REVIEW ARTICLE

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Iron Chelation in Movement Disorders: Logical or Ironical

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ABSTRACT: Iron is probably as old as the universe itself and is essential for sustaining biological processes. The remarkable property of iron complexes to facilitate electron transfer makes it a significant component of redox reactions that drive the essential steps in nucleic acid biosynthesis and cellular functions. This, however, also generates potentially harmful hydroxyl radicals causing cell damage. In the movement disorder world, iron accumulation is well known to occur in neurodegeneration with brain iron accumulation, while dysfunctional iron homeostasis has been linked with neurodegenerative diseases like Parkinson's disease and Huntington's disease to name a few. Targeting excess iron in these patients with chelation therapy has been attempted over the last few decades, though the results have not been that promising. In this review, we have discussed iron, its metabolism, and proposed mechanisms causing movement disorder abnormalities. We have reviewed the available literature on attempts to treat these movement disorders with chelation therapy. Finally, based on our understanding of the pathogenic role of iron, we have critically analyzed the limitations of chelation therapy in the current scenario and the various unmet needs that should be addressed for selecting the patient population amenable to this therapy.

RÉSUMÉ : La chélation du fer dans le cas de troubles du mouvement : logique ou ironique? Le fer est probablement aussi vieux que l'univers lui-même et demeure essentiel pour le maintien des processus biologiques. La propriété remarquable des complexes du fer leur permettant de faciliter le transfert des électrons en fait un des éléments importants des réactions d'oxydoréduction qui dirigent les étapes essentielles de la biosynthèse des acides nucléiques et des fonctions cellulaires. Il faut savoir toutefois que cela a pour effet de générer des radicaux hydroxyles nocifs qui peuvent potentiellement endommager les cellules. Dans le champ d'étude des troubles du mouvement, il est bien connu qu'une accumulation en fer survient dans le cas de la neurodégénérescence avec excès en fer tandis que l'homéostasie ferrique dysfonctionnelle a été associée à des maladies neurodégénératives comme la maladie de Parkinson et la maladie d'Huntington pour n'en citer que quelques-unes. Le fait de cibler un excès en fer chez ces patients au moyen d'un traitement par chélation a été tenté au cours des dernières décennies ; cela dit, les résultats n'ont pas été si prometteurs. Dans cet article, nous entendons aborder le métabolisme du fer ainsi que les mécanismes qui provoquent les troubles du mouvement. Nous avons aussi passé en revue la littérature scientifique disponible portant sur les tentatives de traiter les troubles du mouvement à l'aide d'un traitement par chélation. Finalement, sur la base de notre compréhension du rôle pathogène du fer, nous avons cherché à analyser de façon critique les limites d'un tel traitement dans l'état actuel des choses et les différents besoins non satisfaits dont on devrait tenir compte dans la sélection des patients qui peuvent se prêter à ce traitement.

Keywords: Iron, Parkinsons disease, Huntingtons disease, Neurodegeneration with brain iron accumulation, Friedrich's ataxia, Chelation therapy

doi:10.1017/cjn.2020.279 Can. J. Neurol. Sci. 2021; 48: 752–759

Introduction

Iron is an essential metal and is required for numerous cellular mechanisms in the central nervous system, including oxidative phosphorylation, myelin synthesis, neurotransmitter synthesis, and immune function. Important iron containing proteins include cytochromes, aconitase, tyrosine, and tryptophan hydroxylase and proteins in the mitochondrial electron transport chain.[1,2] Iron is obtained from diet in heme and non-heme forms. Sources of heme iron are animal products like poultry, meat, and fish, while non-heme iron is obtained from legumes, breads, cereals, and supplemental iron. Heme iron is rapidly absorbed and has a high bioavailability, aided by specific heme transporters in the gut allowing it quick access across the cell membranes, while non-heme iron needs to be reduced from a ferric to a ferrous state before it gets absorbed.[3] This property of switching between a ferrous (Fe^{2+}) and ferric (Fe^{3+}) state by exchanging an electron renders it an essential component in many oxidation-reduction reactions. However, the same property is deleterious to cellular functions by generating hydroxyl radicals that enhance lipid peroxidation, protein aggregation, and glutathione dysfunction (Fenton reaction; $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH + OH^-$, where H_2O_2 – hydrogen peroxide, OH^- – Hydroxide, OH·– hydroxyl radical). Hydroxyl radical, considered as one of the most reactive species in biology, is responsible for many of the harmful effects of iron-mediated cell damage.[2] Also, iron can convert dopamine and other catechols to potentially neurotoxic semiquinone radicals by non-enzymatic peroxidase activity (pseudoperoxidase reaction).[4] Thus, the benefits and harmful effects of iron in the body and the brain in particular need to be tightly regulated, and any increase in the labile iron pool (LIP) in the cytoplasm can be

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Received November 19, 2020. Final Revisions Submitted December 16, 2020. Date of Acceptance December 21, 2020.

