neuronal iron in AD augments Aβ production via several mechanisms, which includes increasing APP expression through IREs located on its encoding mRNA (Rogers et al., 2002; Belaidi & Bush, 2016; Greenough, 2016; Lane et al., 2018; Wang et al., 2019). Conforming to Cho *et al*., unlike IREs in ferritin and IREG1 mRNAs that can attach either IRP1 or IRP2, only IRP1 is capable of binding and regulating IREs at the 5'-UTR of the APP mRNA (Cho et al., 2010; Lane et al., 2018). Furthermore, high Fe concentrations accelerate amyloidogenic processing of APP, triggering Aβ aggregation (Belaidi & Bush, 2016; Greenough, 2016; Lane et al., 2018; Wang et al., 2019). The universality of Fe^{2+} allows it to bind to Aβ peptides directly on His6, His13 and His14 which are located in the N-termini (Bousejra-ElGarah et al., 2011; Wong & Duce, 2014; Lane et al., 2018; Wang et al., 2019). Intriguingly, certain studies suggested that Aβ has a neuroprotective and chelating role against AD neurotoxicity due to its ability to suppress iron redox potential, giving rise to the possibility of iron chelation as a potential therapeutic approach (Belaidi & Bush, 2016; Lane et al., 2018). On top of that, some findings on APP discovered its protection against catalysed oxidative stress and stabilization of transmembrane IREG1 expression which subsequently promotes iron efflux (Fujioka et al., 2003; Wang et al., 2019). Experiments on neuronal cultures and mouse subjects resulted in intracellular iron retention under APP depletion, while overexpression or exogenous transfection of APP facilitates Fe-export ferroxidase activity to relieve this phenomenon (Duce et al., 2010; Wan et al., 2012; Wang et al., 2019). These observations indicate that iron overload mediates Aβ production through regulation of APP expression, while APP modulates intracellular iron homeostasis via cell-surface IREG1 stabilization to increase iron efflux (Wang et al., 2019).

Other than Aβ peptides, iron also binds to τ, inducing hyperphosphorylation and NFT aggregation (Belaidi & Bush, 2016; Lane et al., 2018; Wang et al., 2019). It was suggested that Fe-induced oxidative stress is responsible for the increased

activity of CDK5 and GSK3β, or suppresses the activity rate of PP2A, a major tau phosphatase (Guo et al., 2013; Jin Jung et al., 2013; Lane et al., 2018; Wang et al., 2019). Tau accumulation in NFTs is also associated with HO-1 to release Fe^{2+} radicals which further aggravates oxidative stress, with evidence of HO-1 expression being upregulated in the hippocampus and temporal cortex of AD and MCI patients that leads to brain iron loading and τ aggregation (Schipper et al., 2006; Hui et al., 2011; Ward et al., 2014; Wang et al., 2014; Belaidi & Bush, 2016). Similar to APP, tau is able to bind and stabilize transmembrane IREG1 to facilitate neuronal iron efflux, and it is required for the proper trafficking of APP to the neuronal membrane (Duce et al., 2010; Lei et al., 2012; McCarthy et al., 2014; Lane et al., 2018). In other words, decreased τ levels could result in neuronal iron retention as observed in AD characteristics, suggesting its indirect effects of τ on controlling the neuroprotective attributes of APP (Ayton et al., 2014; Wong et al., 2014; Lane et al., 2018). Collectively, iron accumulation causes τ dysfunction by means of preventing iron export through impaired transport of APP to neuronal surfaces (Lane et al., 2018; Wang et al., 2019).

The devastating impact of Fe-induced oxidative stress has been advocated to initiate multiple apoptosis signalling pathways (e.g., neuroinflammation) in neurons, as well as damaging key biological components such as Ca^{2+}-ATPase, glutamate transporters, APOE, Na^{+}/K^{+}-ATPase, NMDARs, DNA, RNA and certain lipids like cholesterol, ceramides, PUFAs and sphingomyelin (Lane et al., 2018; Wang et al., 2019). Much evidence has confirmed that Fe-induced oxidative damage to intracellular molecules causes synaptic dysfunction and neuronal apoptosis, with increased levels of such molecules existing in oxidized forms in brain tissues of AD patients (Lane et al., 2018; Wang et al., 2019). Iron is heavily involved in lipid peroxidation and accountable for disrupting membranous structures and functions of proteins and biomolecules (Wang et al., 2019). Contrastingly, both oxidative stress and lipid peroxidation were found to incite Aβ accumulation according to animal model experiments (Wang et al., 2019). Raised oxidative stress also increases oxidative damage on nucleic acids (DNA/RNA) via ROS mechanisms, which is observed in cortical and hippocampal neurons during AD onset (Bradley-Whitman et al., 2014; Violet et al., 2015; Hofer & Perry, 2016; Wang et al., 2019). In comparison to normal human brains, AD brains have a 30- to 50-fold increase of DNA fragmentation in neurons and glial cells (Radi et al., 2014; Lane et al., 2018). Supportive findings by Lu *et al.* show that oxidative DNA damage preferentially occurs in promoter regions of selected genes controlling synaptic plasticity, vesicular transport and mitochondrial function (Lu et al., 2004; Wang et al., 2019). As for RNA oxidation, it was observed in post-mortem brains of early AD onset and appears to be pre-symptomatic in familial AD (Nunomura et al., 2004; Wang et al., 2019). Redox-active iron has been known to bind with RNA and ribosomes that oxidizes rRNA in AD, with rRNA cleavage being present in primary astrocytes and neurons (Honda et al., 2005; Wang et al., 2019). Yet, the mechanism behind nucleic acid alterations in neurons and glial cells is poorly understood, and the type of neuronal apoptosis or necrosis in AD remains debatable (Radi et al., 2014; Hofer & Perry, 2016; Ayton et al., 2017; Lane et al., 2018; Wang et al., 2019). Nevertheless,

excluding brain cells that are associated with Aβ plaques and NFTs, nuclear alterations which trigger cell death were rare in AD (Lane et al., 2018).

Interestingly, ferroptosis has recently been investigated by scientists for being a possible patho-mechanism of cell death in AD brain tissues (Dixon et al., 2012; Belaidi & Bush, 2016; Hambright et al., 2017; Stockwell et al., 2017; Lane et al., 2018). It is a programmed Fe-dependent pathway that regulates necrotic cell death, distinguishing itself from other modes of cell deaths through a unique dependence on the RAS-RAF signalling pathway, and is involved in iron disorders, lipid peroxidation and inflammation as predominant markers (Dixon et al., 2012; Belaidi & Bush, 2016; Dixon, 2017; Lane et al., 2018; Galluzzi et al., 2018). Ferroptosis can be activated by structurally diverse small molecules like erastin, sulfasalazine and RSL3, while it is inhibited by lipophilic antioxidants (e.g., Trolox, vitamin E), iron chelators (e.g., deferoxamine) and aromatic amine inhibitors (e.g., ferrostatin-1, liproxstatin-1) (Dixon et al., 2012; Dixon & Stockwell, 2014; Xie et al., 2016; Belaidi & Bush, 2016; Stockwell et al., 2017; Lane et al., 2018). Although the specific role of iron in ferroptosis is unclear, it is hypothesized that glutathione depletion causes Fe-catalysed ROS accumulation to trigger apoptosis (Dixon et al., 2012; Belaidi & Bush, 2016). Based on recent discoveries, the knockout of glutathione peroxidase 4 (GPX4) due to lipid peroxidation, was found to promote lipid hydroperoxide (LOOH) accumulation and has been identified as a cause of ferroptosis (Xie et al., 2016; Stockwell et al., 2017; Lane et al., 2018). Kagan *et al.* also discovered that ferroptosis involves a highly systemized oxygenation complex within ER-associated membrane compartments, which is responsible for producing ROS that can act as ferroptosis signals (Doll et al., 2017; Kagan et al., 2017; Lane et al., 2018). By referring to experiments where GPX4 was conditionally ablated in mouse models, an occurrence of degeneration was observed in spinal motor and midbrain neurons, as well as forebrain regions including the hippocampus and cerebral cortex (Chen et al., 2015; Hambright et al., 2017; Lane et al., 2018). The results on these GPX4 knockout mice (also known as GPX4BIKO) also exhibited significant deficits in spatial function and severe hippocampal neurodegeneration, which is associated with iron imbalance, elevated lipid peroxidation and neuroinflammation (Seiler et al., 2008; Hambright et al., 2017; Lane et al., 2018; Wang et al., 2019). Such findings indicate that the CNS especially forebrain neurons, are susceptible to ferroptosis as a result of GPX4 inactivation, hinting that ferroptosis could play an important neurodegenerative mechanism in AD (Hambright et al., 2017; Lane et al., 2018; Wang et al., 2019).

In relation to Aβ and τ, the ferroptosis pathway may potentially explain deeper into the action of iron on AD neurotoxicity (Lane et al., 2018). Speculations can be plausibly made that Aβ and τ dysfunction may amplify ferroptosis rates on vulnerable neurons under circumstances of high iron concentrations, glutathione exhaustion and/or low GPX4 activity (Ayton et al., 2017; Lane et al., 2018). A recent study suggests that APP expression and $A\beta_{42}$ enhances RAS-ERK signalling and GSK3β activation, which leads to APP and τ hyperphosphorylation (Kirouac et al., 2017; Lane et al., 2018). Furthermore, the same study showed that RAS expression was hyperactivated in post-mortem AD brains compared to healthy controls (Kirouac

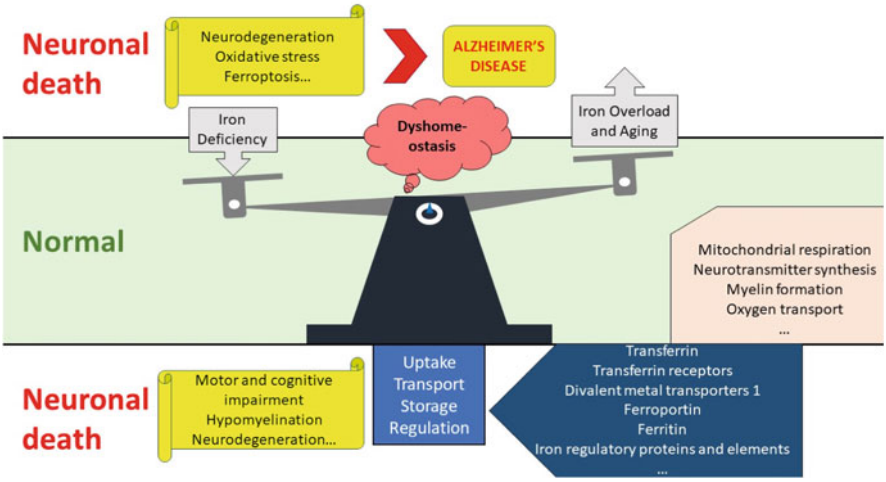

Fig. 7.1 The interplay between iron and Alzheimer's disease (AD). The effects of iron on AD are largely based on iron dyshomeostasis in the brain rather than the properties of iron itself. Under normal brain iron concentrations, iron acts as an important mineral to carry out cellular respiration and produce important cellular apparatus within neurons like neurotransmitters and myelin. The dysregulation in brain iron concentrations (either deficient or excessive) causes brain health to be compromised, leading to neuronal apoptosis. In terms of Alzheimer's disease, with iron overload and aging as the main risk factors in play, it creates a harmful and toxic environment within the CNS that cascades towards oxidative stress/lipid peroxidation, neurodegeneration and ferroptosis. Such side effects are associated with the overproduction and aggregation of beta-amyloid (Aβ) plaques and neurofibrillary tangles (NFT), all of which contributes to the onset of AD

et al., 2017; Lane et al., 2018). Since ferroptosis relies on RAS activation, it may be relevant that redox-active iron overload is somewhat connected with fundamental AD pathologies including Aβ and τ accumulation, eventuating in the neurodegeneration and brain tissue necrosis in AD (Dixon et al., 2012; Lane et al., 2018) (Fig. 7.1).

5 Conclusion

Iron is a transition metal that is abundant in the brain and is a key component for many vital metabolic processes, especially in the nervous system. Even so, its ability to readily switch between redox states bestows its oxidative harm towards brain tissues for its potential to intensify ROS production to facilitate neurodegeneration and cell death. It is extremely important to note that iron itself in nature is not the only culprit that contributes towards AD pathology, as dysregulation in brain iron homeostasis is believed to cause excessive iron concentrations which could instigate multiple AD pathological pathways and vice versa which includes Aβ and phosphorylated τ deposition, mitochondrial dysfunction, oxidative stress and

neuroinflammation. Although excessive iron deposition was found within brain parenchymal tissues, the mechanism behind brain iron homeostasis under normal circumstances and its alterations due to aging or inflammatory factors remain above one's head. This is because brain iron metabolism is unaffected by peripheral iron levels, which is supported by the fact that no evidence has been reported on peripheral iron-loading diseases like haemochromatosis and thalassaemia leads to an increased incidence in neurodegeneration or elevated brain iron levels. Future studies are required to establish a deeper concept into the pathways of brain iron homeostasis to understand better its contribution towards AD development under brain iron changes.

Even though the true cause and pathophysiological mechanisms of AD development are incompletely understood, it may appear that the convergence of both proposed and existing knowledge of AD pathologies will serve as puzzle pieces that will unravel a larger and complete picture on the pathogenesis of AD. Thus, the effects of iron overaccumulation and ferroptosis may prove to be intertwined with fundamental AD pathologies known to date. The recent discovery of the possible action of iron and ferroptosis on AD pathology has endowed iron as a research hotspot for opening new possibilities for pharmacological interventions and therapeutic approaches. Currently, iron chelators have become a trending proposal for being a viable AD treatment by removing excess brain iron in AD patients. However, such proposals and currently approved therapeutic drugs have neither achieved satisfactory results based on clinical expectations nor sufficiently implemented into clinical application, due to the existence of BBB that barricades the entry of most drug molecules into the brain to be put into effect. It should also be mentioned that AD itself is a multifactorial disease, implying that the reliance solely on a single therapeutic strategy is obviously not a realistic procedure for treating or curing AD. As such, utilising various therapeutic approaches is the most feasible method while attempting to reverse AD by resolving the multiple origin points of its development. Nevertheless, further research based on drug effectivity is necessary to provide a greater impact on AD treatment. Indeed, drugs such as ferroptosis inhibitors and nanotechnology-based drug delivery systems that can pass through the BBB are currently under extensive research, which may prove to be a significant medical advancement and a huge leap for mankind towards the cure of AD.

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Chapter 8
Iron and Multiple Sclerosis

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1 Introduction

Multiple sclerosis (MS) is an autoimmune disease that affects the central nervous system (CNS) in young adults, resulting in severe cognitive and neurological impairments. Plaques/lesions arise in both grey and white matter of the CNS as a result of multifocal lymphocytic infiltration (Sospedra & Martin, 2004). Dysarthria, ataxia, tremor, optic neuritis, trigeminal neuralgia, lethargy and dizziness, dysphagia, dysphonia, depression/anxiety, bladder, and sexual dysfunctions are all clinical manifestations of MS. According to the Atlas of MS, research produced by MSIF (Multiple Sclerosis International Federation), anticipated global MS patients increased from 2.3 million in 2013 to 2.8 million in 2020, representing a 30 percent rise (Walton et al., 2020). A breach of the blood-brain barrier, multifocal inflammation, demyelination, oligodendrocyte loss, reactive gliosis, and axonal degeneration are all part of the pathophysiological development of MS.

2 Brain-Iron Homeostasis

Brain iron is independent of the total body iron mainly because of the presence of BBB. Although brain iron forms around only 2% of the total body iron, it varies according to the specific areas of the brain. After absorption oxidized form of iron (ferric iron) binds to serum transferrin and moves to circulation in the body. Many metabolic activities in the central nervous system (CNS), such as oxidative phosphorylation, myelin creation, neurotransmitter generation, nitric oxide metabolism, and oxygen transport, require iron (Fe). It is a cofactor for a large number of

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enzymes, including a number of key enzymes involved in neurotransmitter biosynthesis in the brain, such as tyrosine hydroxylase (involved in the synthesis of catecholamines, including dopamine), tryptophan hydroxylase (involved in the synthesis of serotonin), and monoamine oxidase (involved in the synthesis of serotonin) (involved in the metabolism of dopamine). Iron entry across the BBB is accompanied mainly by different transporters present in the endothelial cells (Hametner et al., 2013). Of the various mechanism of iron entry into the brain, Tf/TfR pathway forms one of the main routes. Iron bound to transferrin is converted to ferric (Fe^{3+}) form by DMT 1 transporters and released in the endosomal membrane, after Tf returns to the luminal membrane of endothelial cells, through transcytosis transferrin bound iron pass BBB. TfR1 is present in the luminal membrane of endothelial cells and the TfR1 complex with Tf mediate iron uptake in the brain. Another mechanism of iron transport through BBB involves through lactoferrin receptor or lactoferrin and GPI anchored melanotransferrin. Iron in Fe^{2+} is transported via FPN and hephaestin receptors, Fe^{2+} is released in the basolateral surface of endothelial cells. This Fe^{3+} is oxidized by astrocytes with help of ceruloplasmin (CP), Fe^{3+} is also bound to Tf produced by choroid plexus and oligodendrocytes (Moos, 2002). Iron enters interstitial fluid or CSF by binding through Tf and then diffusing via CSF & interstitial fluid of brain parenchyma. From there it supplies iron to the brain cells expressing TfR in CNS. Neurons acquire iron by Tf, astrocytes via DMT 1 and oligodendrocytes via TfR1, and also via TIM-2 receptor. Microglia acquire iron via ferritin. Iron detachment from Tf occurs in the cytosol by DMT1. Iron transport in the abluminal membrane occurs through FPN1 (Morris et al., 1992). Iron from CNS is exported to PNS via FPN 1 with the help of ferroxidase. BB express all types of iron regulatory proteins. The main source of iron for CNS is Tf bound iron and ferritin while for PNS it is predominately Tf- TfR1 pathway and NTBI through DMT1 that serves the purpose. PNS does not have ferritin as an iron source (Nnah & Wessling-Resnick, 2018). Non-transferrin-bound iron (NTBI) is also present in BBB. Iron transport into the brain is decided by endothelial junctional complexes of BBB and astrocytes. TfR1 and Tf release iron in the interface between endothelial surface and astrocytes end foot process which is then oxidized by CP to ferric form. The main pathological hallmarks of iron accumulation in CNS is represented in the Image 8.1. Neurons having a greater number of TfR1 receptors utilize more iron from Tf. Neurons take this imported iron and are further stored in the form of ferritin or are exported via FPN1. Ferrous iron move as NBTI & attach either with ATP or citrate released from astrocytes (Rouault et al., 2009). Motor, sensory, and interneurons are all shielded by glial cells including oligodendrocytes, astrocytes, Schwann cells which express iron regulatory transport receptors like TfR/Tf and FPN1. With aging iron deposition is increased mainly in the globus pallidus and substantia nigra. IRP1 and IRP2 are involved in controlling iron homeostasis and any changes lead to iron deposition. IRP1 interacts with IRE and upregulates TfR, further increasing iron accumulation. CSF is mainly involved in exporting iron from brain to blood. Lactoferrin, ferrin, nonprotein bound iron also are involved in exporting iron (Benarroch, 2009). Mitochondrial proteins are also involved in exporting iron. Fe/s cluster decrease iron from mitochondria.

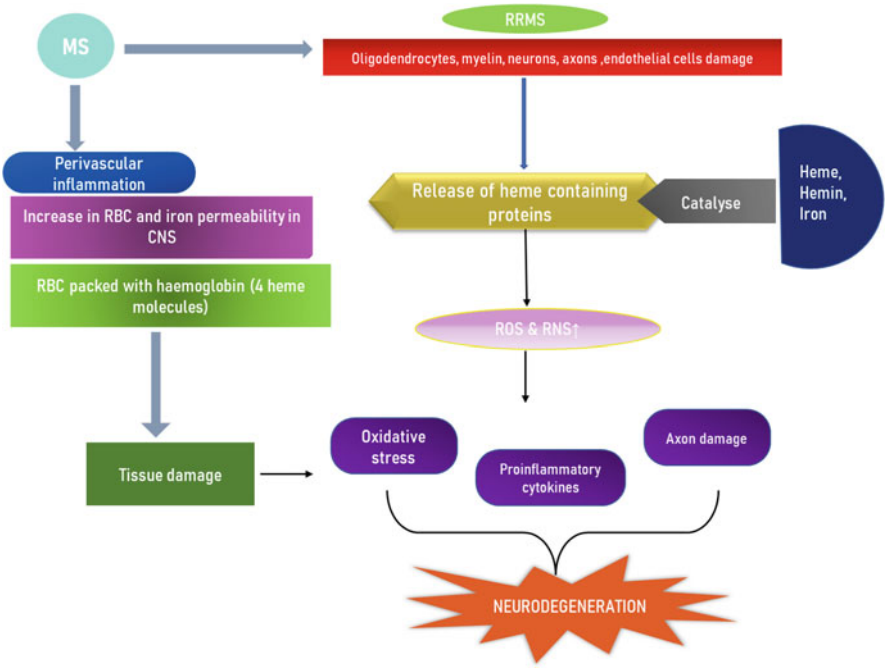

Image 8.1 Iron accumulation in multiple sclerosis

Ferritin a form of storage protein decreases free iron in cytosol by sequestering. NBIA which refers decrease in brain iron levels is also linked with iron homeostasis gene. Disturbances in the iron brain homeostasis causes gait problems, motor cognition problems. Peripheral cellular iron uptake is mediated by endocytosis of diferric transferrin (Tf-Fe2) transferrin receptor 1 (TfR1) via DMT1 transporter (Ke & Qian, 2007). Hence iron is transported into the cytoplasm. Ferroportin (Fpn) which is an iron export protein involved in transporting iron out of the cells. Fpn along with ferroxidase ceruloplasmin (CP) and hephaestin load ferric iron onto apo-Tf. Translation of TfR, DMT1, Ft and Fpn mRNA is regulated by iron regulatory protein (IRP). When iron is abundant hepcidin interacts with Fpn, resulting in degradation of Fpn and block exportation. Hepcidin synthesis is declines during deficiency of iron and iron exportation is resumed.

2.1 Iron Uptake in the Brain

The brain is the only organ in the body that is buried behind a somewhat impermeable vascular barrier, limiting its access to plasma nutrients like iron. Although the specific process of iron transport into the brain is still unknown, it is widely assumed that it includes the transferrin-to-cell cycle and the utilisation of transferrin receptors

Table 8.1 Iron uptake mechanisms

S. no.	Protein	Source	Role in iron—brain homeostasis	Reference
1.	Lactotransferrin receptor	Monocytes, intestinal cells, brain	On the surface of brain capillary endothelial cells and neurons, it plays a similar role to TfR. Overproduction of this protein has been linked to increased intraneuronal iron levels and nigral dopaminergic neuron loss in Parkinson's disease.	Leveugle et al. (1996)
2.	Melanotransferrin	Surface of melanoma cells, liver cells and intestinal cells	The soluble form of MTf could bind iron and subsequently mediate its uptake by cells via a receptor system, while the GPI-anchored form could fulfil the combined function of both Tf and TfR.	Baker et al. (1992), Food et al. (1994)
3.	Ceruloplasmin	Glial cells, retina	Through ferroxidase activity, CP may enhance iron outflow from brain cells.	Klomp et al. (1996)
4.	Divalent cation transporter	Brain	An active and H -dependent process.	Gunshin et al. (1997)

inside epithelial cells lining the blood–brain barrier (BBB). Tight junctions, a basal lamina, pericytes, and astrocyte endfoot processes connect cerebral capillary endothelial cells in the BBB proper. An astrocytic endfoot is also shown establishing close contact with the neuron, suggesting that it might operate as a gatekeeper in controlling brain iron intake and metabolism at the BBB junction. Iron is transferred into the neuron linked to transferrin after iron-transferrin binds to the transferrin receptor on the cell surface. DMT1 is present in the resultant endosome, which aids iron transfer past the endosomal membrane into the cytoplasm. Because ferroportin is found in neurons, it might be the mechanism by which iron is exported from these cells.The pathways of iron uptake by and release from brain cells, as well as iron homeostatic control in the brain, differ from those in tissues and cells outside of the brain, at least to some extent. Other proteins or compounds, such as lactotransferrin receptor (LfR), melanotransferrin (MTf), ceruloplasmin (CP), and divalent cation transporter (DCT1), may be implicated in brain iron metabolism alongside transferrin (Tf) and transferrin receptor (TfR). The role of these proteins in transporting iron in the brain and its metabolism is discussed in the Table 8.1.

3 Imaging and Brain Iron in Multiple Sclerosis

In vivo imaging of iron can be attained by the virtue of MRI. MRI is one of the most powerful tools at present for the detection and diagnosis of numerous diseases utilizes a sophisticated technology that stimulates and detects variations in the rotational axis of protons in the water incorporated in living tissues (Young & Zorab, 1997). Iron concentration in the brain is quite high enough for its detection using MRI. Magnetic resonance signaling is caused by mobile protons in tissue that contrast with alterations in the density of the solvent water in tissues, resulting in two protons relaxation times: T1 (longitudinal relaxation time) and T2 (transverse relaxation time). These two relaxation times result from the interaction of water with protons along with magnetic and paramagnetic ions. The longitudinal and transverse relaxation periods of mobile protons in the brain are shortened by magnetic and paramagnetic ions. As a result, regions with a short T1 seem to be hyperintense on T1-weighted images, and in T2-weighted images, areas with short T2 seem hypointense (Stankiewicz et al., 2007). Longitudinal (T1) and transverse (T2) relaxation durations of mobile protons in the brain are shortened by brain iron accumulation, resulting in signal loss or hypointensity on T2-weighted imaging (T2 hypointensity) and T1-weighted pictures show hyperintensity (T1 hyperintensity). T2 weighed hypointensity signals were seen in lesions, the basal ganglia, thalamus, and cerebral cortex. Only two nonheme form of iron, ferritin and hemosiderin are present sufficiently to form a contrast image during MRI (Schenck, 2003). Dysregulation in the homeostasis of non-heme iron content has been linked to neurodegeneration. Avoiding the comprehensive knowledge of MRI technology, here we only discuss the alterations and utilization of MRI during analysing the brain iron content. Moreover, the detection of brain iron in GM and WM is facilitated using high field (3 T) and ultrahigh-field (>3 T) MRI. One of the methods that MRI offers to brain iron mapping is mapping of the spin-echo and gradient-echo transverse relaxation rates (R2 and R2*, respectively). 3 T and 7 T MRI performed by Bagnato and team revealed that normally large amounts of iron are present in white matter–cortical grey matter, where iron is mainly associated with oligodendrocytes and myelin sheath. In MS lesions high iron deposition is detected by high R_2*(transverse relaxivity) and in white matter lesions, perivascular iron accumulation is displayed in the higher magnification of the iron staining (Bagnato et al., 2011). In MS hypointensity on phase and R2* images occur due to loss of myelin, whereas accumulation of iron leads to hypointensity on phase images and hyperintensity on R2* images (Walsh et al., 2013). Quantitative susceptibility mapping (QSM) facilitates field-to-source deconvolution methodology for iron quantification, avoiding the shortcomings of conventional MRI. The distribution of magnetic source—tissue susceptibility, which is quantitative susceptibility, may be reliably determined by deconvolving the GRE phase pictures or, more precisely, the magnetic field. The iron mass map for the iron-rich DGM nuclei is generated by dividing QSM by iron molar susceptibility (Stüber et al., 2016).

4 Disruption of Iron Homeostasis in Multiple Sclerosis

4.1 Iron Accumulation in Brain

The imbalance of iron metabolism, as well as the cytotoxicity that results, is increasingly being linked to MS. The definitive mechanism for increased iron accumulation in the brain is still unknown. For instance, oligodendrocytes destruction, myelin degeneration, impregnation of immune cells at the site of neurodegeneration, heam leakage during vascular hemorrhage, dysregulated iron transport proteins alongside other pathological processes. Oligodendrocytes and oligodendrocytes precursor cells (OPC) being involved in myelination exhibit abundant enzymes requiring iron for oxidative metabolism. One of the potential iron sources in activated macrophages and microglia in the process of destruction of oligodendrocytes and myelin sheath (Abo-Krysha & Rashed, 2008). Changes in the iron regulatory protein and transporters can also be an explanation for the changes in iron distribution (Hametner et al., 2013). Infiltrating immune cells like monocytes could be a source of iron entry in CNS as they are involved in the iron homeostasis and in sequestering iron that is present in the periphery. Along with this, iron is also present in the rim of active lesions. Another potential source of increased iron deposition in MS patients is vascular injury or interaction with the blood-brain barrier, which leads to erythrocyte lysis and hemoglobin breakdown (Gebril et al., 2011). The presence of iron around blood vessels has been shown in histopathological examinations. A central vein runs through many MS lesions, and iron staining has revealed haemosiderin deposits (a breakdown product of hemoglobin within and outside white matter lesions in MS patients (Adams, 1988). Activated microglia in MS results in the release of proinflammatory cytokines like TNFα and IL-6, which increase DMT1 synthesis and increase the accumulation of iron in neurons and microglia, furthermore these cytokines along with TLR-4 through regulation of DMT1 mRNA decreases ferroportin protein. Additionally, it activates the enzyme NADPH oxidase and releases hydroxyl radicals. An increase in iNOS levels elevates the NO radicals' levels via STAT1 and NfKB pathways. An increase in NO radicals along with ROS production increase the expression of DMT1, TfR1, Fpt1, and cytosolic ferritin levels, regulated by the IRE/IRP system (Gregory & Hayflick, 2005). Brain iron exists bound to ferritin and neuromelanin. Once iron is bound to transferrin crosses BBB through the TfR1 receptor, it is taken by either neurons or astrocytes from the extracellular compartment. Then the iron is either utilized by a low molecular weight complex (citrate, ATP, ascorbate) or bound to transferrin via Tf-TfR pathways. Transferrin is synthesized by choroid plexus /oligodendrocytes but is secreted only by choroid plexus. Neurons take iron via the Tf-TfR system and export it via ferroportin. IRP2 and iron-responsive elements found in the brain are important in cellular iron homeostasis. Iron causes an increase in the formation of ROS, therefore, prove to be harmful. NTBI of reticulocytes is present in the BBB. Upon entering BBB iron binds to Tf by oligodendrocytes or choroid plexes.

Transport forms of iron are Tf-Fe taken via TfR and NTBI by DMT1 or TCT (Hayflick et al., 2018).

4.2 Ferroptosis: Tissue Damage Via Iron Accumulation

Ferroptosis is a newly discovered regulated type of cell death that is iron-dependent and characterized by the accumulation of lipid peroxidation products and fatal reactive oxygen species. It is very much distinct from other cell deaths likewise autophagy, apoptosis, and necrosis, and can be called as a nonapoptotic cell death. Mediated by iron it leads to accumulation of lipid reactive oxygen species Smaller mitochondria than usual, higher mitochondrial membrane density, and decreased mitochondrial length are the most common pathologies of ferroptosis. (P. Zhang et al., 2020). Intracellular accumulation of iron induces mitochondrial damage and an increases of reactive oxygen species via Fenton reaction. Excess iron, namely the divalent ferrous ion Fe2+, can combine with hydrogen peroxide (H2O2) or organic peroxide (ROOH) to produce soluble hydroxyl (HO) or lipid alkoxy (RO) radicals (Stockwell et al., 2017) . The Fenton process, which produces reactive oxygen species (ROS) in the cell, can eventually result in a novel type of controlled cell death called ferroptosis, which is characterized by iron-dependent lipid peroxidation (Angeli et al., 2017). The neuronal membrane is abundant in cholesterol and polyunsaturated fatty acids (PUFAs), both of which are easily oxidized by reactive oxygen species (ROS) (Hirschhorn & Stockwell, 2019). Ferroptosis is a newly described type of controlled cell death marked by iron-dependent lipid peroxidation, which leads to oxidative stress and cell death (Fanzani & Poli, 2017). Apoptosis, necrosis, autophagy, and pyroptosis are all kinds of cell death that are morphologically, biochemically, and genetically distinct from ferroptotic cell death. Ferroptosis is distinguished by cytological alterations such as diminished or absent mitochondria cristae, condensed mitochondrial membrane, and mitochondria volume shrinkage. The increase of iron-dependent ROS, the reduction of glutathione (GSH), and the inactivation of glutathione peroxidase 4 (GPX4) are all hallmarks of ferroptosis, and this redox dyshomeostasis causes cell death. Ferroptosis inducers were discovered before the name ferroptosis was created, which is interesting (Yang & Stockwell, 2016) . To begin, researchers discovered that the tiny chemical erastin caused non-apoptotic cell death in tumorigenic cells, which was unexpected . The researchers then looked for two ras-selective lethal small molecule compounds (RSL3 and RSL5) that caused non-apoptotic and iron-dependent oxidative cell death. An iron chelator (desferrioxamine) and an antioxidant (vitamin E) were found to be effective in preventing this type of cell death, which had comparable characteristics to erastin-induced cell death (Mou et al., 2019). The iron-dependent buildup of harmful lipid ROS characterises ferroptosis. Because the lipid hydroperoxidase glutathione peroxidase 4 is inactive, ferroptosis results whenever the oxidation of membrane polyunsaturated fatty acids (PUFAs) is permitted to run out of control (GPX4). Unrestricted lipid oxidation and lipid ROS production are

thought to lead to membrane degradation and perforation [26], but the exact molecular specifics of how this happens are unknown. Unlike other types of cell death, this one does not appear to necessitate transcriptional upregulation or posttranslational alteration of any cell death effector or pore-forming protein. Indeed, there's also no ferroptosis programme in the cell that is ready to be activated, as far as we know. As a result, ferroptosis necessitates the depletion of glutathione (GSH) or inactivation of the glutathione-dependent antioxidant enzyme glutathione peroxidase 4 (GPX4), as well as the incorporation of oxidizable polyunsaturated fatty acids into phospholipids.

5 Astrocytes

Astrocytes do not exhibit TfR, take iron by DMT1 expressed at end foot process. The efflux takes place via ferroprotein, glycolytic, and Ceruloplasmin. Astrocytes take iron from circulation and also distribute it to other cells of the CNS. The express IRP1 and IRP2, DMT1, IREDMT for regulation of iron (Gaasch et al., 2007).

6 Oligodendrocytes

Oligodendrocytes have a large amount of iron for axon myelination. They extract iron from adjacent blood vessels or uptake from intestinal ferritin through ferritin receptors. At the time of neuroinflammation glial cells are activated stimulating iron accumulation in neurons and microglia. Oligodendrocytes take up iron via ferritin receptor Tim-2 or non-transferrin bound iron via DMT1. Apart from those microglia take up iron via Tf and efflux through ferroportin (Chen et al., 2019).

7 Grey Matter Iron Accumulation

Iron is mostly deposited in ferritin in the aging human brain, where it is present in the non-toxic ferric form. Iron is released into the extracellular space and the bloodstream after the breakdown of myelin and oligodendrocytes in MS (Haider et al., 2014). Diffuse hypointensity of the cortical and deep GM regions (e.g., the red nucleus, thalamus, and dentate gyrus) is a typical finding in spin-echo T2-weighted clinical MRI scans in patients with MS (nucleus, lentiform nucleus, caudate, and rolandic cortex) vs (nucleus, lentiform nucleus, caudate, and rolandic cortex) typical controls of the same age (Y. Zhang et al., 2007). In individuals with MS, T2 hypointensity in the GM has been linked to brain shrinkage, disability progression, and cognitive impairment. T2 intensity in the caudate nucleus was shown to be lower in individuals with the clinically isolated syndrome (CIS) compared to healthy

controls. T2 hypointensity was a stronger predictor of disability progression over time in individuals with established MS than other measures such as total brain atrophy and T2-lesion volume. T2 hypointensity of deep GM in CIS patients was not linked to the development of clinically confirmed MS. Studies in pediatric MS patients have offered more evidence that iron can accumulate early in the disease course (Bagnato et al., 2013). Selective T2 hypointensity in the caudate nucleus of pediatric MS patients was discovered, similar to CIS, with other deep GM structures spared. Furthermore, despite their better clinical outcomes and less total brain tissue damage, benign MS patients had similar T2 intensity to secondary progressive MS patients (Neema et al., 2009). A recent year-long pilot trial of natalizumab therapy in MS patients found a therapeutic impact on slowing the progression of T2 hypointensity in GM, suggesting that inhibiting the inflammatory cascade might lead to reduced iron accumulation in the brain. Iron deposition in various deep GM locations, including the caudate, putamen, pallidus, and pulvinar nucleus, has been reported in CIS patients using 7-T MRI and quantitative magnetic susceptibility mapping, further validating and expanding prior findings (Ceccarelli et al., 2010). GM iron-related alterations may precede GM atrophy in CIS patients, according to recent research employing susceptibility-weighted filtered phase imaging, suggesting that aberrant iron deposition may be an early surrogate of the disease (Hagemeier et al., 2012).

8 White Matter Iron Deposition

It has been claimed that as illness duration increases, iron in normal-seeming white matter (WM) decreases owing to alterations in oligodendrocytes and myelin. Iron deposition in the WM is typically seen at the level of MS lesions and around the veins, according to pathologic investigations (Hametner et al., 2013). However, owing to the confounding influence of edema, inflammation, gliosis, and myelin content on MRI signals, detecting iron deposition in the WM is still difficult. The use of a multimodal strategy that includes modern iron-sensitive MRI methods including phase imaging, R2*, and ultrahigh-field scanners has improved our understanding of WM iron deposition in MS. It is feasible to see phase hypointense WM lesions that are likely rich in iron content and are typically overlooked by standard MRI sequences using phase imaging (Yao et al., 2012). hypointense WM in different phases Iron deposition might be within or at the edge of phase WM lesions in MS, according to MS lesion patterns such as nodular, ring, and dispersed morphologies (Mehta et al., 2013). Even during the early stages of MS, such phase WM lesions have been documented. Future integrated histopathologic multi-modal MRI investigations will give information on the processes behind iron-related MRI abnormalities identified in WM, perhaps revealing the relationship between WM damage and clinical state.

9 Iron Genetic Relation in Multiple Sclerosis

HFE rs1800562 (C282Y) and HFE rs1799945 (H63D), both linked to hereditary hemochromatosis, and rs1049296 (TF-C2), linked to iron transport have been reported. The C282Y genotype was shown to be 8.6% prevalent in a large population-based study with 5171 people, while H63D was found to be 23.3 percent prevalent. The H63D gene variation is linked to an increase in iron in healthy adult's right putamen. Unadjusted variations in right putamen susceptibility and volume (C282Y) and thalamus volume (H63D) of HCs had also been discovered. MS patients with the H63D mutation demonstrated a higher vulnerability to the left putamen. There were no changes in susceptibility or volume between carriers and non-carriers in any other location. H63D was found in the left putamen across the MS group, but progressing patients with the C282Y gene mutation showed significantly decreased susceptibility in the bilateral thalamus, indicating lesser thalamic iron. In comparison to HCs, RRMS patients have decreased thalamic susceptibility, according to a recent study. They also noticed an increase in the likelihood of developing (main) progressive MS (Burgetova et al., 2017). A more recent study looking into the link between iron-related polymorphisms and MS severity found that H63D- carriers had a higher MSSS and disease progression than C282Y-carriers (Hagemeier et al., 2018).

10 Iron Chelation Therapy in Multiple Sclerosis

An iron chelator binds iron and facilitates its elimination, and it has been proven that chelators can change the concentration of iron within cells in some situations. Chelators are used to either enhance the elimination of excess iron or to enhance safety iron levels in circumstances where poisonous levels of iron are a problem. Iron accumulates in identical parts of the brain in many of these diseases as it does in MS, or iron has a potential harmful mechanism that's also shared between the several neurological disorder and MS (Kakhlon et al., 2008). Examining the usage of chelators for such circumstances could thus be useful in planning MS investigations. Mitochondria can be damaged by oxidative stress in MS, and frataxin expression is down-regulated in early MS lesions, indicating mitochondrial injury (Vaubel & Isaya, 2013) (Hametner et al., 2013). Furthermore, in both MS and Friedreich's ataxia, iron accumulates in the dentate. Iron chelator experiments have been conducted on Friedreich's ataxia. Additional structures for aceruloplasminemia and neuroferittinopathy include the putamen, caudate, and possibly the thalamus. These are the same deep grey matter structures that show iron accumulation in MS, which is interesting. Additional structures for aceruloplasminemia and neuroferittinopathy include the putamen, caudate, and possibly the thalamus (Schneider et al., 2013). These structures are very similar to the deep grey matter structures that show iron buildup in MS. For NBIA illnesses, iron chelation

treatment has been investigated (Williams et al., 2012). In a trial of nine individuals with PKAN (12.5 mg of deferiprone/kg, twice daily for 6 months), deferiprone, which does cross the BBB, reduced brain iron but did not improve clinical symptoms (Zorzi et al., 2011). In two patients with NBIA of unknown cause, deferiprone treatment (15 mg/kg, twice daily) improved clinical symptoms (e.g., gait, dysarthria, dystonia) and reduced brain iron (Kwiatkowski et al., 2012).

11 Chelation Therapy in EAE Model of Multiple Sclerosis

Chelation treatment has been investigated in MS EAE models. Lewis/JC rats were fed with guinea pig spinal cord homogenate as an encephalitogen 70 mg/day of deferoxamine via osmotic pump for 7 days. When taken before the commencement of clinical signs, deferoxamine prevents the development of symptoms, and when given after the onset of clinical signs, it speeds up the recovery process (Bowern et al., 1984). Deferoxamine did not alleviate illness in rats administered passive transfer of cells of MBP or spinal cord homogenate-injected rats at the preclinical stage of EAE. Deferoxamine treatment, on the other hand, began one day before cell transfer and lasted for 7 days (Willenborg et al., 1988) When given during active disease to male SJL mice given purified MBP and pertussis toxin injections, deferoxamine (40, 80, or 157 mg/kg, three times a day) reduced disease activity (Pedchenko & Levine, 1998).

11.1 Impact of Brain Iron Accumulation on Cognition and Memory

The overall concentration of iron in a healthy adult human brain is roughly 0–200 g per gramme of tissue, with lower concentrations in the White Matter (WM) and cortical Grey Matter (GM) (60 g per gramme). Only 0.05% of brain iron is kept in the labile iron pool, while 90% of brain iron is stored in ferritin. Iron accumulates heterogeneously in various areas of the brain during healthy ageing, bound mostly to ferritin and neuromelanin and primarily localized in the deep GM nuclei. From birth until approximately the age of 20, there is a significant rise in iron buildup (which varies depending on brain region), after which the pace slows in certain areas, reaching a plateau in middle life and growing after 60 years. Several ideas have been proposed to explain the involvement of brain iron in cognitive decline (Spence et al., 2020). Many of these methods are based on iron's capacity to cause oxidative stress through Fenton's reaction. Excess iron combines with reactive oxygen species (ROS) such as hydrogen peroxide to form highly reactive OH radicals, which can cause iron release from mitochondrial iron-Sulphur cluster proteins and iron storage proteins during Fenton's reaction . Fenton's reaction can then take place with the

released iron, boosting ROS production. When the amount of ROS and free radicals produced by Fenton's reaction exceeds the antioxidant capacity of brain cells, oxidative stress occurs, resulting in DNA damage, lipid peroxidation, mitochondrial malfunction, protein misfolding, and neuronal cell death (Jomova & Valko, 2011). The activation of neuroinflammation is expected to increase this oxidative stress. Long-term activity of HO-1 in glia may be implicated in iron sequestration, intracellular stress, and mitochondrial insufficiency, which may lead to neurodegeneration. Ferroptosis is another process through which brain iron levels may impact cognitive decline/neurodegeneration. Shrunken mitochondria with increased density and outer membrane rupture characterize this iron-dependent necrosis process (Schipper, 2000). Memory function is the most commonly reported cognitive measure linked to brain iron, but it was also the most frequently tested cognitive result. The Caudate nuclei, Hippocampus, and Thalamus were the areas where iron was most commonly linked to memory performance. Except for the Globus Pallidus, where regional iron had no known correlations with memory, all other areas were linked to memory in at least one research. The links between iron and memory in the caudate, hippocampus, and thalamus are somewhat unsurprising because each of these regions is known to be involved in different aspects of memory function, making it plausible that disrupting these circuits via iron accumulation would result in memory dysfunction (Thomas et al., 2020). The availability of dopamine receptors has been linked to the efficacy of interactions between the caudate and hippocampus in memory function, which has been linked to a potential involvement in iron buildup. According to studies, iron and dopamine can form a toxic pair that causes oxidative stress and neurodegeneration. Iron deficient mice and rats had lower amounts of dopamine transporters and receptors, as well as overall dopaminergic dysfunction, according to animal research. Higher iron levels in the caudate nuclei have also been linked to a decline in overall cognitive ability (Altamura & Muckenthaler, 2009). The putamen, on the other hand, has the greatest documented connections with general cognition, with the Globus Pallidus and the Substantia Nigra being linked to general cognition in many studies. The putamen is involved in a variety of neurological processes, including sensory and motor information processing, learning, and language. There were associations between reduced motor function and increased striatal iron content, as well as increased iron in the Putamen and increased disability scores, such as the Dementia rating scale, Extended disability status score, and the UPDRS-III for rating Parkinson's pathology, though these were assessed in fewer of the studies reviewed (Krämer et al., 2015). Atrophy in the Putamen is recognized to be implicated in the pathophysiology of various disorders, including Parkinson's disease, Multiple Sclerosis, and Dementia with Lewy Bodies, due to its multiple neurological roles and connections (Luo et al., 2019).

11.2 Brain Iron in Fetus Development

Iron deficiency has been demonstrated to impair newborn behaviour and development in pioneering investigations.Our emerging understanding of the biology of embryonic iron shortage points to iron's significance in neurocognitive and neurobehavioural development (Beard, 2008). During the first 6–18 months of postnatal life, when the brain is rapidly developing, morphological, biochemical, and bioenergetic changes may impact how the brain operates later in life, iron requirements are predicted to surpass iron intake. It has been observed in a number of epidemiological studies that children with iron deficiency anaemia score worse on tests of particular cognitive abilities (Rao & Georgieff, 2007). Some of the negative effects of low iron availability on brain function have been discovered in animal studies. Posttranslational alterations (which result in a failure of iron incorporation into protein structures, which are then destroyed), susceptibility of the developing hippocampus (with loss of the neuronal metabolic marker cytochrome c oxidase), and altered dendritic structure are all examples of this (Ward et al., 2007). Because iron is required for a variety of enzymes, including tryptophan hydroxylase (serotonin) and tyrosine hydroxylase, iron shortage will have a direct effect on myelin, including a reduction in myelin lipids and proteins, as well as neurotransmitter systems (norepinephrine and dopamine). Long-term studies of iron deficiency in the human baby brain show that such myelination changes cause delayed conduction in both the auditory and visual systems (Burhans et al., 2013). During an iron deficit, both of these sensory systems quickly myelinate, and they are essential for learning and social interaction. This, along with the lower energy, poor glial function, and altered monoamine circuit activation, may affect experience-dependent processes, which are crucial to brain shape and function throughout early development.