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https://doi.org/10.1017/cjn.2020.279 Published online by Cambridge University Press

detrimental to the cellular functions and harbinger of the iron-induced neurodegeneration. In the movement disorder world, it has been hypothesized that iron accumulation may contribute in the pathogenesis of Parkinson's disease (PD), neurodegeneration with brain iron accumulation (NBIA), Friedrich's ataxia, and Huntington's disease (HD). Attempts to remove this excess iron from the brain by chelation therapy have not been very successful. In this review, we analyze the pathogenic mechanisms of iron-induced neurodegeneration in movement disorders and studies on iron chelation to ameliorate the symptoms. Finally, we share our point of view on the disappointing results of iron chelation and possible future directions to manage iron-induced neurodegeneration in movement disorders by chelation therapy.

Storage and Metabolism of Iron

Iron obtained from diet is absorbed by the enterocytes through the gastroduodenal junction. Non-heme iron is reduced to ferrous salt (II), internalized by divalent metal transporter 1 (DMT1), and then exported to the plasma by a protein, ferroportin 1.[4,5] Ferrous iron is converted to ferric ion via a ferroxidase hephaestin and ceruloplasmin, and the ferric iron is then bound to transferrin, the transporter of iron, as holo-transferrin molecule. Holo-transferrin binds to the transferrin receptor (TfR1) on the target cells and the complex undergoes endocytosis. Ferric ion is again reduced to Fe (II) by metalloreductase, which either binds to chaperones for transport to the target protein or enters mitochondria via mitoferrin 1 and 2. Excess iron gets stored as ferritin and later utilized or degraded by lysosomes. In the central nervous system, TfR1 mediates endothelial iron uptake.[4–7] Transferrin is mainly seen in oligodendrocytes, ferritin in microglia, and the neurons have many TfR1 as seen on specialized stains. Iron ferroxidases, ceruloplasmin, and hephaestin are also expressed in central nervous system. Iron regulatory proteins (IRPs) are posttranscriptionally regulated by cellular iron levels, and the absorption, distribution and export are hence closely balanced.[8,9] Also, hepcidin hormone secreted by hepatocytes can bind to ferroportin to halt iron uptake in cases of iron overload[9] (Figure 1). IRPs are responsible for feedback regulation of iron homeostasis. Of the two sub-types, IRP1 is mostly expressed in kidney, liver, and brown fat, while the expression of IRP2 is seen in central nervous system. When the cytoplasmic LIP is low (iron-deficient state), IRP1 binds to iron-responsive element (IRE) of mRNA to decrease the translation of ferritin and ferroportin (reduces iron storage and export) and repress the degradation of TfR1 and DMT1 (increases iron uptake). When the cytoplasmic LIP is high (iron replete state), IRP1 promotes iron–sulfur cluster [4Fe–4S] complex and its physiological effects are reverted. Also, the cluster complex acquires an aconitase activity that catalyzes the conversion of citrate and isocitrate and increases NADPH production.[10,11] On the other hand, IRP2 lacks iron–sulfur cluster and aconitase activity. IRP2 is degraded by an E3 ubiquitin ligase complex containing FBXL5 (F-box protein). Iron and oxygen binds with FBXL5 and promote E3 ubiquitin ligase complex activity that in turn degrades IRP2. Iron deficiency state destabilizes FBXL5 protein and thus decreases E3 ubiquitin ligase activity. IRP2 deficiency in neurons decreases the expression of TfR1 and increases the expression of ferritin. As a result, there occurs functional iron deficiency state that leads to mitochondrial dysfunction and neuronal degradation.[10,11]