11.3 Association of Aging to Iron Induced Neurodegeneration

It's becoming clear that a variety of pathophysiological conditions, like as ageing and inflammation, have an impact on the BBB's function. Immune cells can pass across the BBB, whether it's the endothelial BBB or the epithelial blood–brain barrier (BBB). At tight junctions, inflammation, as well as reactive oxygen and nitrogen species (ROS) and reactive nitrogen species (RNS), can disrupt BBB (Penke et al., 2012). Under pathological situations, 4-Hydroxynonenal (HNE), a second messenger of free radicals, is present in the BBB and might render the endothelial component of the BBB permeable. When brain iron deposition was reduced in the globus pallidus, substantia nigra, red nucleus, and temporal cortex of elderly rhesus monkeys on a calorie-restricted diet, both age-related inflammation and oxidative damage were reduced. Recent research has revealed that iron homeostasis parameters in the blood, such as serum iron and transferrin saturation, as well

as hepatic iron content, may be associated with iron content of specific brain areas, as measured by MRI proton traverse relaxation time, R2 (House et al., 2010).

12 Conclusion

In summary, various evidence proved the accumulation of iron in MS lesions and further worsening of demyelination and an immune response is a hallmark of the disease. The accumulation of iron in various parts likewise grey matter, white matter, and its interaction with glial cells like astrocytes, oligodendrocytes leads to a more exaggerated immune response. However, whether iron buildup is one of the causes of MS or a secondary pathogenic alteration is still to be known. Future studies should focus on the chemical role of iron in MS and its disturbed in various pathological hallmark stages of MS. Additionally, different randomized, double-blind, and multicenter trials should be conducted to study the role of iron chelators in reversing the diseased state.

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Chapter 9
Iron and Epilepsy

Rajesh Thangarajan and Pugazhandhi Bakthavatchalam

1 Introduction

1.1 Epilepsy- a Neurological Disorder

Epilepsy was theoretically defined as a brain condition characterized by an enduring proclivity for epileptic seizures. This definition is commonly implemented in practice as having two unprovoked seizures separated by more than 18 hours (Fisher et al., 2014). Epilepsy is a term used to describe a group of disorders that all reflect underlying brain malfunction and can be caused by a range of factors. The terms seizure and epilepsy have little in common in terms of definition. Such definitions are critical for communication among medical experts, as well as other stakeholders in law, disability benefits, driving restrictions, workplace safety, education, and a variety of other areas (Fisher et al., 2005). The definitions on this page are intended for a wide range of people, including physicians, educators, researchers, government officials, and epilepsy patients and their families (Blume et al., 2001). Epilepsy is defined as a patient who has had a seizure and whose brain has a pathologic and lasting tendency to suffer recurring seizures for any reason. When compared to people who do not have the disorder, this tendency might be thought of as a pathologic reduction of the seizure threshold. Epileptogenesis is a pathologic process in which the brain undergoes physiological and anatomical changes that increase seizure vulnerability and the chance of spontaneous recurring seizures (SRS) (Pitkänen et al., 2015). Oxidative stress is a significant pathogenic mechanism of

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epileptogenesis in epilepsies of various etiologies (Pauletti et al., 2019; Shekh-Ahmad et al., 2019).

1.2 Epilepsy Prevalence around the World

Epileptic seizures affects 60 million individuals globally, with 4–five million in the United States, eight million in Europe, and at least 50 million in underdeveloped countries (Galanopoulou et al., 2012). Epilepsies affect a large number of children in their early years. People under the age of six and individuals over the age of sixty have the highest age-specific incidences of >50 per 100,000 in the population (Symonds et al., 2021). Drug-resistant seizures develop in a significant number of children with neurological conditions in their first three years of life (40%). These individuals are at an increased risk of neurobehavioral disorder, as well as premature death (Jennum et al., 2017). While it is evident that early initiation, poor seizure management, and neurological disorder are all associated, the cause of these relationships is unknown. Even if it is expected that the fundamental underlying cause will have a significant impact on outcomes, it has never been addressed at the population level utilising modern neuroimaging and genetic technology (Symonds et al., 2021).

1.3 Epilepsy in Adults

One of the most common serious brain disorders is epilepsy. They can affect persons of various ages and manifest themselves in a variety of ways. Although the incidence of juvenile cancer has declined in industrialized countries over the last three decades, this decline has been accompanied by a rise in the number of elderly people (Duncan et al., 2006). Various mutations in the same gene might cause different epileptic syndromes, hence a clinical manifestations could have multiple genetic causes. On the other hand, most epilepsies are most likely complex features involving environmental influences on inherited susceptibility, which are mediated by common polymorphism in specific genes. Epilepsy is diagnosed through clinical examination, with neurophysiological studies assisting in the diagnosis (UK, N.C.G.C, 2012). The application of brain imaging to detect the structural and functional causes and effects of epilepsies is quickly evolving. Antiepileptic medications decrease seizures in 60–70 percent of persons without altering the underlying tendency to have seizures. Pharmacogenetic studies hold the possibility of better individualising medication for each patient, resulting in the greatest likelihood of benefit and the fewest negative effects. For patients with refractory focal epilepsy, neurosurgical excision holds the possibility of a life-changing treatment. Novel treatments include precision seizure prediction and focused therapy with pharmaceutical delivery, brain stimulation, and biological grafts (Kwan & Brodie, 2006).

1.4 Risk Factors of Epilepsy

Risk factors include age, genetics, family history of epilepsy, history of febrile seizures, alcohol consumption, CNS and other infections, brain trauma, head injury, perinatal stroke, preterm birth, and geographic location. Epilepsy induced by a head injury, central nervous system illnesses, and tumours can strike at any age. The most frequent risk factor in people over 65 is cerebrovascular disease (Granger et al., 2002). In adulthood, external non-genetic risk factors such as vascular disease, such as stroke, are increasingly common. Certain types of epilepsy, whether in childhood or adults, may be linked to modifiable risk factors such alcohol use, traumatic brain injuries, or CNS infections (Walsh et al., 2017). Knowing these risk factors could enable for more regular outpatient clinic examinations, warning families about seizures, advising to record video in case of seizure suspicion, and, if necessary, obtaining an early EEG.

1.5 Epilepsy Classification

The seizures and epilepsies classified as per the International League Against Epilepsy's (ILAE) in 2017 is considered as the latest. This classification was aimed to assist the patients and clinicians in deciphering language and distinguishing between seizures with generalized and localized onsets (Sarmast et al., 2020). Seizures and epilepsy are better diagnosed and managed when they are categorized into various medications beneficial for different seizure types. The clinical aspects of epilepsy are divided into three stages by the ILAE: seizures, epilepsies, and epilepsy syndromes. This focus has been on the cause and complications at each stage (Zuberi & Brunklaus, 2018).

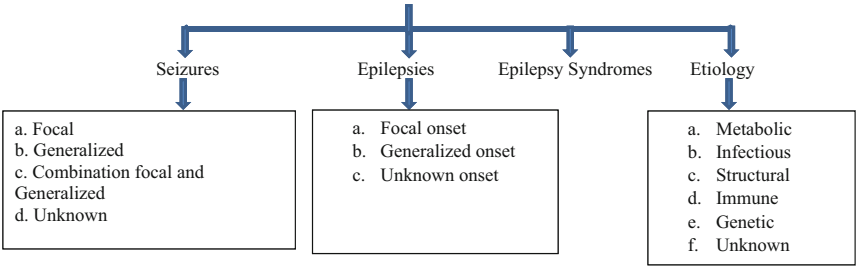
1.6 Seizure

Seizures are symptoms and signs that occur when a group of neurons in the brain experience unusually intense or concurrent neural excitation. While epilepsy is characterized as a severe neurological ailment marked by a persistent proclivity for unprovoked seizures as well as the neurological, intellectual, and psychosocial implications of the condition (Brodie et al., 2018). At least two uncontrolled seizures that occur more than 24 hours apart are required to diagnose epilepsy. A syndrome is characterized as a recurring seizure that is accompanied by abnormal examinations in a predictable pattern. It frequently comprises several different types of epilepsy (Sarmast et al., 2020).

When diagnosing epilepsy, factors such as the model and incidence, seizure type, genetic predisposition, Electrophysiological, and Magnetic resonance imaging abnormalities are all considered (Aaberg et al., 2017).

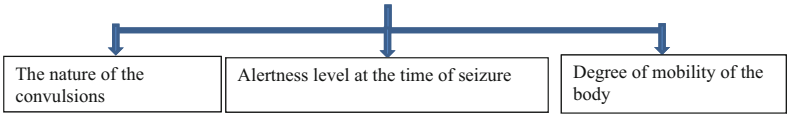
1.6.1 The Structure of Classification

The new classification has four components in general which is as follows: (Sarmast et al., 2020).

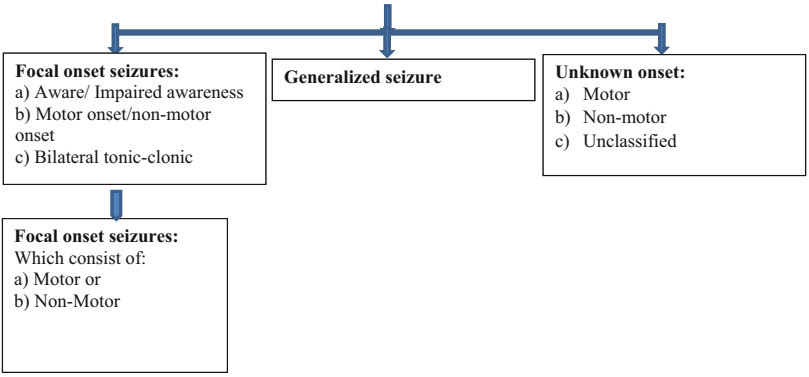


1.6.2 Classification of Seizure

Seizures are divided into three categories based on the following characteristics (Falco-Walter et al., 2018):



1.6.3 Seizures Are further Classified into Three Based on the Onset (Auvin, 2018)



FOCAL SEIZURES WITH MOTOR SYMPTOMS	
TYPES OF SEIZURE	**INTERPRETATION**
1. Focal Akinetic Seizure	In this type, the seizures represent rapid loss of muscle tone on one limb and one side of the body that lasts only a few seconds. The majority of the time, consciousness is sustained.
2. Focal Stereotyped Seizure	Recurrent actions, such as repeating something again and again, lip-smacking, kneading, or strolling, are examples of recurring motor activity. It's a common sign of a seizure that causes localized loss of awareness.
3. Focal Grand Mal Seizures	A sustained rise in muscle tension that persists for a few seconds or minutes causing the patient's extremities or neck rigidity.
4. Clonic Seizures	A symmetrical syncopated twitching of a muscle group happens over time.
5. Focal Epileptic Spasms	Muscle spasms that are uncontrollable and occasionally painful, which are prevalent in youngsters. Video-EEG is commonly used to diagnose it. Infantile spasm is the name given to it when it happens in infants.
6. Hyperkinetic Seizures	Characterized by excessive and frequently uncontrollable muscle movements such as frenzied kicking, thrashing, and pedaling.
7. Myoclonic Seizures	It's related to a complex partial seizure in that it's characterized by fast twitching in one portion of the body and face, as well as brief, un-sustained muscle spasms.
NON-MOTOR FOCAL SEIZURES	
TYPES OF SEIZURE	**INTERPRETATION**
1. Focal Autonomic Non-Motor Seizures	This type of convulsions that affect the sympathetic nervous system, resulting in symptoms such as increasing gastrointestinal pressure, hot and chilly sensations.
2. Focal Behavior Arrest Non-Motor Seizures	These seizures are characterized by the halt of all activities and the inability to respond for the duration of the seizure.

(continued)

3. Focal Cognitive Non-Motor Seizures	If the individual has delusions, hallucinations, short-term memory loss, or mental confusion during the episode.
4. Focal Emotional Non-Motor Seizures	Anxiety, nervousness, fright, exhilaration, grief, sadness, or other sensation can trigger these seizures, which are non-motor seizures.
5. Focal Sensory Non-Motor Seizures	Can cause ocular, nasal, perceptual, gastronomic, somatic delusion, or disorientation.

MOTOR GENERALIZED SEIZURE	
TYPES OF SEIZURE	**INTERPRETATION**
1. Tonic-Clonic-Myoclonic seizures	Individuals with juvenile myoclonic epilepsy are more likely to experience this episode.
2. Myoclonic-atonic seizures	This type was previously known as myoclonic Astatic seizures and is typically found in people with Doose syndrome.

GENERALIZED NON-MOTOR SEIZURES	
TYPES OF SEIZURE	**INTERPRETATION**
1. Petit Mal Seizures	Seizures like this are distinguished by abrupt cessation in activities, accompanied by a blank look and, on rare occasions, eye deviation, followed by fast recovery. It may be linked to eyelid fluttering.
2. Atypical Absence Seizures	It begins gradually, with more significant reductions in muscle tone than in normal absence.
3. A myoclonic-absence seizure	A sequence of syncopated jerks precedes this seizure, accompanied by a period of gazing.
4. Jeavons Syndrome	It's a rare type of epilepsy in which seizure includes a sudden upward twitching of the eyelids, which could be related to the gazing phase (absence seizure). It is frequently triggered by closing one's eyes.

2 Mortality in Epilepsy

Epilepsy patients are at a higher risk of dying young. Epilepsy with symptoms might cut your life short by up to 19 years. Early death, trauma, homicide, infections, and epileptic seizures are all more common in epilepsy patients than in the general population (Gaitatzis & Sander, 2004). Although little is documented about fatalities in resource-poor nations, research suggests it is higher than other countries, which could help to explain why impoverished countries have an increased prevalence and decreased incidence of active epilepsy (Sander, 2003). Although the pharmacological causes of early unexplainable mortality in epileptic seizures remain unclear, cardiovascular arrhythmias, notably asystole connected to convulsions, have been identified in methodology to achieve and are thought to occur only in rare cases (Duncan et al., 2006). Protracted Electrocardiogram tracking is required to discover

patterns that indicate a high probability of ventricular contraction and advise myocardial synchronization as a preventive measure.

3 Neuropathology of Epileptic Seizures

A brief episode of clinical manifestations, or both, in the brain caused by abnormally high or synchronised neuronal activity is known as a seizure activity. A transient synchronised discharge of a network of neurons that lasts less than 70 milliseconds and is distinct from a seizure is known as an interictal spike (De Curtis & Avanzini, 2001). The paroxysmal surging region can, in fact, be distinguished from the seizure onset zone. Seizures are thought to be triggered by a disruption in the brain's usual balance of excitation and inhibition, however this is now regarded an oversimplification. Communication among dissimilar circuits is required for the brain's function, which is most likely mediated through waves among these circuits. The creation of oscillations in cortical networks is dependent on interneurons, neural transmission (e.g., synaptic transmission), and inherent neuronal properties (Ward, 2003). The emergence of epileptic discharge as an epiphenomenon of such asynchronous circuits is possible. Greater spread and neuronal recruitment, as a result of a combination of greater connection, increased excitatory transmission, a failure of inhibitory mechanisms, and changes in intrinsic neuronal properties, are thought to be the beginning of the transition from normal to epileptiform behaviour. In human studies, the electroencephalogram (EEG) becomes less chaotic in large areas of the cortex before a seizure, indicating extensive synchronisation (Litt & Echauz, 2002).

In localized epileptic seizures, focal cognitive interruption related to focal clinical abnormalities (i.e., tumours) or, less typically, a hereditary diathesis results in seizures that start small and grow as more brain areas are recruited. The location of the focal, as well as the speed and degree of spread, influence the seizure's clinical manifestation (Duncan et al., 2006).

Seizures occur across the cortex due to a broad decrease of the seizure threshold in global epilepsies, which are mainly genetically based (Duncan et al., 2006).

Absence seizures, a type of generalised seizure, are caused by the thalamocortical loops. Subcortically, absences were assumed to be caused by thalamic neurons driving neocortical neuron recruitment (McCormick & Contreras, 2001).

4 Iron in Brain

Despite the fact that iron is required for appropriate brain function as a component of cellular proteins, iron-sulfur complexes, haemoglobin, and neurotransmitter, triglyceride, and genetic synthesis, too much iron can be neurotoxic. The brain's ability to store a quickly available source of iron is crucial for appropriate neurologic function, despite the fact that both insufficiency and excess have substantial neurological

consequences (Connor et al., 2001). Because of the blood-brain barrier, getting iron to the brain in a timely and adequate manner is difficult. The regional differentiation of cerebral activity and the complexity of cellular processes add to the complexities. Age and geography have an impact on iron-dependent processes in the central nervous system (CNS). As a result, the procedures that keep the CNS iron level under control must be examined by region and age. In addition to ageing and regional requirements, dietary variables and disease are confounding factors that affect brain iron uptake (Beard et al., 1993). The role of iron in a number of CNS activities, as well as the consequences of altered iron metabolism in a variety of neurotoxic disorders, highlight the need for further research into various aspects of iron homeostasis. Iron is in high demand in the brain, which correlates to its high energy needs (Piñero & Connor, 2000). Adenosine Triphosphate (ATP) is required by the brain to sustain membrane electrochemical gradients, synaptic transmission, and axonal transport (Beal, 1998). Iron is required for the creation of lipids and cholesterol, which are crucial substrates for myelin synthesis, as well as metabolic enzymes found in oligodendrocytes. Iron is also suggested to play a role in the action of the GABAergic system. As a result, it's expected that variations in iron availability to the brain and iron metabolism in the central nervous system will have a negative impact on a number of neurologic activities. Intelligence, motor function, endorphin activities, and myelination are the most typically observed problems associated with CNS iron deficiency (Shinobu & Beal, 1997). Iron levels in the brain fluctuate with age and disease, and they decline when the diet is deficient in iron. Low brain iron levels in neonates and children have been related to behavioural and cognitive difficulties, as well as an iron-deficient diet. Pantothenate kinase-associated neurodegeneration, vascular dementia, Parkinson's disease, and corticospinal dementia have all been connected to abnormal iron accumulation and, in some cases, changes in iron-related components in sick brain circuits (Fleming et al., 1998). Iron-mediated oxidation appears to play a role in apoptosis in a number of disorders, according to a growing body of research. When it comes to iron availability, multiple sclerosis and other demyelinating diseases demand special consideration (Gunshin et al., 1997). Oligodendrocytes require a steady supply of iron because axonal management and implementation necessitate a large amount of it (Vulpe et al., 1999). On the other hand, higher oxygen consumption, lipid concentration, and white matter mineral content all contribute to an increased risk of oxidative injury. This article discusses the present state of knowledge about iron homeostasis in the brain, as well as its probable role in neurotoxicity (Piñero & Connor, 2000). Iron is essential for cognitive function, as evidenced by the presence of integrins transporters on brain vascular endothelial cells (Moos, 2002). The transmission of iron into the central nervous system from the vascular system is governed when the brain's iron requirement is significant, such as in circumstances of micronutrient deficiencies or during neurodevelopment, so that in iron-replete conditions, the excavation of iron by frontal cortex endocytosed is low, and the opposite is true when the brain's iron requirement is high. While it is widely accepted that iron is taken up at the brain's borders via receptor-mediated iron-transferrin absorption (Moos, 2002).

5 Modulation of Erythropoiesis in the Blood-Brain Barrier (BBB)

Because of its high metabolic rate, the central nervous system contains a lot of non-heme iron. The majority of the iron is found in the ventral striatum, with the latter reaching levels comparable to the liver. The BBB protects the brain from systemic iron variations, and disruptions in iron homeostasis in peripheral organs have little impact on brain iron metabolism. As a result, iron and iron-modifying polypeptides levels in the serum, as well as cerebrospinal fluid (CSF) that surrounds the brain, vary drastically (Moos, 2002). A monolayer of polarized capillary endothelial cells with tight connections forms the BBB, which regulates cargo transfer from the luminal or apical surface of blood to the abluminal or basolateral surface of CSF and brain interstitial fluid (Deane et al., 2004; Rouault et al., 2009).

6 Brain Iron Deposition and Neuronal Death

Neurodegeneration with brain iron accumulation (NBIA), a collection of hereditary neurologic illnesses, is distinguished by excessive iron deposition in the limbic system, substantia nigra, striatum, and cerebellar dentate nuclei (Gregory et al., 2008). The beginning age varies, and most instances present with a wide range of overlapping clinical symptoms, such as progressive extrapyramidal indications with diverse combinations of movement problems, seizures, and visual difficulties, eventually leading to the cognitive deterioration (Kurian et al., 2011; Kruer et al., 2012).

7 Iron in Epilepsy

Iron is a trace element that is necessary for human development and growth. Many redox events, including oxidative metabolism, the electron transport chain, the pentose phosphate pathway, and DNA transcription, require iron molecules (Thirupathi & Chang, 2019; Abbina et al., 2020). Iron, on the other hand, is involved in the creation of myelin and the metabolism of epinephrine, norepinephrine, and dopamine in the nervous system, as well as intellectual development and neurodegenerative illnesses (Thirupathi & Chang, 2019).

As a result, the human body's iron metabolism should be closely monitored. Abnormal iron metabolism has been associated with several depressive illnesses, including ischemic post-stroke and posttraumatic epilepsy (PTE) (Yokoi et al., 1995; Mori et al., 2004).

8 Epilepsy Induced by Iron

Among the most common causes of intractable epilepsy in ischemic stroke patients is iron overload. Blood extravasates and erythrocytes and hemoglobin are destroyed when a brain injury or acute cortical infarction occurs. Hemoglobin and iron produced by hemoglobin are linked to reactive oxygen species(ROS) and nitrogen species(RNS). ROS as well as RNS, on the other hand, have been linked to iron-induced epileptic convulsions in mice (Chen et al., 2020). In recent studies, injections of ferric chloride into the cortex of rats were shown to cause protracted epileptic episodes in rats (Chen et al., 2020). O2 and OH are produced after ferric chloride is injected into the cerebral cortex of rats. These hydroxyl radicals may cause epilepsy by promoting reactive oxygen species (ROS) in neuronal membranes and an increase in guanidine molecule production in the brain.

9 Iron Metabolic Process in Epilepsy

Hemosiderin is formed when hemoglobin is broken down in the brain. Hemosiderin is one of the most frequent types of accumulated iron in the nervous system, and it has been connected to degenerative disorders including epilepsy (Zhang et al., 2018). The human body accumulates chelating ferrous, which is then metabolized into transition metals in the bloodstream via ceruloplasmin (Mukhopadhyay, 2018; Naito et al., 2021). This finding demonstrated that iron controls inflammation in the epileptic brain, which serves a role in the initiation and progression of epilepsy. Finally, abnormal iron oxidation and transport in epileptic patients' brains could be one of the factors of epilepsy's origin and recurrence. Although iron injections into the brain cause seizures, the link between epilepsy and iron metabolism is yet unknown and requires further research. Imaging technologies can be used to diagnose and evaluate epilepsy based on the abnormal distribution of iron in the epileptic brain (Chen et al., 2020).

10 Histopathological Changes in the Epileptic Brain Tissue

Gliosis, neuronal degeneration, vascular malformation, Hippocampal sclerosis, Ganglioglioma Tumor, Focal cortical dysplasia, Glial scar, Cavernous angioma were found in the routinely processed biopsy specimens collected from brain resections utilising the peroxidase-antiperoxidase technique (Kallioinen et al., 1987).