Iron and PD

Iron is a "double-edged sword" for dopaminergic neurons. Substantia nigra pars compacta (SNc) is rich in iron that is needed for tyrosine hydroxylase-mediated dopamine synthesis. However, the redox-active form of iron interacts with hydrogen peroxide (produced from dopamine catabolism and as a by-product of mitochondrial electron transport chain) and generates toxic hydroxyl radical via the Fenton reaction. Numerous studies in PD have shown increased iron deposition in SNc. In PD, iron dyshomeostasis causes increased intracellular iron that is beyond the capacity to sequester via ferritin and neuromelanin. In dopaminergic cells of SNc, increased intracellular iron can lead to: 1) auto-oxidation of phospholipids with subsequent lipid peroxidation, depletion of protective glutathione peroxidase (Gpx4), and loss of membrane integrity (ferroptosis), 2) formation of iron–dopamine complexes that lead to dopamine auto-oxidation and formation of toxic quinones that interacts deleteriously with mitochondrial complex I and IV, and 3) alpha-synuclein aggregation and Lewy body formation (Figure 2).[12–15] Apart from that, once the buffering capacity of neuromelanin is exhausted, toxic iron–melanin complexes are formed that promote lipid peroxidation and oxidative stress. Extracellular neuromelanin leads to microglial activation causing further neuroinflammation and neurodegeneration.[16] Another mode of iron sequestration in degenerative diseases like Alzheimer's disease (AD) and PD and a probable potential therapeutic target involves heme breakdown enzyme, heme oxygenase (HO). It cleaves heme to biliverdin, carbon monoxide, and free ferrous ion. Mammalian HO exists in two isoforms, HO-1 and HO-2. HO-1 has a role in augmenting the breakdown of prooxidant heme to antioxidants biliverdin and bilirubin. However, this generates carbon monoxide and Fe^{2+} that promote free radical formation and exacerbate cellular injury.[17] HO-1 is detectable in glial cells, neurons, choroid plexus epithelial cells, senile plaques, and neurofibrillary tangles in Alzheimer's brain and in the cytoplasmic Lewy bodies within a□ected dopaminergic neurons in SN of patients with PD.[17] Zukor et al. transfected primary astrocyte cell cultures derived from Sprague–Dawley rats with human HO-1 complementary DNA. The transfecting dose resulted in an astroglial activity simulating that seen in AD. There was an increased mitochondrial permeability with redox-active iron sequestration in astroglial mitochondria.[18] HO-1 inhibitors were found to be protective in rat astrocytes transfected with HO 1 gene.[19] Recent studies with iron-sensitive imaging like susceptibility-weighted imaging (SWI), quantitative susceptibility mapping (QSM), and true SWI (tSWI) images have shown different patterns of brain iron accumulation in PD and atypical parkinsonian syndromes. Iron deposition in nigrosome-1 at early stage of PD leads to loss of the dorsolateral substantia nigral (SNc) hyperintensity (loss of "swallowtail" sign or loss of "N1 sign").[20] In multisystem atrophy parkinsonian type, iron deposition predominantly affects posterolateral putamen with a striking lateral to medial gradient. In progressive supranuclear palsy, iron deposition is mainly seen in red nucleus and globus pallidus.[21]

Bergsland et al. studied 18 PD patients for iron accumulation over a 3-year period and compared them to healthy controls. They found maximal iron accumulation in ventral and posterior SN correlating with the earliest pathology of "ventral tier"

https://doi.org/10.1017/cjn.2020.279 Published online by Cambridge University Press

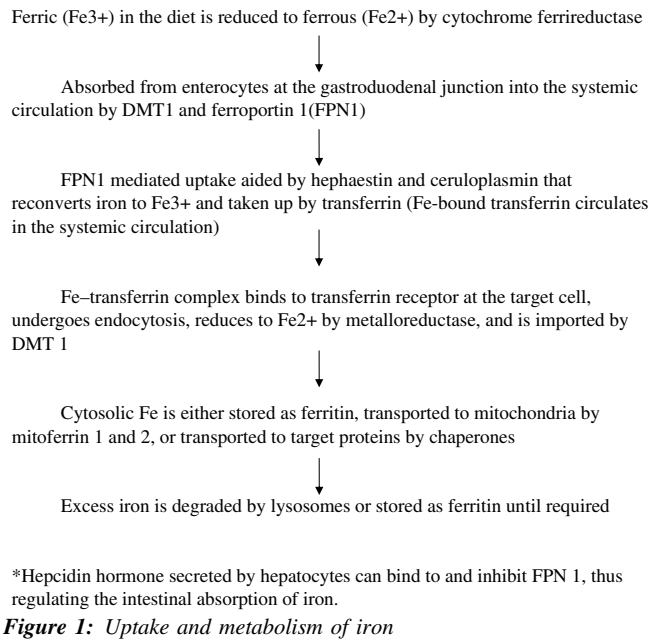

Figure 1: *Uptake and metabolism of iron*

dopaminergic deficit in PD.[22] Studies in familial PD have also suggested the role of iron dyshomeostasis. Mutation in parkin (PARK2) and PLA2G6 (PARK14) can lead to enhanced iron import via upregulation of DMT1, while mutated ATP13A2 (PARK9) can impair lysosomal iron handling.[18]