Hippocampal sclerosis is more common in patients with status epilepticus. The Cornu Ammonis (CA) 1 field of the hippocampus is characterised by cellular infiltration and neurodegeneration, followed by the hilus, Cornu Ammonis 4, and Cornu Ammonis 3 fields. The dentate granular cell layer and neurons in the CA2

field are relatively undamaged. The dentate granular cell layer is also commonly scattered, with ectopic neurons found in the molecular layer. Neuronal loss is accompanied by axonal reconfiguration, which includes both excitatory and inhibitory neurons (Mathern et al., 1995).

The mechanisms that link seizures to hippocampal damage or changes in excitatory and inhibitory pathways remain a mystery. One of the primary theories for explaining the hyperexcitability of hippocampal principal cells and seizure activity is GABA-mediated inhibition. GABAergic neurons innervate a varied range of morphological and neurochemical types of primary cells. The somata (and proximal dendrites) and axon beginning segment (AIS) of main cells, respectively, receive a considerable GABAergic input from huge basket cells and chandelier cells (DeFelipe, 1999).

11 Histopathological Changes in the Iron Induced Epileptic Brain Tissue

Serial sections stained with Nissl, hematoxylin, and eosin, as well as Methylene blue, indicated delamination, neuronal pyknosis and loss, and astrogliosis in untreated animals (Willmore & Rubin, 1981). Golgi-Cox and Cresyl violet stain methods revealed (i) desecration of Golgi-stained neurons, (ii) astrocytosis, (iii) dendritic spine loss, (iv) reduced dendritic branching, and (v) excitotoxic injury of dendrites.

12 Management of Epilepsy

12.1 Initial Management of Epilepsy

Main and foremost, with any seizing patient, the first concern is to guarantee the patient's safety while awaiting for emergency services (Biazzo-Ashnault et al., 2001). To avoid falls or mishaps, anything that will lead to serious injuries should be put out of the way, and the patient should be moved to the floor or another flat surface if at all possible. The patient's airway, breathing, and circulation should all be assessed (Petit, 2005). When a patient is suffering a seizure, fingers or other objects should not be inserted into their mouth because this can induce aspiration or further injury (Shuster, 1994).

12.2 Diagnosis of Epilepsy

Epilepsy diagnosis is still made clinically, with neurophysiological tests confirming the diagnosis. Many structural causes of epilepsies can be identified via brain imaging. Antiepileptic medicines (AEDs) that are presently accessible stop epilepsy without altering the existing susceptibility to cause them in 60–70 percentage points of individuals. Numerous modern drugs are just as effective as ancient therapies, yet they come with substantial advantages such less drug interactions interactions and increased inflammation (Kutlubaev et al., 2018).

Epilepsy is associated to a higher diagnosis and treatment of mental mental illnesses such as depression, stress, and homicidal ideation (Dunn et al., 2018). The proper therapy of persons with epilepsy requires an awareness of the psychological correlates of epilepsy. It's critical to anticipate typical errors in epilepsy diagnosis and treatment. Early diagnosis errors include non-epileptic psychosomatic convulsions, dizziness with muscle twitching, wandering leg dysfunction, and REM behavioural abnormalities, the latter of which is more common in elderly men (Lin et al., 2020).

It is important to prevent overtreatment with too rapid gradation, excessively high doses, or too many AEDs. Vagus nerve stimulation is a palliative treatment with the potential for mood improvement for persons with refractory focal epilepsy, whereas neurosurgical excision is a life-changing cure (Sartori et al., 2019).

12.3 Pharmaceutical Intervention

Antiepileptic drugs are the cornerstone of treatment (AEDs). Even though "antiepileptic" is a far more precise term, "antiseizure" is a better fit as these medications target the symptoms (epilepsy) rather than the core cause (Kaal et al., 2020). The target of AED therapy is to provide the best feasible seizure control while limiting drug toxicity, resulting in the best possible quality of life. Approximately multiple of epilepsy patients benefit from AEDs, with outcome varying based on a range of factors such as epileptic condition, aetiology, and also before the seizure frequency (Perucca & Tomson, 2011).

12.4 Few Common Antiepileptic Drugs (AEDs)

Monotherapy with antiseizure medicine is the first step in treating epilepsy. For effective epilepsy treatment, understanding the efficacy range, pharmaceutical actions, and modalities of administration for specific antiepileptic medicines is critical.

Cenobamate as well as fenfluramine, two new anti-seizure medications, have been approved in the United States Drug Administration (FDA). Anti-seizure medications from the past were effective, but they had concerns with tolerance and pharmacokinetics. Several modern antiseizure medications have shown efficacy and tolerability that are at least equivalent to or better than previous antiseizure medications as first-line therapy for focal epilepsy as compared to older antiseizure medications. Among the medications on the list are topiramate, levetiracetam, zonisamide, oxcarbazepine, lacosamide and lamotrigine. When compared to lamotrigine, pregabalin was found to be ineffective. Lacosamide, pregabalin, and eslicarbazepine have all been successfully converted to monotherapy for focal epilepsy (Abou-Khalil, 2022). Additional therapeutic options include newer antiseizure medicines with a variety of modes of action. Since 2016, antiseizure medications have benefited from an FDA regulation that allows for the extrapolation of a drug's efficacy as supplementary therapy in adults to monotherapy efficacy (Cardoso-Vera et al., 2021). Additionally, efficacy in adults can be extrapolated to children aged 4 and higher. For both extrapolations, data demonstrating that an antiseizure medication's pharmacokinetics are equal between its initial approved use and its extrapolated use is required. Negative pharmacokinetic or pharmacodynamic interactions linked to mechanism of action should be avoided in anti-seizure medication combinations (Asconapé, 2002).

12.5 Common Basic Issues Using Anti-Epileptic Drugs

By using newer AEDs, chronic toxicity associated with previous AEDs, such as osteoporosis, gingival hyperplasia, and alterations in reproductive endocrine function, can be avoided. Hyponatremia appears to be more prevalent with oxcarbazepine than with carbamazepine. Because felbamate has been connected to a high prevalence of aplastic anaemia and liver failure, it should be used only in exceptional circumstances. Acute angle closure glaucoma has been connected to the use of topiramate. This side effect occurs early in the course of therapy and is promptly reversed when the drug is stopped, therefore physician and patient awareness is crucial (Asconapé, 2002). By reducing serum immunoglobulin levels, anticonvulsant drugs can cause secondary immunodeficiency. Patients using these medications should have their serum immunoglobulin levels tested by their doctors on a regular basis (Kalantari et al., 2022).

12.6 Epilepsy that Is Resistant to Medication

After getting additional anti-epileptic drugs, fewer than 20 percentage of individuals who continue to have seizures after two approved AED trials become seizure-free (Brodie et al., 2012). Drug-resistant epilepsy is defined by the failure of two

well-tolerated, carefully chosen, and used AED regimens (as monotherapies or in combination) to achieve persistent seizure-freedom, according to the world organisation named ILAE (Kwan et al., 2010). Drug-resistant epilepsy is associated with increased disability, morbidity, and mortality. When a patient has failed two AEDs, the idea of epilepsy surgery should be considered. For those who are not surgical candidates, alternative anti-epileptic medications may be explored. The advent of a slew of second-generation anti-epileptic drugs, on the other hand, has had minimal impact on overall clinical outcomes, with around a third of patients' seizures remaining uncontrolled (Brodie et al., 2012).

12.7 Surgical Therapy

For drug-resistant epilepsy patients, epileptic resection is the most effective remedy. It entails the removal or resection of epileptic tissue, or, less often, the detachment or removal of epileptic tissue (Ryvlin et al., 2014). To determine surgical candidacy, an array of diagnostics is employed, encompassing skull monitoring systems, structural MRI, wide spectrum of applications single - photon emission, ictal and pre - ictal mono emission magnetic resonance, functional Magnetic resonance imaging, and critical concentration. These studies are attempting to determine the "epileptogenic zone" (the smallest area of cortex that, when resected, disconnected, or destroyed, results in seizure freedom) as well as the risk of post-operative morbidity (Ryvlin et al., 2014). Cranial Electroencephalogram is also necessary in some patients to improve epileptogenic zone localisation, either as intra-operative electrocorticography or chronic extra-operative recordings. When surgical cure is not achievable, palliative epilepsy surgery, such as corpus collostomy, may be performed in selected individuals with the goal of improving quality of life by reducing seizure frequency and severity (Ryvlin et al., 2014).

12.8 Alternative Treatment Options

Vagal nerve stimulation is a non-medicated therapeutic option for those seizure patients who are resistant to drugs. Only 10% of patients become seizure-free, despite the fact that it has been demonstrated to reduce seizures by 40% in half of the patients (Englot et al., 2011). Transcutaneous vagal or trigeminal nerve stimulation are emerging approaches that need to be validated in well-designed trials (DeGiorgio & Krahl, 2013). Some neurotransmission therapeutic approaches that may be used in the epileptic patients who are resistant to AEDs include intracranial stimulation of the anterior dorsal striatum and responsive prefrontal stimulation, which delivers brain impulses when anomalous electrocorticographic movement is detected via a closed-loop system implanted device. Seizures can be minimised with

these treatments, but seizure-free individuals are unusual (Fisher et al., 2010; Morrell, 2011).

12.9 Precision Medicine

Healthcare has long sought to deliver treatments that target the disease's molecular aetiology. The emergence of next-generation sequence analysis has given confidence with a new lease on life, especially in light of successful chemotherapy paradigms. Epilepsy presents a huge opportunity for precision medicine because of several gene discoveries, the availability of experimental in vitro and in vivo models for drug screening, and the possibility of conducting small, cost-effective trials of novel medications (Consortium, E., 2015). Precision medicine is already a reality for some genetic epilepsies. These patients benefit from the low fat diet, which provides an alternative energy substrate for the brain. The discovery of the epileptic seizure's genomic aetiology also allows for the mitigating the impacts of AED side effects. AED medication is the mainstay of epilepsy treatment, with roughly two-thirds of patients experiencing complete seizure control. Despite the availability of second-generation AEDs, the epidemiology of epileptic seizure with drug-resistance, as well as the accompanying risks of impairment, comorbidity, and fatalities, has remained substantially unchanged for decades.

13 Treatment of Epilepsy Induced by Iron

In iron-induced epilepsy, the localized epileptogenic activity spreads across the overall neocortex of both left and right hemispheres (Moriwaki et al., 1990; Moriwaki et al., 1992; Sharma et al., 2007). Various thalamic areas are thought to collaborate in the complexity and worsening of unexpectedly expanded seizures once they begin in the cortical core during this extension of seizure activity (Semple et al., 2020).

Varsha Sharma et al. investigated the antiepileptic impact of ethosuximide in an animal model using epileptic electrographic activity (Sharma et al., 2007). Ethosuximide has been shown to desynchronize the reticulo-thalamocortical circuit's hyper synchronizing electrical activity. This activity of the medicine could be responsible for the medication's anti-absence effect in humans (Pellegrini et al., 1989). Because thalamic and cortical interaction is important in iron-induced cortical focal epilepsy (Sharma & Singh, 1999), It would be interesting to see if ethosuximide can help with iron-induced epileptiform electroencephalographic epileptic seizures. The concept that absence seizures are caused by a subcortical malfunction has recently been proven (Manning et al., 2004; Timofeev & Steriade, 2004), Thus, rather than the diencephalon, it appears that the motor cortex of the cerebrum is a localized seizure origin site for status epilepticus (Sharma et al., 2007).

The effect of ethosuximide on iron-induced convulsions is of special interest since iron-induced epilepsy is regulated by mitochondrial peroxidation, and ethosuximide, as a calcium channel inhibitor, may have an anti-lipid peroxidative effect (Janero & Burghardt, 1989).

Curcumin is a coloring agent and a primary active polyphenolic component isolated from the Curcuma longa (turmeric) plant's rhizome. It's a crystalline orange-yellow powder that's almost insoluble in water (Ladol & Sharma, 2021). It binds redox-active metal ions and passes the blood-brain barrier. Its antioxidative, anticancer, and anti-inflammatory effects are also well-known (Ladol & Sharma, 2021). Curcumin, given at a dose of 500 ppm, can normalize BDNF and its downstream genes, preventing the cognitive deterioration associated with traumatic brain injury (Wu et al., 2003). Curcumin may also prevent neuronal cell death in kainic acid-induced seizures by blocking the apoptotic cell death signaling pathway and indirectly affecting the blood-brain barrier (Shin et al., 2007).

Gastrodia elata Bl. (GE), an oriental medicine used to treat convulsive disorders and lightheadedness contains vanillyl alcohol (VA) (Hsieh et al., 2000). Iron-induced epileptiform discharge in rats may be prevented by pretreatment with antioxidants such as a-tocopherol and dimethyl sulfoxide (Willmore & Rubin, 1981; Rubin & Willmore, 1980; Willmore & Rubin, 1984), According to the findings, antioxidant therapy may help to avoid the emergence of post-traumatic epilepsy (Hsieh et al., 2000).

Uncaria rhynchophylla (Miq) Jack (UR) is an oriental drug for treating adrenergic disorders such as epilepsy for generations (Hsieh et al., 1999). Both the antiepileptic and inhibitory effects of UR on Kainic acid-induced wet dog tremors and oxidative stress are dose-dependent, according to Ching-Liang et al., implying that the therapeutic action of UR may be attributable to its inhibitory effect on oxidative damage (Hsieh et al., 1999).

Antiepileptic drugs (AEDs) can help with bipolar disorder, migraine, movement problems, myotonia, and neuropathic pain, among other things (Rogawski & Löscher, 2004). Antiepileptic medications are chosen for their effectiveness in treating a certain ailment, differential cytotoxicity and Anticonvulsant compatibility, and vital organ dysfunction (Dichter & Brodie, 1996; Sankar, 2004).

On the pharmaceutical market, there are several anti-epileptic pharmaceuticals for the treatment of epileptic seizures and related diseases. Benzodiazepines, Phenobarbital, Vigabatrin, Tiagabine, Valproate, Topiramate, Gabapentin, Phenytoin, Carbamazepine, Oxcarbazepine, Lamotrigine, Zonisamide, Levetiracetam, Ethosuximide, and Felbamate are only a few of them. Uncaria rhynchophylla, in combination with the medications Ethosuximide, Curcumin, and Vanillyl alcohol (VA), performs a critical function in the treatment of seizures caused by iron.

14 Conclusion

This chapter focuses on improving researchers' and clinicians' knowledge on iron and its role in epilepsy in order to aid in the management and treatment of patients with neurological disorders. Iron is a well-known source of harmful oxidizing agents, demanding complex absorption, use, and retention processes in systemic organs and the central nervous system. Over the last few years, the modulation of erythropoiesis in central organs has become increasingly obvious, providing crucial information on iron transport across the BBB and management inside the brain. Whereas the majority of ferric regulating peptides are generated directly in the brain, their physiological homology has aided in the understanding of the purpose in the brain's dynamic environment. The brain, unlike most other systemic organs, has a region- and mitochondrial ferrous concentration. Additionally, each cell type in the brain has its own mechanism for ion transport, storage, utilization, and sensitivity to changes in the intra- and extracellular environment. Progress toward this goal has been impeded by several limitations in our understanding of brain ion homeostasis. To comprehend the aetiology of iron improper metabolism in hereditary and episodic neuronal diseases linked with ferrous disparity, a thorough understanding of these pathways and their disruption by pathogenic processes implicated in diverse brain disorders is required. Each condition's primary cause of ferrous storage or shortage is likely to be different. The succeeding set of circumstances that leads to the production of free radicals and the accompanying self-enriching multiplier effect is likely to be identical across all brain illnesses. Constant attempts at understanding the nature of ferrous imbalance and seeking for therapies that restore brain iron homeostasis are essential to create therapeutic treatments that can help the rising population suffering from neurological and other illnesses associated to ferrous imbalances.

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Chapter 10
Iron and Subarachnoid Hemorrhage

Anika Zainab and Aneeqa Hamid

1 Introduction to Subarachnoid Hemorrhage (SAH)

SAH has been recognized as the most lethal form of stroke. SAH might not be the prevalent of all strokes but it is significantly responsible for all-stroke associated mortality and disability. High mortality and morbidity rates are frequently associated with the incidence of SAH. These devastating consequences result in prolonged or permanent disability. The patient leads a poor quality of life and it affects the socioeconomic structure of the society (Yu et al., 2021; Heinsberg et al., 2020a).

2 Epidemiology

Previous studies exhibit the prevalence of SAH to be 5% among all types of strokes. SAH relatively affects men in young ages while after 55 years of age, it seems to affect women (de Rooij et al., 2007).

The reported incidences of SAH are found to be 9.1 per 100,000 person years in number (Nieuwkamp et al., 2009). The recorded incidence of subarachnoid hemorrhage (SAH) is comparatively less than that of acute ischemic stroke. In fact, SAH is the rare type of all stroke and accounts for only 1–6% of all incidences of stroke. It is linked to high mortality and morbidity rate. It has poor prognosis and the patient leads a poor quality of life (Veremakis, 1991). In 80% of the cases reported, SAH occurs due to rupture of aneurysm. The other reasons behind this occurrence are; vascular irregularities and vasculitis (Lawton & Vates, 2017).

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3 Signs and Symptoms

Patients with SAH frequently report "the worst headache of their life". This is the classic manifestation of subarachnoid hemorrhage (Connolly et al., 2012).

The presentation of patients after the onset of SAH is highly dependent upon the magnitude and the great speed at which the hemorrhage diffuses in various regions of the brain.

The early manifestations are Jacksonian epilepsy and after sometime, hemiparesis takes place due to mechanical pressure exerted on motor cortex. These findings are not present when the pressure is localized in the base of brain. The manifestations are intermittent because the blood travels from one region to another rapidly. The late manifestations are nausea, vomiting, headache, dizziness and disorientation and there is chance of falling into coma. These late presentations occur due to raised intracranial pressure. A rupture of a small cerebral vessel leads to unconsciousness (Campbell, 1932).

The classic manifestations observed due to extravasated blood are neck rigidity, headache in the occipital region, pain that originates from the back and travels towards limbs, moderate fever with chills and Kernig's sign (the patient is unable to extend his knee or there is pain on extension of the knee (Alyssa et al., 2022). This presentation is typically seen in basal meningitis (Campbell, 1932).

4 Introduction to Iron

Iron holds immense importance as a nutrient in the body as it engages in various biological processes that includes redox reactions in the cells, formation of myelin, cell multiplication and DNA synthesis. It remains vital to maintain the levels of iron in equilibrium in the brain. The balance is maintained by the delicate process of homeostasis (Kühn, 2015). Although Iron has essential physiological function i.e., formation of myelin and neurotransmitter, electron transport chain and nervous tissue development but free iron in the body leads to disastrous consequences. Free iron causes oxidative stress, production of free radicals and neuronal injury (Helbok et al., 2021).

5 Overview of the Anatomy of Brain

The brain is protected by three coverings namely dura matter, arachnoid matter and pia matter. Dura matter is the outer fibrous tough covering whereas pia matter is the inner most thin fragile covering of the brain. Arachnoid matter is the middle covering which comprises of filaments of connective tissue. These filaments of connective tissue are known as arachnoid trabeculae and they build a connection between pia

matter and arachnoid matter. They also form subarachnoid space which is filled with cerebrospinal fluid. Cerebral vessels travel through this space.

6 Homeostasis of Iron in the Brain

Iron can be largely found in the brain in its non-heme form. This indicates increased level of metabolic activity in the brain linked to iron. Substantia nigra pars compacta (SN) and basal ganglia contain high concentration of iron. The Blood Brain Barrier is an intricate one cell thick endothelial cell layer which is polarized and it is held by tight junctions. This molecular structure tightly regulates the transport of iron into the brain from rest of the system.

The transport of iron into the brain is controlled by two pathways namely Tf-TfR and DMT1-Fpn pathways. Fpn carries Fe2+ and it is released at the basolateral side of the endothelial cells. Cp expressed on astrocytes foot processes which lines the endothelial layer. Cp oxidizes Fe+2 to Fe+3. The Fe+3 is arrested by Tf which is found in CSF and interstitial fluid of the brain. Citrate, ascorbate and ATP also transport considerable quantity of iron in the brain. An unknown receptor on the apical side of the endothelial cells is also responsible for the transport of iron into the brain as ferritin (Bradbury, 1997; Guo et al., 2016; Moos et al., 2007; Rouault & Cooperman, 2006).

7 Early Brain Injury Post-SAH

Early brain injury (EBI) and cerebrovascular spasm are the fatal consequences of SAH (Liu et al., 2019). Several mechanisms and pathways have been identified that are responsible for these appalling consequences. EBI results in nervous tissue damage, neuronal injury, BBB disruption (blood brain barrier), cerebral edema, cerebral ischemia and hypoxia and significant exposure to oxidative stress. There is complex pathophysiology involved in the development of EBI. There is a dire need to determine accurate pathways associated with EBI so that therapeutic targets can be recognized. As a result, significant detrimental morbidity and mortality linked to SAH can be prevented (Cahill & Zhang, 2009).

8 Cerebral Vasospasm Post-SAH

The most commonly occurring complication of SAH is cerebral vasospasm. This leads to devastating consequences i.e., cerebral hypoxia and ischemia (Bederson et al., 1995). Endothelin(s) are known as the active vasoconstrictors and play a primary role in causing cerebral vasospasm post-SAH (Bickford et al., 2014). Iron

bound heme is responsible for causing vasospasm (Joerk et al., 2014). Nitric oxide a vasodilator opposes the vasoconstrictive effects of endothelin. Iron from the heme attaches to NO, the inhibitory effect NO on endothelin is lost and as a result, vasospasm occurs (Pluta & Oldfield, 2008; Stow et al., 2011) (Garton et al., 2016).

9 Role of Iron after SAH

Scientists believe that the initial brain damage occurs within 72 hours of incidence of SAH. Blood builds up in the subarachnoid space which means Hb levels increase in the brain. The bleeding activates heme–hemopexin scavenging system that removes all the extra Hb accumulated in the brain. The activation of this system is significantly involved in the buildup of intracellular iron and subsequently cause damage to the brain after the event of SAH. The expression of CD91; the receptor of hemopexin increases when iron deposits in the brain tissue (Garton et al., 2016).

Three studies prove relationship between iron toxicity and brain damage after SAH. SAH created in a lab setting in the monkeys showed prominent increase in the levels of heme oxygenase-1 in the microglia and iron induced oxidation in the neuron leads to permanent DNA damage. This results in neuronal death and ultimate brain damage (Ono et al., 2000).

The preliminary data obtained from cerebrospinal fluid samples of 12 patients diagnosed with aneurysmal subarachnoid hemorrhage revealed the presence of free iron and iron mediating proteins (Gomes et al., 2014).

SAH induced rats were studied, significant increase in the expression of heme oxygenase 1 was seen in the acute phase after SAH. The expression of iron regulating proteins such as Transferrin factor and Transferrin factor receptor also increase. These proteins are responsible for transportation and storage of iron within the basal region of the brain. Thus, iron toxicity takes place which means generation of oxidative radicals and permanent cell damage (Lee et al., 2010).

Once inside the cell, the oxidative radicals enter the mitochondria. The integrity of the cell is compromised and cell death pathway gets activated. Caspases, a protease primarily involved in programmed cell death, is released from the mitochondria. The process of programmed cell death is called apoptosis. Consequently, programmed neuronal death takes place. Therefore, it can be said that buildup of iron after the SAH event induces apoptosis and ultimately leads to severe brain damage (Garton et al., 2016).

10 Body's Defense against Unbound Heme

Blood brain barrier provides protection to the brain against various harmful substances. The structure of BBB consists of endothelial cells, pericytes, basement membrane and astrocytes end-foot It plays a prominent role in the stabilization of

the internal environment of the brain tissue by maintaining the hemostasis. It usually does that by controlling the transport of various substances inside and outside the brain. It defends the brain tissue from neurotoxic substance i.e., unbound heme, iron etc. (Chen et al., 2020).