Iron and NBIA

NBIA is a group of genetic disorders resulting in excessive and pathological iron accumulation primarily in the basal ganglia with movement disorders like dystonia and parkinsonism as the predominant presenting feature. Pantothenate kinase-associated neurodegeneration (PKAN) and PLA2G6-associated neurodegeneration were the core syndromes, but genetic mapping has revealed additional NBIA conditions that include aceruloplasminemia, neuroferritinopathy, Kufor–Rakeb disease, mitochondrial membrane protein-associated neurodegeneration, fatty acid 2 hydroxylase-associated neurodegeneration, beta-propeller protein-associated neurodegeneration (BPAN), and Woodhouse–Sakati syndrome.[23,24] Among NBIAs, aceruloplasminemia and neuroferritinopathy are directly linked to iron metabolism, while iron chelation has been attempted in PKAN and, hence we are briefly discussing these diseases here.

Aceruloplasminemia is caused by a mutation in the ceruloplasmin gene, encoding the protein ceruloplasmin (CP). As discussed earlier, CP is a ferroxidase, facilitating iron export from cell via ferroportin. In the absence of CP, ferroportin cannot export iron and it leads to accumulation of iron within astrocytes and resultant cell damage.[25] Neuroferritinopathy is caused by mutations in the ferritin light chain (FTL1). As a result, the ferritin polymer with the mutated chains incorporate iron less efficiently which leads to release of free iron into the cytoplasm. Free cytosolic iron stimulates more ferritin expression leading to a vicious cycle. It also stimulates reactive oxygen species (ROS) production and oxidative damage. In the long term, it causes ferritin aggregates and cell death.[25,26] Pantothenate kinase catalyzes the phosphorylation of pantothenate, the first and limiting step of coenzyme A (CoA) biosynthesis in mitochondria and cytosol.[25] The definite link between impairment of CoA synthesis and iron accumulation in basal ganglia in PKAN is still unclear. There is evidence of accumulation of cysteine in the globus pallidus of PKAN patients, as a result of an enzymatic block in the metabolic pathway from cysteine to taurine. Accumulated cysteine chelates iron and increases the local iron content. Combined excess of cysteine and ferrous iron then generates free radicals and damages neuronal membranes.[27] Iron accumulation alters the morphology and physiology of mitochondria due to disruption of the iron–sulfur clusters in the electron transport chain. Globus pallidus appears to suffer the major brunt of injury with the "eye of the tiger sign" on the magnetic resonance imaging (MRI) showing the classical hypointensity on gradient sequences due to excessive iron deposition.[25,28]

Iron and Friedrich's Ataxia

Loss of function mutations in the frataxin gene cause Friedrich's ataxia, an autosomal recessive condition causing degeneration of the dorsal root ganglia and the posterior columns of the spinal cord and leading to progressive sensory ataxia followed by involvement of the corticospinal and spinocerebellar tracts.[29] Frataxin protein is synthesized in cytoplasm and then imported to mitochondria where it has a possible role in iron homeostasis.[29,30] Frataxin-deficient yeast cells have reduced mitochondrial iron–sulfur cluster enzymes and more oxidative stress. In postmortem studies of patients with Friedrich's ataxia, increased iron deposition is seen in heart, liver, spleen, dentate nucleus in the cerebellum, and red nucleus in the mid-brain, a distribution consistent with mitochondrial location adding further support to the yeast experiments.[31,32] This iron overload by generation of ROS has been linked to the pathogenesis of Friedrich's ataxia which might be potentially amenable to chelation therapy.

Iron and HD

Striatal degeneration in HD has been linked to a dominant mutation in exon 1 of the HTT gene that codes for the huntingtin protein. The resultant cytosine, adenine, and guanine trinucleotide repeats result in an abnormally long polyglutamine protein (mutant Htt).[33] Amongst the various theories proposed to explain the pathogenesis in HD, altered iron homeostasis has been suggested by brain imaging studies showing increased iron signal in basal ganglia in HD patients. Dexter et al., on an autopsy study on HD brains, found a 56% increase in the iron levels in the caudate and 44% in the putamen.[34] Simmons et al. demonstrated increased ferritin in the striatum and cortex on immunohistochemical analysis of HD brains.[35] The accumulation of iron in HD has also been linked to dysregulation of IRP1 and IRP2.[36] On a molecular basis, the increased iron uptake in mitochondria secondary to increased mitoferrin 2 activity leads to dysfunction of iron–sulfur enzyme aconitase, as seen in FA. The resultant mitochondrial dysfunction leads to reduction in oxidative phosphorylation and free radical production, altering the striatal functions and causing the symptomatic manifestation in HD.[33,36,37]

https://doi.org/10.1017/cjn.2020.279 Published online by Cambridge University Press