A traumatic event like SAH disrupts this barrier and it results in accumulation of heme in the subarachnoid space. Human body has two protective scavenging systems against extracellular heme and iron toxicity namely; Heme-Hpx complex and haptoglobin-CD163-heme oxygenase-1 pathway. Haptoglobin-CD163-heme oxygenase-1 pathway is the major scavenger system and it is known as the first line of defense mechanism against unbound iron toxicity. Haptoglobin has high affinity for Hb dimers. The expression of CD163 (a phagocytic receptor) increases at cellular level and binds avidly with the hemoglobin-haptoglobin complex. CD163 mediates Haptoglobin-heme complex transport into the macrophage and endosomal degeneration occurs. Haptoglobin is recycled. Heme-hpx pathway is the alternative iron scavenging pathway. When haptoglobin becomes concentrated with hemoglobin after SAH, the rate of recycling does not match with the rate of consumption of haptoglobin. As a result, exhaustion of haptoglobin reserves occur and there is no haptoglobin left to clear the extravascular hemoglobin. During this time, the backup hemoglobin scavenging system gets activated. The hemopexin-hemoglobin pathway is known as the second line of defense against iron toxicity. Hemopexin-hemoglobin complex formation neutralizes the redox toxicity produced by unbound heme. The uptake of this complex is facilitated by plasma member receptor called CD91 via endocytosis. (Chen-Roetling et al., 2018a, b; Garland et al., 2016; Kinner-Bibeau et al., 2018).

11 SAH Markers

11.1 Hepcidin

Patient outcomes after SAH events are poor and variable. There is a need to explore and investigate authentic and reliable biomarkers in patients who show poor response. As a result, supportive treatment for these patients can be improved. Two studies have been done studying relationship between iron related genotypes and poor outcome of the patients (Heinsberg et al., 2020a, b).

Hepcidin is a major player in controlling iron hemostasis in the brain tissue. It maintains optimum levels of iron in the brain tissue. A study investigating the pathophysiology of early brain injury in SAH induced rats revealed that iron accumulation in the subarachnoid space cause increased expression of hepcidin. The increased expression of hepcidin intracellularly gives rise to apoptosis and iron dependent oxidative injury. All of these catastrophic events occur via downregulation of iron handling proteins i.e., ceruloplasmin and ferroportin-1. These proteins are involved in the removal of iron from the brain tissue (Tan et al., 2016).

Previous literature has established that increased expression hepcidin in the brain is responsible for the poor prognosis of patients with aSAH (aneurysmal subarachnoid hemorrhage). Hepcidin antimicrobial peptide gene (HAMP) holds instruction for the production of hepcidin. One study presents a hypothesis that the ability to handle iron buildup depends on genetic variability in HAMP. The genetic variability in HAMP is established by DNA methylation. Therefore, genetic variability of HAMP DNA methylation can determine outcome of patients with aSAH. HAMP DNA methylation can be detected in the CSF. Additionally, HAMP can be used as therapeutic target to improve the prognosis of these patients after aSAH. This indicates that hepcidin can be used as a reliable and stable biomarker to predict the poor outcome of patients following SAH event (Heinsberg et al., 2020b).

11.2 Haptoglobin

Haptoglobin is an iron handling protein that binds to the free iron. This way it prevents the damaging oxidative effects of iron. Increased levels of haptoglobin have been observed in patients who suffered from vasospasm after SAH event. Haptoglobin is responsible for the uptake and clearance of hemoglobin. It is also known as acute phase protein. Acute phase proteins produced by the hepatocytes as a body's response mechanism to systemic disturbance. Therefore, it can be said that haptoglobin modulates the process of inflammation in the body.

11.3 Haptoglobin Genotype

A meta-analysis of six studies reveals that HP1 and HP2; genotypes of haptoglobin have opposite effect on the outcome of SAH. Short-term outcomes and long-term outcomes were investigated. Short-term outcomes include cerebrovascular spasm and delayed cerebral ischemia. Long-term outcomes include functional status assessment through the modified Rankin Scale (mRS) or the Glasgow Outcome Scale. Short-term outcomes are the reason for prolonged hospital stays and prominent disability after SAH. The association between HP2 allele and the high risk of cerebrovascular spasm have been observed. This allele also has associations with cerebral salt wasting and poor functional outcomes. On the other hand, HP1 allele has shown protective effect against early cerebral injury after SAH event. Therefore, the goal of scientists must be to produce therapeutic interventions directed at HP1 allele. To prove the reliability and validity of this hypothesis larger prospective studies (Gaastra et al., 2018; Bulters et al., 2018).

11.4 Total Iron Binding Capacity

The analysis of 366 patients who undertook iron studies has shown that low total iron binding capacity is linked to aSAH. It was also found that serum ferritin levels were high in the short-term post-SAH. One possible explanation for these higher levels is that ferritin is released in the acute phase of inflammatory process. It is necessary to identify biomarkers for ruptured aSAH so that mortality and neurological deficits associated with aSAH can be reduced (Can et al., 2019; Northrop-Clewes, 2008).

12 Other Markers

After SAH, hemoglobin, heme, ferritin and iron levels in the CSF (cerebrovascular fluid) increases. Elevated levels of hemopexin in the CSF have also been observed after SAH. Hemopexin is a glycoprotein and it plays a role in the removal of free heme intracellularly and extracellularly. It transports free heme to the liver where it is broken down into stable products. This indicates that hemopexin provides protection against oxidative and damaging effects of iron (Latunde-Dada, 2016). In a study with 30 patients with SAH and 20 control individuals at tertiary care hospital raised levels of hemopexin have shown worst outcome (Garland et al., 2016).

13 Heme-Oxygenase 1

A link between higher levels of HO-1 (heme oxygenase 1) and higher chance of cerebrovascular spasm was found (Pyne-Geithman et al., 2005). These elevated levels were also associated with reduced functionality in the patient and the study concluded that at Day 7 after SAH event, heme oxygenase-1 levels (HO-1) in the CSF can be used as a biomarker for the indication of poor outcome in the patients with Fischer Grade III aSAH (K. C. Wang et al., 2014). A prospective study conducted on 39 patients with SAH revealed that metabolites of HO-1, ferritin and bilirubin levels were not related to cerebral vasospasm in the hospital setting (Suzuki et al., 2003). These conflicting results warrant further research with larger cohorts in a clinical setting to determine both favorable and unfavorable effects of HO-1 after SAH.

In a study conducted in SAH-induced rats, aerobic capacities and their response to EBI were investigated through MRI, behavioral testing and brain examination. Greater BBB disruption, ventricular damage and brain edema was observed in rats with low aerobic capacities. Upregulation and increased expression of CD163 and HO-1 was seen in the brain tissue of low aerobic capacity rats. This also indicates high neuronal stress in the brain after SAH. Identifying risk factors i.e., aerobic

capacity can help to determine therapeutic targets. These risk factors are significantly associated with increased incidence of EBI and consequently, lead to worse neurological and functional outcome in the patient with SAH (Toyota et al., 2021). This study is relevant to human subjects as in a retrospective cohort of more than 60,000 revealed that cardiorespiratory fitness is linked to reduced occurrences of all forms of stroke (al Rifai et al., 2020). In a prospective population-based study with long-term follow up observed that physical activity reduces the incidence of aSAH in both genders and exercise is particularly beneficial in smokers (Lindbohm et al., 2019). Another prospective general population-based study conducted in Norway failed to show any correlation between physical activity and SAH (Lindbohm et al., 2019).

14 Ferroptosis

Several other cellular death pathways have been identified that may be involved in the EBI. The known cell death processes identified after a hemorrhagic stroke are; autophagy, apoptosis, pyroptosis, necrosis, necroptosis and ferroptosis etc. (Fricker et al., 2018). The most accepted cell death pathway via mitochondrial caspases has been associated with neuronal demise in EBI post SAH. Previously, apoptosis, necrosis and autophagy were detected neuronal death pathways in EBI. In animal study, melatonin was proposed as therapeutic agent that can be used to attenuate autophagy and apoptosis in EBI. Therefore, melatonin can prevent neuronal death during EBI post SAH (Edebali et al., 2014; Shi et al., 2018).

A newly emerging cell death pathway has come into spotlight namely ferroptosis. Ferroptosis is a cellular death pathway which is nonapoptotic in nature. The mechanism is iron and lipid oxidative species dependent (Y. Sun et al., 2020).

Ferroptosis is linked to deposits of iron in the brain tissue and it is also triggered by lipid peroxides. The intriguing results found in the experimental SAH study exhibit that ferroptosis is involved in EBI post SAH. This detrimental process initiates due to several reasons namely; accumulation of iron in the tissues, reduction and deactivation of glutathione and glutathione peroxidase respectively, and lipid oxidative species buildup. Fer-1 is a compound that penetrates into the cell and it minimizes the buildup of lipid peroxides. As a result, it blocks the process of ferroptosis and brain tissue demise. It has been determined that ferroptosis participates in the EBI. Subsequently, avoiding EBI in patients with SAH can improve the prognosis and functional outcome (Li et al., 2021).

Another has also suggested ferroptosis as therapeutic target post-SAH. Fer-1 increases the expression of cysteine-glutamate antiporter SLC7A11 and GPX4 which prevents neuronal damages. Combined data of this study revealed that activation of p53 is also involved in the process of ferroptosis. Deactivation of p53 can inhibit ferroptosis (Kuang et al., 2021).

15 Biomarker for Ferroptosis

ACSL4 has been suggested to be the biomarker of ferroptosis. This marker can be used to detect and investigate this pathway for research and therapeutic purposes in future (Yuan et al., 2016). Another recent study has detected human transferrin receptor 1 protein as ferroptosis biomarker (Feng et al., 2020). No absolute biomarker has been recognized till this date to detect the mechanism of ferroptosis. Transmission electron microscopy is the most accepted method of detection for this pathway (Stockwell et al., 2017).

16 Ferroptosis and GPX4

It has been observed that raised iron level and inhibition of glutathione peroxidase 4 (GPX4) induce and enhance the process of ferroptosis (Dixon et al., 2012). An experimental SAH animal study has demonstrated that decreased expression of GPX4 after 24 hours of SAH leads raised levels of lipid peroxidation and cell injury. Thus, an increased expression of GPX4 can prevent radical formation and subsequently, neuronal injury. GPXP4 has also shown to reduce neurological deficit and brain edema 24 hours post-SAH. GPX4 is an antioxidant enzyme and it blocks lipid peroxidation. Lipid peroxidation occurs in the process of ferroptosis which basically is iron dependent regulated cell death pathway. Ferroptosis has been determined to play a significant role in post-SAH brain cell injury. Prominent GPX4 expression has been identified in the animal brain and neuronal cultures. The expression of GPX undergoes many changes due to activation of several inflammatory factors i.e., tumor necrosis factor-alpha, interleukins-1 beta and radical formation. The clinical use of GPX4 can be proposed to inhibit ferroptosis which can help to avoid initial brain injury post SAH. For this reason, this antioxidant can pave a new way to improve functional outcome and prognosis of SAH (Gao et al., 2020).

17 Ferroptosis and Liproxstatin-1

Liproxastin-1 can also be used for the treatment of SAH. It has the following beneficial mechanisms and effects

- Terminates the process of lipid peroxidation located in the mitochondria
- reduces the formation of reactive oxidative species
- enhances the activity of glutathione
- re-establish the levels of GPX4 (Fan et al., 2021)

In a recent single centered prospective study with human subjects found that CSF lipocalin-2 released in the inflammatory process can be used as prognostic biomarker in SAH patients (Yu et al., 2021).

18 Intracerebral Iron Accumulation

The volume of blood accumulated in the subarachnoid space and intraventricular space. This amount is associated with reduced functional status, prolonged hospital stays and global cerebral ischemia. Additionally, the number of complications also increase and worse outcome is inevitable (Helbok et al., 2021).

An observational study conducted on 32 patients with poor grade SAH found that iron can be measured quantitatively in the extracellular space, iron levels are raised in the white matter, the concentration of iron is associated with intraventricular blood accumulation and raised levels of iron are correlated with secondary brain injury. There is buildup of blood in the white matter during the acute phase of SAH, the patients develop mitochondrial dysfunction in the neurons. The disruption in the normal functioning of mitochondria is the cause of post-SAH cerebral vascular constriction (Helbok et al., 2021).

19 SAH and Acute Seizures

A prospective observation cohort of 554 patients with SAH concludes that lower levels of hemoglobin were associated with acute seizures. The mechanism behind the incidence of seizures after aSAH is still not determined yet. The hypothesized mechanism reveals that post-SAH inflammation and intracranial bleeding disrupts the levels of iron and induces iron deficiency anemia. There is decreased serum iron levels and intracranial hypertension. This causes ischemia and hypoxia of cerebral tissues and eventually, metabolic disturbance and cell injury occur in the neurons which triggers acute seizures (D.-L. Wang et al., 2019). Previous data shows that in acute phase of aSAH, the volume of subarachnoid hemorrhage and cerebral vasospasm might give rise to acute seizures (Hart et al., 1981; Ibrahim et al., 2013). Post-SAH acute seizures are correlated with worse prognosis and neurological deficits. No specific biomarkers have been identified till date to predict acute seizures after aSAH. A follow up study has revealed that the volume of cerebral bleeding has been associated with long-term epilepsy (Huttunen et al., 2015). Therefore, Wang et al. have proposed the use of prophylactic antiepileptic drugs for anemic patients who have suffered from an aSAH event (D.-L. Wang et al., 2019).

20 SAH and Acute Hydrocephalus

9–67% of the patients with SAH have reported the occurrence of hydrocephalus in the acute phase of aSAH (Graff Radford et al., 1989; Paisan et al., 2018; Shishido et al., 2016; Zaidi et al., 2015). The mechanism behind this complication is also linked to iron overload after SAH. Buildup of iron in the arachnoid granulations and leptomeninges. This leads to development of hydrocephalus which occurs due to hindrance in the CSF flow when BBB injury takes place along with deposition of iron from lysed red blood cells (Chen et al., 2017). Zhang et al. in their prospective observational study concluded that low serum iron levels are associated with hydrocephalus after SAH. Low serum iron levels can act as biomarkers to predict the onset of hydrocephalus. Hence, these low iron levels can predict worse functional outcomes in patients with SAH (Zhang et al., 2019).

21 MRI-QSM (Magnetic Resonance Imaging—Quantitative Susceptibility Mapping)

MRI-QSM technology can be used to detect iron deposition located inside the aneurysmal wall. The iron deposition is basically a micro-hemorrhage. The deposition of iron causes the aneurysmal wall to undergo several structural modifications. This gives rise to sentinel headache also called thunderclap headache. The real incidence of sentinel headache varies from 0–40% in SAH patients (Polmear, 2003; Schwedt et al., 2006).

MRI-QSM can be utilized to diagnosis cases with small aneurysms SAH when results of lumber puncture and CT scan are negative. This tool can also be useful to differentiate sentinel headache from all other forms of headache (H. Sun et al., 2018).

22 Nimodipine and Deferoxamine

In an animal study comparing the efficacy of both drugs in the elimination of cerebral vasospasm has found both drugs to be neuroprotective in nature. Nimodipine prevents vasospasm in the acute phase and it fails to improve the prognosis of SAH. On the other hand, deferoxamine (DFX) an iron chelator, penetrates the BBB and decreases iron overload in the brain. Subsequently, it improves cognitive function and prevents neuronal death (Qin et al., 2019).

In another animal study, DFX has shown to target iron deposition and reduced BBB breakdown. In return, this therapeutic effect has ameliorated brain edema, cerebral impairment and cognitive abnormality (Lee et al., 2010; Li et al., 2017).

Fatal lung damage was reported in four patients who were being treated with persistent administration of DFX in a phase 2 trial documented in 1992 (Tenenbein et al., 1992). Another study also suggested increased susceptibility of neuronal tissue to HB with the use of DFX (Peng et al., 2020).

23 Treatment of Neurotoxicity Caused by HB with Vitreous

In an experiment, vitreous consisting of iron deficient transferrin, ferritin, hyaluronan and selenium provided absolute protection to neuronal cell cultures from HB toxicity (Chen-Roetling et al., 2018b).

24 Heat Shock Protein (HSP) and SAH

HSP70, HO-1, HSP20 and HSP27 are responsible for cerebral vasospasm. HSP70, HSP90, HSP20 and HSP27 also play a prominent role in apoptotic cellular death pathway. HSP70 and HO-1 are neuroprotective in nature and save neuronal tissue from HB toxicity. These proteins are also cellular stress markers. HSP90 has shown to cause neurotoxicity and initial EBI (Shao et al., 2019).

25 Conclusion

Keeping in view all the previous and recent findings, it can be said that SAH is a fatal traumatic event. Patients who recover from this event are left with serious disabilities. The therapeutic advances made to treat SAH have been of little clinical value. Therefore, more experiments and larger studies are required to pave innovative ways to treat SAH in its acute phase. In recent times, artificial intelligence has been showing promising revolution in the early detection, investigation and treatment of several cerebrovascular diseases.

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Chapter 11
Iron Deficiency and Psychiatric Disorders

Feten Fekih-Romdhane and Haitham A. Jahrami

1 Introduction

Health and disease have been related to iron since ancient times. Ancient Egyptians, Hindus, Greeks, and Romans used iron as a medicine for multi-system diseases. Modern science show ample evidence that iron is an essential micronutrient for humans and is necessary for several biological processes, including delivery and storage of oxygen for breathing and metabolism (Harahap et al., 2000; Kim & Nemeth, 2015), protein and DNA synthesis (Wu et al., 2020), cell proliferation and energy metabolism (Ganz & Nemeth, 2006). Iron, as trace element, also plays a vital role in multiple brain functions, such as mitochondrial function, electron transfer, myelination of axons, and neurotransmitter synthesis (Beard, 2003; Beard & Han, 2009; Hare et al., 2013; Moos & Morgan, 2004; Stankiewicz et al., 2007). Evidence has thus shown that iron is necessary to neurocognitive and neurobehavioral development (Beard, 2008).

Reduction in iron supplies through iron loss from dietary sources or insufficient iron absorption may cause iron deficiency (ID) (Wu et al., 2020). Iron deficiency (ID) is defined as a reduction in the total iron level of the body. Iron deficiency anemia (IDA) arises when ID is severe enough to impair erythropoiesis. This is the most common kind of chronic anemia. ID can be caused by either excessive loss or,

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less commonly, inadequate absorption (Brunner & Wuillemin, 2010; Wu et al., 2020).

ID is frequent worldwide (Camaschella, 2019). It affects more than 30% of the world's population, and is thus the most prevalent nutritional deficiency on a worldwide basis (De Benoist et al., 2008). According to the Global Burden of Diseases, Injuries, and Risk Factors Study 2016, IDA was among the five leading causes of years lived with disability in 2016 ("Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016," 2017). A lack of sufficient iron intake may result in significant alterations in morphology, neurochemistry and bioenergetics, leading to delay the development of the central nervous system (Beard, 2008) .

As a result, ID might be harmful to human health, leading to a series of dysfunctions such as weakened immune function (Xiao et al., 2016), unexplained fatigue (Verdon et al., 2003), dizziness, fatigue, lethargy, apathy, and difficulty concentrating (Eftekhari et al., 2006). In addition, iron homeostasis is crucial for the integrity of the brain systems (Hyacinthe et al., 2015), and its alteration caused by ID was found to be associated with a range of psychiatric disorders, such as anxiety disorders, depression, and bipolar disorders (Chen et al., 2013).

To date, the relationship between ID and psychiatric disorders has received little attention in the literature despite its promising clinical implications (Bodnar & Wisner, 2005). We aimed through this work to review existing literature on the relationship between ID and psychiatric disorders in adulthood. In our chapter, we report findings on the plausible mechanisms underlying this relationship. We finally discuss the effects of iron supplementation on risk of psychiatric disorders.

2 The Association Between ID and Psychiatric Disorders

2.1 Anxiety Disorders

Only a few prior clinical studies have assessed the relationship between ID and anxiety. First observations reported an increase in anxiety and hesitancy related to ID (Lozoff & Brittenham, 1986; Lozoff et al., 1998). Then, a prospective clinical longitudinal study showed that children displayed increased risk of problematic behavior and anxiety concerns more than years after treatment for severe, chronic iron deficiency in infancy (Lozoff et al., 2000). In a nationwide population-based study performed among children and adolescents in Taiwan, Chen et al. found that IDA was associated with increased risks of anxiety disorder in all genders (Chen et al., 2013). A large 2020 study in Taiwan found that people with IDA had a significantly higher incidence and risk of anxiety disorders (Lee et al., 2020). A Chilean longitudinal follow-up study published in 2018 by Doom et al. found that ID in infancy was associated with increased social problems, anxiety, and PTSD in adolescence (Doom et al., 2018).

Some animal studies also reported similar findings regarding the association between ID and anxiety-like behaviors (Beard et al., 2002; Erikson et al., 2001). For example, in their experimental study, Beard et al. examined the association between ID and behavioral measures of activity and reactivity and found that, compared to controls, male and female weanling rats fed an iron-deficient diet showed more anxiety-like behaviors that are inversely related to dopamine receptor densities (Beard et al., 2002).

Apart from anxiety, other behaviors have been shown to be affected by ID including social disengagement and psychological stress (Shah et al., 2021). East et al. found that early IDA led to more socially disengaged infants and consequently more disengaged parents (East et al., 2019). Animal studies showed that iron concentrations may be significantly decreased by stress exposure (e.g., Teng et al. (2008); Wei et al. (2008)). Human studies suggested that stress levels in mothers are associated with altered iron concentrations in infants even later on, but literature on the effects of stress on iron concentrations remains inconclusive (Lopresti, 2020).

2.2 Depressive Disorders

Several epidemiological dietary studies have explored the association between iron intake and depression and reported controversial findings. For instance, Li et al. (Li et al., 2018) examined the associations of total iron intake from diet and supplements with depression in 14,834 US adults, and found that a higher iron intake may be negatively associated with depression. Similarly, a case-control study by Kim et al. in 849 Korean adolescent girls (Kim et al., 2015) and a cross-sectional study by Miki et al. in a Japanese adult population (Miki et al., 2015) found that a higher dietary consumption of iron was associated with a decreased risk of depression even after controlling for important confounding variables. Two studies in older adults showed a negative association between low serum ferritin level (Stewart & Hirani, 2012) or iron intake (Woo et al., 2006) and depressive symptoms. Previous comparative studies performed in Turkish and Korean patients diagnosed with depression also found that amounts of iron consumed were lower in depression group as compared to the control group (Kaner et al., 2015; Park et al., 2010). Contrary to these findings, Fulkerson et al. found no significant association in 4734 American adolescents (Fulkerson et al., 2004).

On the other hand, prior dietary studies that measured blood ferritin concentrations have also led to controversial conclusions. Three studies performed in Japanese healthy employees (Yi et al., 2011), in adults from the German community (Baune et al., 2010), and in Iranian female medical students (Vahdat Shariatpanaahi et al., 2007) found a significant negative association between serum ferritin and depressive symptoms, whereas two studies in American premenopausal women (Hunt & Penland, 1999) and in an elderly German population (Baune et al., 2006) showed no significant association. Possible explanations of these controversies include the fact that serum ferritin is increased under certain conditions such as inflammation

(Huang & Lee, 2007), and that brain iron uptake was suggested to be constitutive and independent of plasma iron levels (Beard et al., 2005b).

In summary, although most of the epidemiological dietary studies have reported an association between a lower iron intake and a higher risk of depression (Li et al., 2017), this association remains poorly understood due to inconsistencies in the existing findings and to the very limited number of studies available in the area to date. Indeed, the first systematic review and meta-analysis that examined the association between dietary iron intake and risk of depression was published in 2017 by Li et al., included three Asian studies, concluded to limited results due to lack of power, and called for further prospective studies (Li et al., 2017).

2.3 Bipolar Disorders

Prior research found that, compared to nonanemic children, children who had chronic ID in infancy displayed more affective alterations and less frustration tolerance, which are key symptoms in the disease progression of bipolar disorder (Chang et al., 2011; Lozoff et al., 2007). More recently, a clinical epidemiological study by Chen et al. revealed that children and adolescents with IDA were at a higher risk of psychiatric disorders including bipolar disorder, as compared with age and gender-matched control group (Chen et al., 2013). In addition, structural and functional alterations in the prefrontal cortex, that has been related to emotional regulation, have been identified as both etiological factors of bipolar disorder (Phillips, 2006; Stein et al., 2009) and adverse effects of ID (Lozoff, 2011; Schmidt et al., 2010). On the other hand, abnormal levels or insufficient functioning of Ceruloplasmin, an iron oxidase which plays a major role in iron homeostasis (Vassiliev et al., 2005), were found to be associated with iron related pathologies (Dean et al., 2020; Heidari et al., 2016) including bipolar disorder, through oxidative stress. In this line, Tunç et al. found that Ceruloplasmin-ferroxidase activity was significantly increased in bipolar disorder followed by the major depression, schizophrenia and healthy controls (Tunç et al., 2019). However, serum iron levels were not tested in this study. Given the scarcity of data on the effects of ID on bipolar disorder, further studies are warranted to elucidate the possible causality between these two entities.

2.4 Schizophrenia and Related Psychoses

There is limited evidence to suggest that iron metabolism plays a significant role in the psychopathology of patients with schizophrenia (Kim et al., 2018; Yanik et al., 2004). However, research on this topic remains scarce, particularly in the early stages of the disease (Kim et al., 2018). First post mortem examinations of the brain concentration of iron in patients with schizophrenia have led to controversial finding, with either a decreased iron deposits in the basal ganglia (Stevens, 1982), or

no significant difference between patients and controls (Casanova et al., 1990). A case-control study found lower serum iron levels in patients with schizophrenia than in sex- and age-matched healthy controls, suggesting that iron might be involved in the pathogenesis of schizophrenia (Yanik et al., 2004). A study by Weiser et al. found decreased serum iron in acutely psychotic, medication free patients with schizophrenia, suggesting that iron and dopamine interact in the brain, and might be one of the causal factors of the disease (Weiser et al., 1994). Also, low serum iron has been observed in catatonic presentation of schizophrenia and related psychoses (Peralta et al., 1999). Using a quantitative susceptibility mapping, Xu et al. recently found that patients with first-episode schizophrenia had significantly decreased brain iron concentration compared to healthy controls (Xu et al., 2021). Another study by Kim et al. (Kim et al., 2018) compared patients with first-episode schizophrenia spectrum disorder who had iron depletion (defined by a low serum ferritin level) with those who had normal ferritin levels. This comparison showed an independent association between ID and negative symptoms in patients with first-episode psychosis regardless of eating patterns and behaviors related to chronic illness and after controlling for the duration of untreated psychosis, suggesting that iron dysregulation may be a cause of negative symptoms rather than a consequence of illness-related variables (Kim et al., 2018). Keleş Altun et al. recently found that iron levels were within normal ranges in schizophrenia patients, while ferroportin levels were increased likely by antipsychotics (Keleş Altun et al., 2021). Further studies are warranted to elucidate the precise role of iron in the pathogenesis of schizophrenia.

2.5 ID and Women's Mental Health

Women are at risk of ID particularly during childbearing age (Zimmermann & Hurrell, 2007). This deficiency has been reported to be mainly due to menstrual bleeding and other factors such as diet, intensive exercise, and the use of an intrauterine device (Hercberg et al., 2001; Liu et al., 2007; Ottomano & Franchini, 2012; Zimmermann & Hurrell, 2007). Previous randomized trials found that ID causes impairment in cognitive function such as concentration, memory, and learning in women during their reproductive age (Ballin et al., 1992; Bruner et al., 1996). In addition, ID has been found to be associated with higher levels of depression among young women using the oral contraceptive pill (Rangan et al., 1998). In this section, we focused on mental disorders related to ID in women, in particular the premenstrual syndrome and peripartum depression.

2.5.1 Premenstrual Syndrome (PMS)

Prior studies have reported an association between dietary intakes of certain micronutrients, including iron, and the development of PMS (Abraham, 1983; Goei et al., 1982), but the relationship between iron and PMS risk has not been

thoroughly examined. In a prospective case-control study, high total intake of nonheme iron (about 22 mg daily) was associated with a 33% decrease in risk of developing PMS after 10 years of follow-up (Chocano-Bedoya et al., 2013). A study by Fatemi et al. (2019) found that the serum concentration of iron of female students with PMS was lower although not significant compared to healthy controls (Fatemi et al., 2019). Apart from studies suggesting that ID might be a cause of PMS symptoms, other studies found that iron deficiency anemia is an aggravating factor, with severity of PMS symptoms being higher in the anemic subjects than non-anemic subjects and decreasing after dietary and iron supplements for 2 months (Sinha et al., 2013). In the same line, a recent Mendelian randomization study found that iron status may inversely impact the risk of certain premenstrual symptoms including headache, confusion, and nausea (Zeitoun et al., 2021). Contrarily, Shamberger found no difference in the iron levels of patients diagnosed with PMS and controls, whereas hair iron was significantly lower in the PMS group (Shamberger, 2003). In sum, existing research has produced inconclusive results, and additional studies are needed to determine whether iron causal or aggravating factor in PMS.

2.5.2 Iron and Pregnancy

According to the World Health Organization, about 38% of pregnant women are anemic in the word (Organization). Indeed, during pregnancy, women are particularly vulnerable to ID because their needs are substantially higher (increased by 150%) than nonpregnant women, which may be difficult to meet through existing stores or an ordinary diet (Thiamin, 1998).

Anemia during the postpartum period is associated with emotional instability and distress, and increased risk of postpartum depression (PPD) (Milman, 2011). For instance, a South African randomized controlled trial found that IDA was strongly associated with PPD, stress, and cognitive impairment in the postpartum period; and that iron supplementation resulted in a significant improvement in depression and stress symptoms among iron-deficient mothers (Beard et al., 2005a). A longitudinal study by Corwin et al. found that early postpartum anemia was negatively correlated with the risk of developing PPD (Corwin et al., 2003). Another prospective cohort study showed that a lower ferritin concentration, which represents a marker of ID, was strongly associated with PPD in Spanish Women 48 h after delivery (Albacar et al., 2011). A meta-analysis of ten studies published in 2019 by Azami et al. concluded that anemia during and after pregnancy increased the risk of PPD (Azami et al., 2019). In their literature review, Wassef et al. stated that low ferritin during the postpartum period but not during pregnancy contributed to increased risk of PPD (Wassef et al., 2019). On the other hand, a lack of association between iron status and PPD has also been reported in previous studies (e.g., (Armony-Sivan et al., 2012; Paterson et al., 1994)). Overall, the lack of previous research studies on the topic prevents to draw any firm conclusion regarding the role of iron in the etiology of PPD, and calls for further investigation.

3 Explaining Mechanisms of the Relationship Between ID and Psychiatric Disorders

Several hypothesized mechanisms have been suggested to explain the associations between ID and psychiatric disorders (Fig. 11.1). Minerals, including iron, are essential to the oxygenation of brain parenchyma, the regulation of cellular function and neuromodulation, and the synthesis of neurotransmitters such as dopamine, serotonin, and noradrenaline (Beard et al., 1993; Dusek et al., 2012; Momčilović et al., 2010). ID may thus impair the activity of enzymes that synthesize these neurotransmitters that are implicated in mood, neuronal activity, and anxiety modulation (Calabrese et al., 2009; Davison & Kaplan, 2011; Ruhé et al., 2007). Indeed, previous animal studies found that IDA is associated with alterations in serotonin, norepinephrine, and gamma-aminobutyric acid (GABA) neurotransmission (Burhans et al., 2005; Shukla et al., 1989). Other experimental studies showed that induced ID in animals alters dopaminergic and serotoninergic transmission in the brain (Hyacinthe et al., 2015; Nelson et al., 1997). Overall, brain iron homeostasis breakdown seems to largely affect monoaminergic systems, suggesting that psychiatric disorders associated with ID might potentially be attributed at least in part to impaired monoaminergic neurotransmission (Leite et al., 2017). As a result, symptoms in schizophrenia patients may be explained by the iron-dopamine interaction. According to some research, ID may have a role in chronic and tardive akathisia in patients diagnosed with psychosis, which is connected to reduced dopamine activity produced by dopamine antagonist usage. Previous research on the relationship between akathisia and iron deficiency in patients with psychosis produced inconclusive results; akathisia was found to be associated with decreased plasma ferritin and iron levels in patients with chronic psychotic disorders (Hofmann et al., 2000; Kuloglu et al., 2003; O'Loughlin et al., 1991), but no association between iron indices and akathisia was found in other studies of chronic and acute akathisia

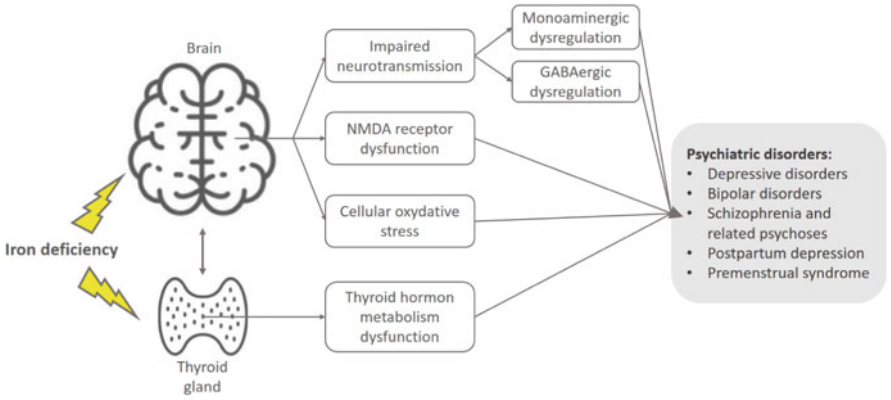

Fig. 11.1 Hypothesized mechanisms of the relationship between iron deficiency and psychiatric disorders

(e.g., (Altamura & Muckenthaler, 2009; Barnes et al., 1992; Sachdev & Loneragan, 1991)). Because of its link with dopamine, ID can also lead to depression (Kim & Wessling-Resnick, 2014). In addition, previous research has linked serotonin deficit to depression recurrence (aan het Rot et al., 2009; Belmaker & Agam, 2008). Similarly, serotonin deficiency has been involved in the etiology of PMS (Kessel, 2000). However, ID may engender a decrease in serotonin levels (Beard et al., 2006), which might partially explain symptoms of PMS in certain cases.

Another suggested biological mechanism is the fact that iron could alter NMDA levels in all brain tissues (Yu et al., 2011). However, NMDA dysfunction has been shown to be involved in a range of psychiatric conditions, including schizophrenia (Carvajal et al., 2016; Kantrowitz & Javitt, 2010) and depression (Ibrahim et al., 2011). Prior research has shown that ID might alter cellular and oxidative processes (Beard, 1995), which might lead to cellular oxidative stress (Khalid & Ahmad, 2012) and several psychiatric disorders, including anxiety disorders, depression, bipolar disorder, and schizophrenia (Salim, 2014). ID could affect thyroid hormone metabolism (Zimmermann & Köhrle, 2002), which in turn has been found to be related to a variety of psychiatric disorders (Radhakrishnan et al., 2013).

A large body of evidence from epidemiological studies has shown that psychiatric disorders have multifactorial causation including a combination of multiple genetic and environmental factors (Uher & Zwicker, 2017). Thus, etiological mechanisms are rather complex, remain largely unknown and poorly understood. ID is likely to contribute on a small part of the causal factors of psychiatric disorders as previously suggested by Lee et al. (Lee et al., 2020). Even though iron would play a minor causal role in mental illness, further elucidating its contribution may hold promise for prevention and treatment.

4 Iron Supplementation and Risk of Psychiatric Disorders

A retrospective population-based cohort study published in 2020 by Lee et al. found that iron supplementation significantly helped to mitigate the risk of psychiatric disorders compared to non-iron supplementation in IDA patients in Taiwan (Lee et al., 2020). Other studies in Japan (Hidese et al., 2018; Miki et al., 2015) and Korea (Kim et al., 2015) found that iron intake is associated with a lower risk of developing depression. Additionally, iron supplementation has been shown to reduce severity of symptoms of depression (Maryam et al., 2020). In sum, dietary iron intake appears to be protective from depression (Li et al., 2017).

It has been suggested that maternal iron supplementation during pregnancy could be beneficial in reducing risk of schizophrenia in offspring (Insel et al., 2008; McGrath et al., 2011). Other evidence supported resolution of first episode psychosis with iron supplementation (Aucoin et al., 2020). Furthermore, it has been demonstrated that iron supplementation could reduce symptoms of PMS (Chocano-Bedoya et al., 2013; Moasheri et al., 2018). Contrarily, several studies have shown that iron supplementation during pregnancy does not seem to have protective role against

PPD (Alharbi & Abdulghani, 2014; Eckerdal et al., 2016; Ezzeddin et al., 2015; Wassef et al., 2019). With regard to the role of iron supplementation on puerperal women, a case-control study found that not receiving iron after delivery was associated with an increased risk of PPD (Ezzeddin et al., 2015).Results of randomized-controlled trials concluded to a significant positive association between iron supplementation after delivery and improvement of depression (Beard et al., 2005a; Holm et al., 2017; Perelló et al., 2014; Sheikh et al., 2017), whereas another trial found negligible effect of iron supplementation on PPD.

To summarize, existing data tend to support the beneficial effect of iron supplementation on the psychiatric diseases cited above. Given that research suggested that ID is connected with decreased emotional behavior via altered dopamine metabolism, these potential biological pathways may explain why iron consumption may lessen the risk of mental diseases (Belmaker & Agam, 2008; Chen et al., 2021; Li et al., 2011). However, prior research suggested that, if the ID occurs in the earliest years of life and/or lasts a prolonged time, its effects may be irreversible with iron supplementation (Shah et al., 2021). Further studies are needed to confirm these findings and to estimate the benefit risk balance of using iron for preventive purposes.

5 Conclusion

Despite a paucity of data, the majority of existing studies suggested a possible underlying association between ID and increased risk of psychiatric disorders. Several mechanisms underlying the relationship between ID and psychiatric disorders have been discussed, but remain little understood and under documented. Our review of the prior body of research also showed promising effects of iron supplementation in the improvement of a range of psychiatric disorders, leading in most of the cases to a substantial reduction of psychiatric symptoms. However, it is worth noting that literature on this topic has major flaws and inconsistencies mainly due to ethnic differences, sample selection criteria, and heterogeneous designs (with most studies having cross-sectional or case-control design). Also, a significant of studies was performed on animals. Further longitudinal and experimental research is necessary to explore the relationship between ID and psychiatric symptoms, and to clarify the mechanisms linking these two entities.

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Chapter 12
Iron and Neurodevelopmental Disorders

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1 Introduction

Human brain development is an extended process that commences with the differentiation of neural progenitor cells during the third week of pregnancy and lasts at least until late adolescence, arguably continuing through entire life. Brain development is influenced by a variety of factors, ranging from molecular events such as gene expression to environmental factors, etc. Normal brain development requires both gene expression and environmental input and disrupting either can have a significant impact on neural outcomes including neurodevelopmental disorders (Stiles & Jernigan, 2010). Complex biological mechanisms including genetics, hormonal interaction with other external and internal risk factors, direct to intricate pathways for neurodevelopmental disorders*(NDDs)* (May et al., 2019). According to the *Diagnostic and Statistical Manual of Mental Disorders (DSM) -5, NDDs are defined as a* cluster of conditions that commence during the developmental period that includes deficits that result in functional impairments (Morris-Rosendahl & Crocq, 2020). NDDs comprise a wide range of disorders such as intellectual disability (ID); Communication Disorders; Autism Spectrum Disorder (ASD); Attention-Deficit- Hyperactivity Disorder (ADHD); Neurodevelopmental Motor Disorders, and Specific Learning Disorders (Morris-Rosendahl & Crocq, 2020). Nutrition is critical during pregnancy and infancy, when the brain is developing and establishing the groundwork for cognitive, social, motor, and emotional skills development throughout childhood and adulthood(Prado & Dewey, 2014).

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Nutritional deficiencies during gestation and infancy potentially affect cognition, behavior, and productivity through the school years and adulthood(Prado & Dewey, 2014). Better nutrition supply can be a cost-effective approach to prevent and manage neurodevelopmental disorders and mental health problems, particularly concerning nutrients like essential fatty acids, iron, and zinc(Bodnar & Wisner, 2005; McNamara & Carlson, 2006; Ramakrishnan et al., 2009). The impact of any nutrient deficiency on the brain development will be a function of the period of the deficiency in regard to given region of the brain requiring that nutrient and the degree and duration of the deficiency (Kretchmer et al., 1996).

Iron is an essential micronutrient during gestation for maternal health as well as the growth and development of the fetus (Cerami, 2017). Dietary intake is being the predominant source of iron for humans and an inadequate supply of dietary iron leads to iron deficiency (ID) and/or anemia due to iron deficiency (IDA). Other causes for iron deficiency are increased demand, impaired absorption, and prolonged blood loss (Cappellini et al., 2020). Globally, about 50% of the population have anemia, IDA is the most common anemia and more prevalent in children of age less than 5 years (41.7%), in women of reproductive age, and during pregnancy the prevalence of 32.8% and 40.1% respectively (Cappellini et al., 2020; Warner & Kamran, 2021). Every cell requires iron for its vital physiological processes like oxidative phosphorylation and energy metabolism. For example, the iron-containing proteins cytochromes and succinate dehydrogenase play vital roles in the Kerb's cycle (Bartnikas, 2012). Iron deficiency is the most common malnutrition in human beings. In general, iron deficiency in newborns and early childhood is considered the key to the abnormal development of the nervous system and mental retardation. ID slows down the rate of development of the nervous system of the child(Mochizuki et al., 1982). The effects of iron on neurodevelopment in premature infants include its effects on the pace of neural processing and general cognition. The documented evidence on the role of iron in neurodevelopmental disorders is scanty.

2 Role of Iron in Nervous System Development

From conception to two years of postnatal life is typically regarded as the most critical time for the development of the nervous system. Any deficits during this growth spurt time might have chronic implications, such as worse academic performance, altered mental health, and economic output throughout one's life (Walker et al., 2007). The developing brain, in the first year of life, undergoes drastic transformation to become a complex organ through various developmental processes such as formation of synapses, neurotransmitter system organization, and commencement of myelination particularly in hippocampal formation, visual and auditory systems(Thompson & Nelson, 2001). The micronutrients iron, folate, and zinc, are crucial for neurodevelopment and proper function of the nervous system (Cusick & Georgieff, 2016). The primitive structures of the brain as well as the major compartments of the central and peripheral nervous systems, are established by the

end of the embryonic stage and continue to postnatal life. Iron is a vital nutrient that contributes to bran development both during intrauterine life as well as after birth and iron is associated with several cellular and molecular processes in developing brain which includes energy status of neuron, myelin formation and homeostasis of neurotransmitter (Bianco et al., 2008; Wang et al., 2019). During the development of the nervous system, several important processes such as myelination, synapses formation, formation of dendrites, synthesis of neurotransmitters and neurotransmission are dependent highly on iron-rich enzymes and hemoproteins (Jenner, 1989; Yu & Chang, 2019). Experimental studies, both *in vivo* and *in vitro*, showed iron is a key player for several biological processes in the brain development and growth such as synthesis of DNA, transport of oxygen, oxidation & reduction reactions and mitochondrial functions (Mao et al., 2010; Thirupathi & Chang, 2019). Iron is a component of cytochrome C oxidase an enzyme in oxidative phosphorylation of intracellular metabolism (Little et al., 2018). Thus lack of nutrients, especially iron, potentially jeopardize intensive metabolic processes of brain development resulting in neurodevelopmental disorders characterized by impaired cognition and behavior with/without motor skills. Not only deficient level of iron, during intrauterine life, induces irreversible impacts in the fetal brain (Crowe & Morgan, 1992; Felt & Lozoff, 1996) but also iron overload in brain regions associated with neurodegeneration (Hayflick, 2006; Hyman M. Schipper, 2012). Iron overload is neurotoxic since the ability of excess iron triggers oxidative stress(Salvador et al., 2010; H. M. Schipper, 2004). Most of the already known facts about the role of iron in the development and function of the brain have been gathered by studying timed models of induced dietary iron deficiency in animal models during rapid and critical brain development duration (Georgieff, 2008). The growing embryo requires iron from the earliest stages of pregnancy, which is demonstrated by the presence of specific receptors and complexes for iron transfer across the visceral yolk sac earlier to the fetal blood system development (Donovan et al., 2005; Young et al., 1997). In mouse experimental studies, it was observed that the closing of the neural tube, a vital event in the nervous system development, begins around embryonic day 8.5 (E8.5) and is completed by E10.5 with the closing of the posterior neuropore. Nutritional support including iron intake is provided by the visceral endoderm and yolk sack until the establishment of the placenta occurs between E9.5 and E10.5 (Bielinska et al., 1999; Mao et al., 2010). Long-term ID during development, in the absence of anemia, causes alteration in the adult mouse hippocampal transcriptome. Reversing iron status during the critical growth period of hippocampal development partially normalized alterations due to ID, suggesting a need for additional studies to recognize the most efficient developmental period for iron therapy and adjunctive treatments that can completely ID-induced alterations (Islam et al., 2018). Iron has a widespread influence on the growth and development of a fetus since iron is a cofactor in hemoproteins and iron-containing enzymes which are essential for fetal energy metabolism, the proliferation of cells, and organogenesis (Anne M. Molloy et al., 2014). The iron uptake in the brain occurs via transferrin receptors on the brain microvascular endothelial cells and the rate of uptake is highly selective and depends on blood-brain barrier permeability (Connor & Benkovic, 1992; McCabe & Zhao,

2021). Iron deficiency during the pregnancy extending till the weaning period (postnatal day 21) causes a massive reduction of up to 40% in iron content in the adult brain and depleted iron stores in the liver (Dallman et al., 1975). In the 1970s Dallman et al. in their landmark studies were first to show that the iron deprivation in the early postnatal period have significantly decreased the iron content of the whole-brain in comparison with 28th postnatal days controls and was resistant to restoring their normal brain iron level (still 20% lower), even with vigorous repletion of iron over 45 days (Dallman et al., 1975; Dallman & Spirito, 1977). In a normal gestation, the body accumulates 80% or more of its iron during the final trimester whereas total iron in body and hemoglobin level, as well as circulating and storage iron levels, are much reduced in preterm infants. The developing brain in neonate is in a highly metabolic state, consume roughly 60% of the total oxygen consumption of the body, while the adult brain consumes about only 20% of the consumption of total body oxygen (Erecińska & Silver, 1989). Documented studies in rodents showed that high rate of metabolism is dependent on iron. In young rats, following feeding with purified diet of various iron levels, showing impact on hemoglobin, cytochrome C and muscle myoglobin (Dallman, 1986). During neuronal and glial cell differentiation, a large amount of metabolic energy is required for migration processes, formation of myelin sheath, synapses formation and prolongation of neuritic process particularly in rapidly developing brain regions (Li et al., 2011; Simons & Trajkovic, 2006; Xiaoli Zhang et al., 2017). Iron is mainly present in oligodendrocytes and microglia and is essential for several metabolic activities including maturation of oligodendrocyte, and activation of microglial (Bishop et al., 2011; X. Zhang et al., 2006). Compared to other cells of brain, oligodendrocytes shows increase in specific iron-requiring enzymes which are required to maintain high metabolic activity, these enzymes includes glucose-6-phosphate dehydrogenase, cytochrome oxidase system, dioxygenase, NADH dehydrogenase, and succinic dehydrogenase(Todorich et al., 2009). The total body iron content at birth in premature infants is reduced less than half of the total iron of term infant (Siddappa et al., 2007; Widdowson & Spray, 1951). Significant variation in the brain iron content between different regions positively correlated with age. The degree of iron content with age differences varied between different regions, with greater effects observed in the basal ganglia in comparison to the hippocampal formation. Advanced age and higher content of composite iron were closely associated with rapid processing velocity and increased general intelligence (Hect et al., 2018). The iron (non-heme part) and its regulatory mechanisms are essential for supportive role in cognitive development during early life(Carpenter et al., 2016; Darki et al., 2016). The higher content of brain iron facilitates better cognitive ability (Carpenter et al., 2016) conversely evidence from studies of cognitive aging showed higher brain iron content is inversely associated with cognitive ability (Daugherty & Raz, 2015; Penke et al., 2012). A better understanding of the role of iron in supporting several neurological processes is vital for constructing a comprehensive model of neuropsychological health throughout the lifespan, with an importance on sensitive critical periods of development.

3 Iron and Neurodevelopmental Disorders

3.1 Iron and Neural Tube Defects

Throughout pregnancy, in the maternal compartment several essential trace elements like cobalt, iron, zinc, manganese, molybednum and selenium play crucial role in maternal and fetal wellbeing (Lewicka et al., 2017; Rautiainen et al., 2016; Yin et al., 2020). Iron deficiency potentially, especially in females, occurs during early life while the brain is developing actively; intrauterine life, childhood, and early adolescent age (Georgieff, 2008). Maternal nutritional deficiencies during gestation and in neonatal life are the major risk factor for various neurodevelopmental disorders. Evidence suggests that fetal/neonatal iron status may be compromised as a complication of maternal ID (Madhikarmi & Murthy, 2014; Rao & Georgieff, 2007). Neural tube defects (NTDs) are one of the most common congenital disorders that occurs due to failure of fusion of neural tube between 21 to 28 days after fertilization. NTDs are a group of several congenital diseases include spina bifida, anencephaly, craniorachischisis, and encephalocele (Botto et al., 1999; Wallingford et al., 2013). Spina bifida and anencephaly, which are the commonest types of NTD, occur in (approximately) 3 lacs newborns across the globe (Botto et al., 1999). The causes for NTDs are uncertain, but both genetic and environmental causes are implicated in the etiopathogenesis of NTDs (A. M. Molloy et al., 2009). Iron is one of the key elements in mediating the closure of the neural tube (Stokes et al., 2017). An epidemiological study by Groenen et al., 2004, showed that low iron diet intake is markedly associated with a higher risk of spina bifida (Groenen et al., 2004). A large number of documented evidence suggests the significance of iron and folate supplementation in preventing NTDs, but the studies investigated the direct effects of iron in preventing NTDs are scanty, as well as with mixed results (Felkner et al., 2005; Groenen et al., 2004; Anne M. Molloy et al., 2014; Weekes et al., 1992). Using a mouse model [*flat iron (ffe)* induced by N-ethyl-N-nitroso-urea (ENU)], Donovan et al. showed NTDs results due to mutation in the ferroportin (*Fpn1)* iron exporter which is essentially expressed to deliver nutrients in several tissues of developing embryo (Donovan et al., 2005) and mutation in *Fpn1* leads to forebrain truncations in addition to NTDs due to iron deficiency or visceral endoderm iron overload (Mao et al., 2010). Case controls studies have suggested that a low iron profile during gestation may be a risk factor for developing NTD affected pregnancy (Felkner et al., 2005; Groenen et al., 2004) but other studies did not find an association (Weekes et al., 1992).

3.2 Iron and Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a complex disorder with characteristic features such as impairment in social communication, object obsessions, and restricted,

repetitive behaviors (Lord et al., 2018). Worldwide about 1 in 160 children has ASD (WHO, 2021) and one-third of them displays intellectual disability. Among other neurodevelopmental disorders, ASD is also most likely caused due to various etiology like malnutritional during gestation, prenatal infection, prenatal stress, environmental factors-dispersal of toxic chemicals and metals (Grandjean & Landrigan, 2014; Vohr et al., 2017). There has been expanding interest in the role of micronutrients especially metals in ASD etiology. Developmental delay likely in ASD occurs as a result of iron deficiency (McCann & Ames, 2007). A study by Bener et al. demonstrated iron deficiency has been linked with ASD in children when compared with controls (Bener et al., 2017). A meta-analysis by Saghazadeh et al. showed low iron levels in ASD children (Saghazadeh et al., 2017). Whereas no significant alteration in iron levels in ASD children as shown in a meta-analysis by Tseng et al., (Tseng et al., 2018a, b). Using magnetic resonance imaging (MRI) of the brain, Tang et al., extensively studied iron content in the frontal white and gray matter, frontal gray matter, thalamic region, red nucleus and substantia nigra of midbrain, dentate nucleus, globus pallidus, and putamen of basal nuclei, caudate nucleus, pons, and corpus callosum (splenium) of the brain of autism children. The results of Tang et al. study showed a decreased iron content in all regions of the brain of autistic children, however, the study participant is limited to the age groups of 2–6 years. The reduction of brain iron content increases as age advances that may further impairs widespread functions such as cognition, movement emotions, etc., (Tang et al., 2021). A higher risk of iron deficiency (ID) and/or ID anemia contribute further to low brain iron content with deficits in learning and behavior (Latif et al., 2002). Further iron deficiency can profoundly impact the myelin sheath composition, particularly lipid and protein. Reduced myelination will lead to a decrease in the neuronal conduction velocity of action potential and delay of response, leading to abnormal brain development, which further causes cognitive, behavioral, and sensory disorders (Lewis et al., 2014). The causes for reduced brain iron content in autism spectrum disorder remains unclear, it requires to be verified by prospective research.

3.3 Iron and Attention-Deficit/Hyperactivity Disorder (ADHD)

The brain growth is a continuous process during infancy, childhood and early adolescent, diet might have a significant influence on cognitive and behavior abilities (Bryan et al., 2004; Huo et al., 2012; Prado & Dewey, 2014). Iron being one of the most crucial micronutrients, and satisfying its demanding requirement is likely to have a beneficial influence on cognitive development in children (Sachdev et al., 2005). Disturbance in the iron homeostasis might negatively affect psychological functions due to alteration in the iron-containing enzymes activities in the brain (Benton, 2008; Scott et al., 2018). The neurodevelopmental consequences of iron in

preterm infants includes its effects on the neural processing speed and on cognition in general (Wang et al., 2019).

ADHD is a widespread and devastating disorder in children and adolescents with symptoms of persistent and developmentally-inappropriate levels of overactivity, inattention, and impulsivity (American Psychiatric Association, 2013). Largely due to impulsive behavior and slow information processing rates, the children and adolescents suffering from ADHD show poor performance in standardized tests, scores lower grades and possibly leading to school dropout (Childress & Berry, 2012). Despite ADHA being the most studied neurodevelopmental condition but the exact etiology is still unclear, however earlier several observational hypotheses suggest decreased volume or functionality of brain cortex/gray and white matter causing impairments in cognitive processing, attention, planning of motor activities, the velocity of processing responses (Cortese, 2012). The preliminary observations suggest that iron deficiency may underlie the pathophysiology of ADHD patients (Cortese, 2012; Konofal et al., 2008). There are several documented evidence that supports the iron deficiency hypotheses in ADHD pathophysiology, as a co-factor iron is essential for enzymes required for the monoaminergic neurotransmitters production and their catabolism which are involved in the pathophysiology of ADHD (Biederman & Faraone, 2005; Youdim et al., 1989). The genetic susceptibility for ADHD has been associated with dopamine transporter gene variation and the reduced expression of dopamine transporter is linked with iron deficiency (Beard et al., 1993; Franke et al., 2012; Mick & Faraone, 2008). Iron deficiency is believed to have a major role in ADHD pathophysiology by altering the functions of basal ganglia, also children with iron deficiency exhibit cognitive and behavioral deficits that principally include poor attention and hyperactivity (Kieling et al., 2008; Betsy Lozoff et al., 2006). Studies determining the precise role of iron and zinc on the progress ofADHD have shown the lack of both minerals in most cases results in hyperactivity (Del-Ponte et al., 2019). Levels of serum iron ferritin is considered as a reliable indicator of body iron deposits—are predominantly utilized to determine iron deficiency(Robberecht et al., 2020). Majority of the reported studies showed low levels of serum ferritin in ADHD patients(Cortese & Angriman, 2014; Mahmoud et al., 2011; Villagomez & Ramtekkar, 2014; Wang et al., 2017; Yazici et al., 2019).

Following iron supplementation, in ADHD children higher levels of serum ferritin and reduced scores of ADHA symptoms indicate ADHD children without anemia may be benefitted from iron supplementation(Sever et al., 1997). Some studies reported low serum ferritin in ADHD children in comparison with healthy controls (Adisetiyo et al., 2014; Cortese et al., 2012a, b; Juneja et al., 2010; Wang et al., 2017). An inversion relation was observed between serum ferritin level and severity of ADHD symptoms, in a study by Juneja et al. (Juneja et al., 2010). A comparison of brain iron in ADHD children with healthy individuals using magnetic resonance imaging showed significantly reduced iron in the bilateral thalami of ADHD children (Cortese et al., 2012a, b). A similar observation was reported by Adisetiyo et al., a significant reduction in estimated brain iron in the striatum and thalamus of ADHD individuals compared with healthy candidates(Adisetiyo et al.,

2014). However, several other studies failed to find an association between serum ferritin and ADHD (Cortese et al., 2012a, b; Juneja et al., 2010). Certainly, serum ferritin is a marker of peripheral iron status but not the central iron content. The degree to which serum ferritin is associated with brain iron levels remains uncertain. (Argyropoulou et al., 2000; Christoforidis et al., 2007). In a study by Cortese et al., there was a tendency, however, that did not show statistical significance, for correlating the serum ferritin levels with brain iron content in various brain regions assessed (Cortese et al., 2012a, b). Low level of iron in thalamus may play a vital role the ADHD pathophysiology (Robberecht et al., 2020). A significant low level of iron in thalamus in ADHD group in comparison to healthy group (Cortese et al., 2012b). A study by using multimodal magnetic resonance imaging, by Adisetiyo et. Al., showed medication-naïve ADHD children and adolescents have low striatal and thalamic iron level in comparison to other groups(Adisetiyo et al., 2019; Adisetiyo et al., 2014).

Iron homeostasis is critical for development of healthy brain and alteration in catecholamine and myelination occurs as reduced brain iron levels and has been highly associated with delay in the developmental milestones and cognitive impairments that are consistent with ADHD (Beard & Connor, 2003; Earley et al., 2014; B. Lozoff, 2011; McCann & Ames, 2007; Sidrak et al., 2014; Unger et al., 2007).

In documented reports of principally psychostimulant-medicated persons with ADHD showed hemochromatosis (HFE) gene variations (gene encoding the iron uptake regulating HFE protein) and low levels of serum ferritin (Nigg et al., 2016; Tseng et al., 2018a, b; Wang et al., 2017). Furthermore, the iron status in infancy has been associated with the sensitivity to psychostimulants medication in ADHD children, a drastic reduction in the iron content is highly linked to increased medication dosage during the first year of treatment (Turner et al., 2012). Whereas the levels of peripheral iron were inconsistent in ADHD patients (Donfrancesco et al., 2013; Tseng et al., 2018a, b). Estimating brain iron levels is critical to link a putative role of iron deficiency in ADHD pathophysiology. A reduced peripheral iron level may hugely affect the brain iron content (Cortese et al., 2012a). Given the mixed findings in documented studies, further extensive research in a larger population including a control group is warranted.

4 Conclusion

This chapter is an attempt to evaluate the state of evidence for the role of iron in neurodevelopment and its disorders. It is accepted that maternal nutritional status in gestation can profoundly influence offspring's brain development, which in turn produce long-term psychomotor, behavioral, and cognitive impairments. The evidence of a relationship between nutrition during pregnancy and neurodevelopment seems to be more reliable for iron, and other micronutrients (Leung et al., 2011). Given the recognized roles of iron in neurodevelopment processes, it is probably that ID or IDA impacts neuro- and cognitive development, predominantly if it occurs

during intrauterine life or early infancy. Maternal iron supplementation has generally been studied during pregnancy, in women with postpartum bleeding, and during lactation to improve the iron status, which may also improve iron status in the brain. At this stage, although not conclusive, the evidence suggests a need for further robust research to examine the potential beneficial role of iron and its mechanisms in the development of the nervous system as well as in neurodevelopment disorders. More evidence addressing the role of iron in the nervous system development and its disorder in real-time and the successful development of blood biomarkers of nervous system disturbance in iron deficiency and iron overload would be stronger.

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Chapter 13
Iron and Neuropathies

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1 Introduction

Neuropathies are a group of diseases that occur due to damage or abnormal functioning of one or more nerves that carry the message to or away from the brain. It is usually characterized by muscle weakness, tingling, numbness, uneasy feeling, and pain in the affected area. There are different factors that can cause neuropathies, however, nutritional deficiency or micro-nutrient accumulation is considered an important factor that may lead to neuropathic pain. Iron is an essential micro-nutrient which not only acts as an oxygen carrier but is also involved in crucial biological functions including replication, DNA repair, respiratory activity, axon

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myelination, and biosynthesis of neurotransmitters (Thompson et al., 2001; Levi & Taveggia, 2014).

2 Iron and Nerve Conduction

The process of nerve conduction involves the propagation of nerve impulse to the site of stimulus along the length of axon. The difference in the ionic concentration on both side of the membrane is responsible for the resting membrane potential (−70 mV). The induction of stimulus causes the depolarization, repolarization, and then hyperpolarization of membrane due to the change in membrane potential. The change in the membrane potential is due to the opening and closing of ion channels. The local membrane depolarization induces the change in the membrane potential of adjacent area and this way the nerve impulse propagates along the entire length of axon reaching the target muscles. The propagation of nerve impulse is stimulated by an insulating sheath present around the axon called myelin sheath which is surrounded by the Schwann cells. This assembly helps in the faster communication between central and peripheral nervous system through motor neurons (Fig. 13.1).

Iron is involved in the proper functioning of the brain, nerve conduction, protein synthesis, myelination, and neurotransmitter synthesis. Hence, its balanced metabolism is crucial for motor and cognitive functions. Since myelination is responsible for the conduction of nerve fibers thus iron is potentially involved in this process (Sharma et al., 2021). The neurotransmitters including norepinephrine, serotonin, dopamine, and epinephrine are synthesized by enzymes that contain iron such as tryptophan hydroxylase, tyrosine hydroxylase, and phenylalanine hydroxylase (Hare et al., 2013). Thus, iron affects neurotransmitter-mediated activities such as movement, attention, reward, emotion, and memory (Ferreira et al., 2019). Besides the role of iron in the synthesis of neurotransmitters, the process of neuronal signaling is also influenced by iron levels. Disturbance in dopaminergic signaling by altering the expression of D2 receptor and reduced uptake of neurotransmitters in catecholaminergic neurons have been reported in rat-model deficient with iron in the brain (Youdim et al., 1989; Beard et al., 2006; Bianco et al., 2008). Iron also functions as a cofactor for mitochondrial enzymes that are involved in the reactions of the electron transport chain, thus it performs a fundamental role in the energy production of the nervous system. Iron deficient condition may lead to mitochondrial DNA damage, and a change in mitochondrial function and morphology (Walter et al., 2002). This condition has, therefore, been reported to induce oxidative stress which is due to dysfunctioning of electron transport chain (Wan et al., 2012; Riaz & Guerinot, 2021). Iron is also required for the proper function of axons and their regeneration. In long axons such as sciatic nerves, iron is acquired by Schwann cells. Mietto and co-workers have shown that Schwann cells are a source of iron in the peripheral nervous system (PNS) due to their close proximity to axons. It has been described that ferroportin and ferroxidase ceruloplasmin work in combination to make the iron available for axonal mitochondria. In ceruloplasmin knockout mice

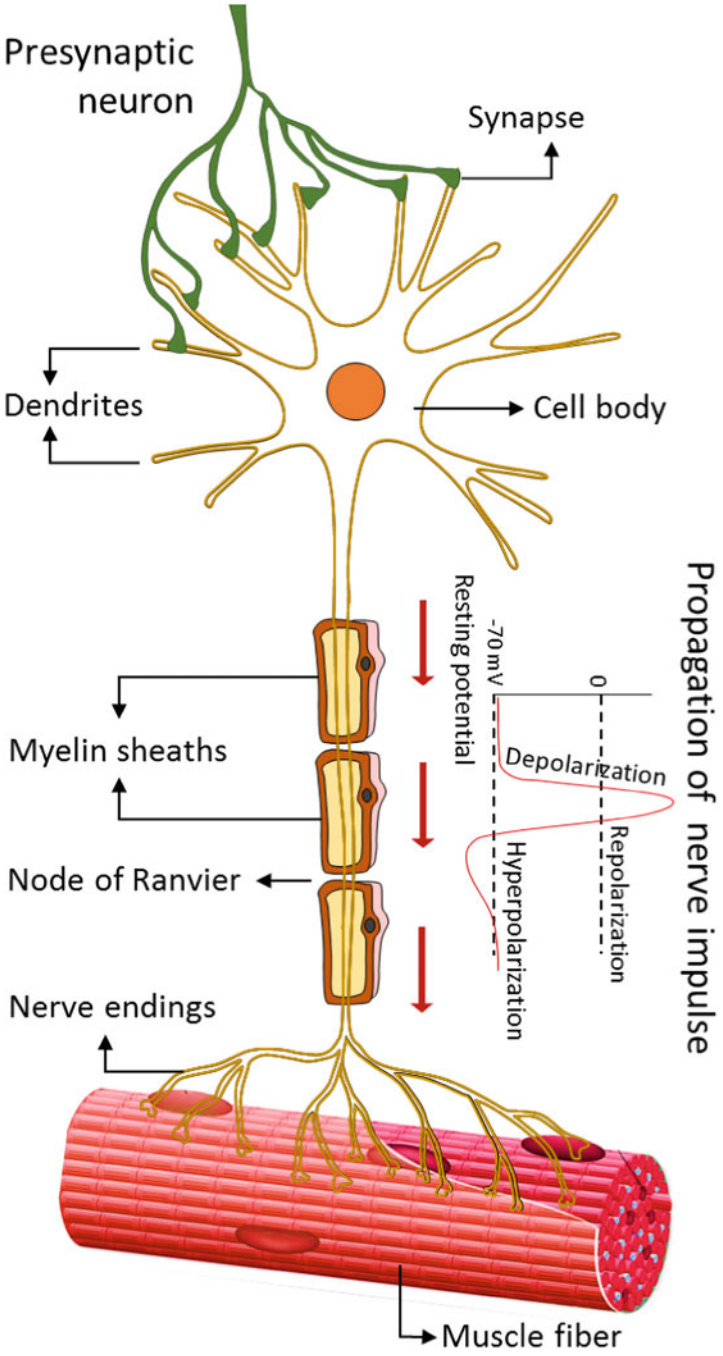

Fig. 13.1 Schematic diagram showing the nerve conduction process in a motor neuron

(Cp KO), iron starts to accumulate in Schwann cells because ferroportin work in combination with ceruloplasmin to transport iron in axons, which is an indication that Schwann cells help to acquire axonal iron (Mietto et al., 2021). Iron is necessary for axonal regeneration but impairment in axonal regeneration due to reduced iron transport from Schwann cells in Cp KO mice was observed (Mietto et al., 2021). It was described that there is a reduction in mitochondrial energy production and motility in Cp KO mice (Rensvold et al., 2016; Bastian et al., 2019). It is reported that there is reduced mitochondria and impaired regeneration in sciatic nerves of Cp KO mice due to minimal availability of iron from Schwann cells (Mietto et al., 2021). The potential role of iron in myelination is also well reported. An adequate level of iron is required for the differentiation and proliferation of oligodendrocytes (Morath & Mayer-Pröschel, 2001; Morath & Mayer-Pröschel, 2002). Iron deficient rat model showed reduced myelination due to altered composition of proteolipid protein, basic protein, cholesterol, phospholipids, and galactolipids in myelin (Ortiz et al. 2004). Axonal myelin sheaths are essential for nerve transmission, thus reduced myelination is considered as the main cause of slowing of nerve conduction (Hare et al., 2013).

It has been observed in iron deficiency anemia (IDA) patients that there is reduced sensory and motor nerve conduction velocity as compared to controls. Sharma et al. (2021) reported peripheral neuropathy observed in the patients of IDA, moreover, treatment by iron therapy improved nerve conduction in these patients. IDA patients underwent electrophysiological analysis for the conduction velocities of motor and sensory nerves. It was observed that conduction of motor and sensory nerves, bilateral median, and radial nerve was reduced in these patients while oral iron treatment for three months led to the restoration of normal nerve conduction velocities (Degirmenci & Kececi, 2011). Nerve conduction velocity was also studied in IDA children and reduced median and posterior tibial nerve conduction velocities in these children were observed as compared to normal healthy subjects. Iron supplementation normalized nerve conduction velocity in children with IDA. It was suggested that peripheral neuropathy could be developed in patients with IDA but it can be reversed by iron treatment (Kabakus et al., 2002). Since iron is involved in the maintenance of normal functioning of the nervous system, therefore, it has been demonstrated in the pathophysiology of neuropathic pain. The accumulation as well as deficiency of iron can lead to neuropathies. In the following sections, the possible role of iron in different neuropathic conditions has been discussed.

3 Iron and Neuropathies

3.1 Optic Neuropathy

Iron is a vital element for cellular metabolism but excess iron has devastating effects on the body. The dietary iron is absorbed through small intestine and it is lost through sweat, intestinal cells, and menstruation. During iron overload, the excess

iron does not excrete out properly and it starts to accumulate in the tissues as age progresses (Kernan & Carcillo, 2017). Excess iron is toxic to the body as it produces reactive oxygen species (ROS) via the Fenton reaction. ROS interact with amino acids, lipids, and DNA and contribute to the pathophysiology of various disorders including optic neuropathy (Wong et al., 2007). Optic neuropathies are the diseases of the optic nerve that are considered as an important cause of morbidity and vision impairment affecting millions of people (Loh et al., 2009). Several evidences describe the potential role of iron in optic neuropathies (Goralska et al., 2005; Dunaief, 2006; Abu-Amero & Bosley, 2006). Iron lines developed in the cornea of the eyes lead to optic diseases. These iron lines develop in normal aging and in keratoconus (Kernan & Carcillo, 2017). Iron lines can be observed as faint yellow or dark brown color in the cornea (Kirkwood & Rees, 2011). Cataract is another optic disease in which lenses of the eye become opaque and iron is also involved in its pathophysiology via producing ROS. It has been described that L-chain ferritin aggregates have been involved in the pathophysiology of human cataracts (Goralska et al., 2005). Excessive iron is involved in the destruction of retinal epithelial pigment via producing ROS and it is also involved in age-related muscular damage (Dunaief, 2006). Many evidences describe the link between oxidative stress and optic neuropathies. Among these optic neuropathies, there are four major types including optic neuritis, traumatic neuropathy, ischemic neuropathy, and glaucoma (Qi et al., 2007; Abu-Amero & Bosley, 2006; Levin & Geszvain, 1998; Swanson et al., 2005; Farkas et al., 2004). In some optic neuropathies, deranged levels of iron-related protein have been observed (Kernan & Carcillo, 2017). High levels of transferrin, ceruloplasmin, and ferritin in human glaucomatous eyes as well as in experimental model of glaucoma have been reported (Tripathi et al., 1992; Farkas et al., 2004). These proteins play a significant role in the maintenance of iron levels in circulation and tissues and ultimately balance iron homeostasis. This regulation is important to deliver an adequate amount of iron for cellular activities and prevent from iron toxicities (Loh et al., 2009). Moreover, high levels of ferritin along with greater iron saturation were also observed in a 38 year old female patient presented with isolated optic neuropathy (Pique et al., 2021). In another study, increased levels of serum ferritin were noted in patients suffering from non-arteritic ischemic optic neuropathy that is the most occurring type of optic neuropathies in adults (Guclu & Doganlar, 2018). Although iron levels are not directly associated with optic neuropathy, however, it can be linked to optic neuropathy via dysregulation of iron-linked proteins and oxidative stress (Kernan & Carcillo, 2017).

Besides iron accumulation, deficiency of iron may also lead to optic neuropathy. Kacer and his co-workers reported two cases of optic neuropathy in patients suffering from IDA (Kacer et al., 2001). They highlighted the fact that in the absence of any other risk factors in these patients, IDA may contribute to the complication of optic neuropathy. It was documented that there is an increased ratio of oxidants/antioxidants in IDA (Aslan et al., 2011) that causes degeneration of ganglionic cells of the retina (Kortuem et al., 2000). It is believed that during severe anemia the hypoxic condition is responsible for reduced working capacity of venous endothelial

cells that may lead to erythrocyte deformability resulting in the occurrence of retinal abnormalities (Kirkham et al., 1971; Chan & Vanhoutte, 2013).

3.2 *Neurodegeneration with Brain Iron Accumulation (NBIA)*

NBIA is a class of neurodegenerative diseases related to iron accumulation in the brain particularly in basal ganglia which leads to movement disorders and reduced intellectual disabilities (Levi & Taveggia, 2014). A few types of NBIA (neuroferritinopathy and infantile neuroaxonal dystrophy) are caused by the alteration in iron homeostasis-related genes or mostly it is caused by the changes in the genes which are unrelated to iron metabolism. Some of these genes showed phenotypic changes in the PNS. Having an insight into the mechanism of alteration in these genes may lead to better treatment of the disease (Levi & Taveggia, 2014).

Iron has been considered as a bystander in NBIA while demyelination is proposed as a subset of NBIA. Iron is not described as a main feature of the disease but it is suggested from animal and human studies that in most of NBIA, iron-myelin homeostasis is a common characteristic of the disease (Heidari et al., 2016b). Mutation in myelin related genes reduced the iron storage in myelin which could result in abnormal deposition of iron in brain (Heidari et al., 2016b). An $Hfe^{-/-}xTfr2^{mut}$ is a mouse model which shows symptoms of iron overload disease called hemochromatosis. This mouse model, in comparison with normal wild type mouse, exhibited higher levels of iron (Delima et al., 2012). The brain of these model mouse was analyzed for iron it showed high iron deposits in all myelinated areas of brain. Transcriptomic studies have revealed that molecular mechanisms related to myelin are earliest pathological sequelae for abnormal deposition of iron in brain (Heidari et al., 2016a).

3.2.1 Neuroferritinopathy

It is an uncommon progressive movement disorder which is caused by mutation in exon 4 of ferritin light chain gene (Curtis et al., 2001). It is autosomal and dominant disorder characterized by abnormalities mainly in nervous system which can be seen in the fourth to sixth decade of life. Cognitive decline, dystonia, spasticity, choreoathetosis, and rigidity are the sign and symptoms of this disease. A significant feature of neuroferritinopathy is the occurrence of spherical inclusions in brain, skin, muscles, kidney, and liver in which iron and ferritin are observed. *In vitro* studies showed that a decrement in the ferritin capacity to store iron could be a cause of its pathogenesis. It was described that ferritin levels decreased in neuroferritinopathy (Heidari et al., 2016a). Furthermore, toxicity is enhanced by iron-induced-ferritin aggregates (Barbeito et al., 2009). Cellular level studies relate pathogenesis to

oxidative damage (Cozzi et al., 2010; Cozzi et al., 2006). Genetic defects in 5 NBIA associated genes have been identified including phospholipase A2, chromosome 19 open reading frame, fatty acid 2-hydroxylase *Fa2h*, ATPase type 13A2 *Atp13a2,* ceruloplasmin *Cp*, and group VI *Pla2g6.* Impairments of myelin are reported in transgenic mice and in NBIA patients with mutation in the aforementioned genes (Heidari et al., 2016a). Furthermore, ferritin genes, myelin associated genes and reduced expression of $Hfe^{-/-}xTfr2^{mut}$ have been observed in NBIA in human studies (Lee et al., 2009). However, there is a need of more genetic analysis to confirm these mutations.

3.2.2 Infantile Neuroaxonal Dystrophy

Within NBIA, it is an inherited disorder in which nerve abnormalities have been observed in CNS and PNS. PLA2G6 gene mutation is the causative agent for this disease which encodes for phospholipase A (Altamura & Muckenthaler, 2009). The mechanism by which the defect in these genes leads to the pathophysiology of INAD is unknown. Spherical bodies have been identified in the brain, peripheral nerves, and spinal cord but unfortunately these spherical bodies have not been detected for iron and related proteins. These spherical bodies need to be further investigated to check iron deposits in it (Itoh et al., 1993). To build a better understanding between the involvement of iron and pathophysiology of peripheral neuropathy, further research is needed to collect data on iron accumulation from patients suffering from NBIA.

3.3 Charcot–Marie–Tooth (CMT) Neuropathies

These are demyelinating neuropathies that are caused by mutation in more than 40 genes that are associated with different cellular localization, cytoskeleton formation, mitochondrial metabolism, axonal transport, and cell signaling pathways (Scherer & Wrabetz, 2008). The frequent form of this disease occurs as a result of myelin 22 gene which accounts for 50% of all cases approximately. Sign and symptoms of CMT include progressive neuropathy that affects myelinated neurons (Pareyson & Marchesi, 2009). It is suggested that iron deposits in myelinated structures lead to downstream consequences in myelinated systems (Khattar et al., 2021). Despite the chances of occurrence of disease is 50/100,000 that affects the quality of life in a worst manner, however, an appropriate treatment is still not available (Pareyson et al., 2011). CMT has been divided in to five categories based on nerve pathology. CMT1 is a demyelinating neuropathy characterized by significant impairment in nerve conduction velocity ($<$38 m/s) and severe alterations in myelin. CMT2 is axonal degeneration with a mild reduction in conduction velocity ($\geq$38 m/s) of nerves. CMTX is X-linked CMT which shows intermediate nerve conduction velocity (30–45 m/s). CMT4 is an autosomal recessive form of CMT

with earlier onset and nerve conduction velocity is <38 m/s. Due to heterogeneity of genes involved, CMT has also been characterized as intermediate form. It has been described the administration of high dietary iron in mice resulted in genetic alteration in ganglioside-induced differentiation-associated protein 1 (Gdap1) and lipopolysaccharide-induced TNF factor (Litaf) (Johnstone & Milward, 2010). Gdap1 is involved in the pathophysiology of CMT4 neuropathy and Litaf is associated with the onset of CMT1 neuropathy (Baxter et al., 2002; Street et al., 2003).

Since Gdap1 gene is involved in the mitochondrial activity hence it is considered that oxidative stress might be involved in the pathophysiology of CMT4. It has been described that overexpression of Gdap1 has a protective role against oxidative stress. Gdap1 gene is involved in the regulation of GSH but in CMT4 patients it is down regulated which hampers antioxidant role of this gene (Noack et al., 2012). It is documented that cellular imbalance of iron is the cause of oxidative stress and cell death which could further worsen by iron aggregation (Cozzi et al., 2010). It has been described that in several neurodegenerative disorders iron starts to accumulate in glial cells of brain and is poorly available to neurons, resulting in the death of both glia and neurons. Mechanism behind this glial degeneration is oxidative stress because of iron overload resulting in neuronal degeneration due to loss of support and nutrition from glia (Zhao et al., 2015). So, here it is suggested that iron-induced oxidative stress and Gdap1 gene down regulation may be a cause of CMT4 neuropathy.

Missense mutation in Litaf is responsible for the CMT1 neuropathy. This mutation was identified in a German CMT family which exhibited electrophysiological features of demyelination characterized by blockade in nerve conduction (Gerding et al., 2009). It has been described that age related iron accumulation in brain leads to demyelination in basal ganglia which impairs executive functions (Biel et al., 2021). Hence, it can be assumed that iron accumulation in brain can be one of the factors involved in CMT1 neuropathy as demyelination is a common process in both CMT1 and iron accumulation in basal ganglia. Axonal CMT is due to defect in mitofusin 2 (*MNF2*) gene which is 20% of all dominant neuropathies. This form is characterized by abnormalities in white matter of CNS (Pareyson & Marchesi, 2009). Mitofusin 1 and *MNF2* genes are required for the fusion of mitochondrial membranes. MNF2 gene is also involved in the axonal transport (Vital & Vital, 2012) So, here it is suggested that proper iron metabolism and balanced mitochondrial activity is crucial to maintain integrity of axon in some forms of CMT.

It can be suggested from the above discussion that oxidative stress is a factor that is involved in the pathogenesis of severe and rare CMT. Particularly in peripheral neuropathy, mitochondrial defects showed that there might be a relation between iron and oxidative stress. In PNS extensive length axons require a continuous supply of energy at a distance. Furthermore, the impact of ROS on axons proposed that mitochondrial metabolism significantly affects the efficiency of peripheral nerves. However, with limited studies on iron in the pathophysiology of the abovementioned disorders, it cannot be concluded that disturbed metabolism of iron is among the cause of these neuropathies (Levi & Taveggia, 2014). There is a fast-growing amount of data showing the involvement of iron in neuronal disorders but to develop

a better understanding of the disease it is necessary to make efforts to gain a mechanistic approach on the role of iron in the formation of myelin sheath.

3.4 Iron and Metabolic Neuropathies

Polyneuropathy is a severe complication of diabetic patients which is indicated by numbness, weak muscles, and pain. It starts from the distal part of the lower limb but it spreads to the rest of the limbs (Said, 2013). This type of neuropathy is commonly occurred in type 2 diabetes as compared to type 1. In type 2 diabetes, there is loss of unmyelinated and myelinated fibers progressively (Levi & Taveggia, 2014). Several factors are involved in the diabetic neuropathy including DNA and mitochondrial damage (Callaghan et al., 2012) which could be further intensified by iron overload (Levi & Taveggia, 2014) as it has been described that excess iron down regulates myelinated structures of the body (Heidari et al., 2016b). Several previous studies have described the relation between iron and the onset of diabetes (Wu et al., 2020; Huang et al., 2011; Fernández-Real & Manco, 2014). It has been shown that insulin injection can elevate the levels of circulating transferrin receptor 1 (TfR1) and administration of iron can cause diabetes which indicates a conceivable function of iron overload in diabetic neuropathy (Levi & Taveggia, 2014).

It has been found that in type 2 diabetes, there is an increase in level of ferritin and NTBI (non-transferrin bound iron) as compared to non-diabetic individuals (Ford & Cogswell, 1999; Lee et al., 2006). However, these studies are not conclusive because the higher levels of ferritin may be a result of inflammation and obesity. Furthermore, diabetic conditions are related to oxidative stress and mitochondrial dysfunctions that are linked to iron metabolism (Rajpathak et al., 2009). More research studies are required to confirm the direct link between iron overload, diabetes, and neuropathy (Levi & Taveggia, 2014).

3.5 Iron Deficiency Anemia (IDA) and Neuropathy

IDA is known as the most common public health problem worldwide, affecting approximately 2.5–5 billion people, particularly infants and children. Iron is an essential element that has a functional role in neurotransmitter metabolism, cerebral energy metabolism, myelin formation, and synthesis of essential proteins such as hemoglobin (Kabakus et al., 2002; Swaminathan et al., 2016). IDA can alter the central nervous system functions such as reduction in cognitive functions. Moreover, iron deficiency in IDA can affect myelin formation and can cause abnormal functioning of PNS which may lead to paresthetic complaints (Degirmenci & Kececi, 2011). Sensory neuropathic processes in polyneuropathy and carpal tunnel syndrome have been predominantly observed in patients of IDA. Additionally, these neuropathic symptoms have been shown to be attenuated by iron supplementation.

The peripheral nerve function may be altered in iron deficient anemic patients. In myelinogenesis, iron has a vital role via direct and indirect mechanisms that could be a possible cause of neuropathic processes in IDA (Degirmenci & Kececi, 2011). The deficiency of iron impairs the activity of monoamine oxidase (MAO), a crucial enzyme involved in the metabolism of monoamines. In animal studies, experimentally induced neuropathy was also found to decrease MAO activity (Kabakus et al., 2002).

Dysfunction in the physiological activity of peripheral nerve may occur due to iron deficiency in anemic patients. However, there is limited scientific data on the relationship between IDA and peripheral motor nerve functions (Swaminathan et al., 2016). Pre-clinical studies described that lack of iron is responsible for decreased myelination and insufficiency of myelin lipids and proteins. It is also reported that iron deficiency impairs myelination, neurochemistry of neurotransmitter, and neuronal energetics (Beard & Connor, 2003). However, there were very few studies about neuropathy linked to iron deficiency but the involvement of this important mineral cannot be neglected as an etiologic factor of neuropathy in patients.

3.6 Diabetic Neuropathy

Diabetic neuropathy was classified by PK Thomas in 1986 into two distinct categories as generalized neuropathy and focal and multifocal neuropathy (Llewelyn, 2003). The first category includes hyperglycemic neuropathy, peripheral diabetic neuropathy (PDN) with/without autonomic neuropathy, and acute painful sensory neuropathy variants. The second category comprises of cranial neuropathies, thoracolumbar radiculoneuropathy, focal limb neuropathies, and lumbosacral radiculoplexus neuropathy (Llewelyn, 2003). The pathophysiology of diabetic neuropathy includes over activity of polyol pathway, advanced glycation end products, increased oxidative burden, reduced nerve growth factors, altered fatty acid metabolism, and nutritional deficiency including iron and vitamin B12 (Baum et al., 2016; Llewelyn, 2003). PDN or distal symmetrical polyneuropathy is the most common and typical form of diabetic neuropathy that is associated with the iron status of the body. Both type 1 and type 2 diabetes mellitus patients usually suffer from these serious complications (Baum et al., 2016). Numbness, burning, tingling sensations mainly in the legs are the common presentation of peripheral neuropathy. These symptoms are mostly observed in patients suffering from diabetes or kidney disorders. In chronic conditions, these patients present an anemic condition along with the symptoms of peripheral neuropathy (Harisudan et al., 2019). Numerous clinical and preclinical studies described a close relationship between iron metabolism and diabetes mellitus (Baum et al., 2021; Baum et al., 2016). In a study, it has been found that a long-term depletion of iron induces distal peripheral nerve pathology (Baum et al., 2016). It was also documented that a low-iron diet is responsible to accelerate inflammatory activity in streptozotocin-induced diabetic rats. Inflammatory response was also found to be elevated in rat models of type 1 and type

2 diabetes (Baum et al., 2021). Preclinical studies on animal models of PDN showed that iron deficiency was associated with the risk of PDN (Baum et al., 2016; Baum et al., 2021). Iron, a trace element, acts as a co-factor of many cellular processes including DNA synthesis, gene regulation, mitochondrial electron transport, and oxygen delivery. In an experimental study, it has been indicated that iron-deficient diet had a strong effect on the development of PDN. A diet deficient in iron led to reduced velocity of sensory conduction in sciatic nerve and showed mitochondrial impairment in various dorsal root ganglion neurons (Baum et al., 2016; Baum et al., 2021).

3.7 Rubrometabolic Syndrome

The term rubrometabolic syndrome is used to describe the role of blood in anemic condition in metabolic syndrome. Metabolic syndrome is a conglomeration of type 2 diabetes, obesity, insulin resistance, dyslipidemia, and high blood pressure which is associated with significant morbidity (Kalra et al., 2020). Worldwide, metabolic syndrome is reaching epidemic proportions and its individual components have been associated with the onset of peripheral neuropathy (Callaghan et al., 2018). It has been described that metabolic syndrome and anemia are the 2 conditions which can coexist. In metabolic syndrome, there is chronic low-grade inflammation which disturbs iron metabolism and can cause anemia (Cepeda-Lopez et al., 2010; González-Domínguez et al., 2020). Anemia is linked to tissue hypoxia which could lead to several complications of diabetes including peripheral nephropathy, optic neuropathy, and cardiovascular disorders (Sahay et al., 2017). Furthermore, anemia also leads to malabsorption of micronutrients which could further complicate the management of obesity (Kalra et al., 2020). A plethora of studies has deduced that there is robust increase in peripheral neuropathy as the metabolic syndrome or its individual components are increasing day by day (Callaghan et al., 2018; Sahay et al., 2017; Kalra et al., 2020). It has been described that diabetes is a most prominent metabolic driver for the onset of peripheral neuropathy (Callaghan et al., 2018). Literature has shown that obese and pre-diabetic population is at high risk for the development of cardiac autonomic neuropathy as obesity has a direct link with ischemia (Williams et al., 2019). So, here it is suggested that there is a need for a change in life style, physical activity, and proper iron metabolism to avoid the metabolic syndrome and its associated neuropathies.

3.8 Restless Legs Syndrome (RLS)

Restless legs syndrome (RLS), also called Willis-Ekbom disease, is a sensorimotor disorder manifested as unpleasant sensations in the lower limbs and an urge to move the legs. During resting position, these conditions are worse while reduced by

voluntary movements (Klingelhoefer et al., 2016; Bastia et al., 2015). The characterization of RLS symptoms is often difficult and these symptoms are described by patients as paresthesia, pain, current-like or shock-like sensations, and tingling. Paresthesia is usually bilateral and symmetric (Bastia et al., 2015). RLS is considered to be more common in small fiber and painful neuropathies. A cohort study on RLS patients described that peripheral neuropathy was the most occurring form of neuropathy associated with RLS (Bastia et al., 2015). There are two categories of RLS, the first is genetic and the second is symptomatic. The symptomatic RLS is associated with the deficiency of iron, folic acid, and B12 vitamin, in addition, some other conditions associated with symptomatic RLS are hypoglycemia, diabetes, uremia, Parkinson's disease, pregnancy, chronic pulmonary failure, hypothyroidism, alcoholism, carcinoma, venous insufficiency, amyloid polyneuropathy, use of certain drugs such as anticonvulsants, serotonin reuptake inhibitors, neuroleptics, lithium, beta-blockers, caffeine or vasodilators, and sedatives (Akyol et al., 2003). In a study, IDA was found in 1 out of 4 RLS patients (Ekbom, 1960). In another study, 43% of the patients suffering from IDA were also diagnosed with RLS (O'Keeffe, 1996; Akyol et al., 2003). It has been indicated that the reduced availability of iron in the brain has a contributing role in the pathogenesis of RLS (Quinn et al., 2011; Klingelhoefer et al., 2016). Moreover, iron supplementation was found to improve the condition of RLS (Allen, 2007; Quinn et al., 2011), so iron status is one of the important targets in the management of RLS.

3.9 Fibromyalgia Syndrome (FMS)

Fibromyalgia syndrome (FMS) is a chronic painful syndrome with unknown etiology and is usually characterized by pain in eleven out of eighteen tender point sites. Memory deficits, sleep disorder, musculoskeletal pain, depression, tickling feeling in limbs, morning stiffness, and digestion abnormalities are also associated with FMS which severely affect the life quality (Bjørklund et al., 2018). Generally, FMS is considered as centralized pain. However, due to some features similar to neuropathic pain such as numbness and tingling, the FMS is thought to have overlapping characteristics of centralized and neuropathic pain (Arnold et al., 2019). Therefore, FMS is recognized as a syndrome with abnormalities in the central nervous system and pain-controlling mechanisms (Fitzcharles et al., 2013). Researchers have linked the FMS with small fiber neuropathy which is defined as an anomalous structure of small nerve fibers and deterioration of distal nerve terminal. The prevalence of small fiber neuropathy in FMS patients is around 20–60% (Kosmidis et al., 2014; Doppler et al., 2015). The exact cause of FMS is unknown but some factors can trigger the pain of FMS such as surgical procedures, trauma, infection, or mental stress. In some cases, symptoms develop progressively with time without any triggering cause (Furness et al., 2018). The occurrence of FMS is more common in females than males (Arout et al., 2018).

Since iron acts as a cofactor for the enzymes such as tryptophan hydroxylase and tyrosine hydroxylase which are involved in the biosynthesis of indolamine and catecholamine neurotransmitters, therefore, iron deficiency has been related to the occurrence and severity of FMS symptoms. The reduced concentrations of biogenic amines including dopamine, adrenaline, and serotonin have been reported in cerebrospinal fluid of patients suffering from FMS (Russell et al., 1992; Legangneux et al., 2001). Based on these observations, Ortancil et al. (2010) suggested that the depletion in iron storage protein (ferritin) might result in reduced synthesis of neurotransmitters and pathophysiology of FMS. They investigated ferritin levels of forty-six patients suffering from FMS in a case-control study and found significantly reduced ferritin levels in these patients as compared to the healthy controls (Ortancil et al., 2010). The reduced ferritin level is suggested to reduce the iron concentration needed for the synthesis of serotonin and dopamine (Russell et al., 1992; Bazzichi et al., 2006). The severity of FMS symptoms has also been negatively associated with reduced density of serotonin transporters (Bazzichi et al., 2006). Serotonin transporters deficiency was also observed in transgenic iron-deficient mice (Morse et al., 1999). Therefore, it is related that iron insufficiency may lead to the etiology of FMS pain due to reduced serotonin transporters (Ortancil et al., 2010). The prevalence of FMS is also observed in patients suffering from blood disorders such as IDA and beta-thalassemia minor. In these two medical conditions brain hypoxic condition due to reduced iron availability is responsible for the altered synthesis of biogenic amines and thus result in FMS-associated symptoms (Pamuk et al., 2008). Recently, Baygutalp et al. (2020) also showed an increased prevalence of iron deficiency in FMS patients which was more associated with females as compared to the male subjects. In addition, these female FMS patients also exhibited reduced ferritin, hemoglobin, and vitamin B12 levels. They also linked these findings with aberration in the activity of synthetic enzymes of biogenic amines (Baygutalp et al., 2020). The connection between iron deficiency and the occurrence of FMS symptoms is further confirmed by Boomershine et al. (2018), who observed reduced FMS pain by the intravenous administration ferric carboxymaltose at the dose of 15 mg/kg to the affected patients. Ferric carboxymaltose is an iron replacement therapy used in the treatment of IDA.

4 Concluding Remarks

The studies that have been reported to date have linked different kinds of neuropathies with dyshomeostasis of iron levels. Deficiency of iron as well as iron overload may lead to the occurrence and progression of neuropathies, however, more research is required to elucidate the underlying disease mechanism due to iron disbalance. Iron deficiency, a common condition in children and women, can be treated by iron supplementation whereas the condition of iron overload requires chelation therapy. Therefore, estimation of iron levels should be included in the diagnosis of neuropathies so that its possible involvement can be identified and appropriate treatment

can be given to provide relief to the patients. However, this aspect needs further pre-clinical and clinical studies to suggest specific treatment for iron-induced neuropathies.

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