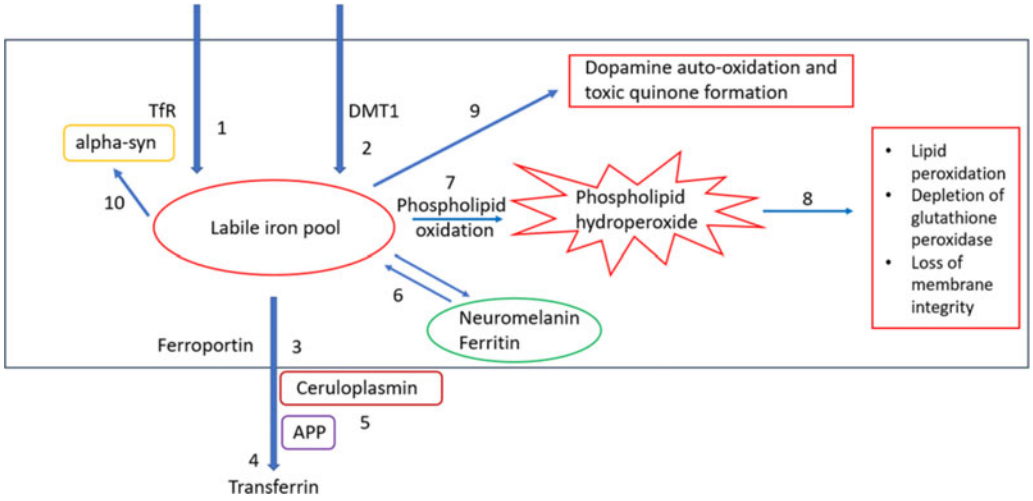

Figure 2: *Increased cellular import of iron via TfR1 (promoted by alpha-synuclein) and DMT1 (1,2). Impaired export of iron via ferroportin and transfer to transferrin, due to destabilization of ferroportin by ceruloplasmin and amyloid precursor protein (APP) (3,4,5). As a result, intracellular labile iron pool increases that surpass the capacity of sequestration via ferritin and neuromelanin (6). Increased labile iron enhances auto-oxidation of phospholipid (7) and subsequent deleterious effects (ferroptosis) (8). Iron interacts with dopamine to form iron–dopamine complexes that promote auto-oxidation of dopamine and toxic quinone formation (9). Increased intracellular iron also enhances alpha-synuclein aggregation (10) and the vicious cycle continues.*

Iron Chelation in Movement Disorders – Studies so far

Iron chelation is most effective when the chelating agent can bind all the six ligand binding sites of the metal. This prevents any uncoordinated exposed site that would generate free radicals by the Fenton reaction. Deferoxamine, a bacterial hexadentate siderophore, can bind all the six sites efficiently and the oral drug, deferiprone does that in higher doses. Deferoxamine had a poor oral absorption and short half-life, necessitating parenteral routes of administration. Iron-bound deferoxamine complex has renal excretion, while fecal iron excretion is derived from intrahepatic chelation. This excess iron is generated from the catabolism of the red cells before it binds to transferring.[38] Deferiprone is rapidly absorbed after oral administration and due to its lipophilicity and low molecular weight, is more stable, can easily cross the blood–brain barrier (BBB), and is considered a better chelator for brain iron overload.[38,39] Tridentate chelator, deferasirox is another oral iron chelator given once a day as against a thrice daily dosage of deferiprone, with equal efficacy.[39]

The human studies on iron chelation are detailed in Table 1. It is worth mentioning that the studies on PD used a strategy of "conservative chelation" or repositioning/redeployment.[41,42] This aims at scavenging extra iron from areas of regional siderosis and redistributes to other areas via the chelator itself or via circulating transferrin, avoiding systemic iron deficiency state.

Iron Chelation in Movement Disorders – Are we there yet?

There is no doubt on the effective role of copper chelation in Wilson's disease but can the same be said about iron chelation? Unfortunately, anecdotal case reports do mention some radiological and clinical improvement, but overall results are not very promising. Also, unlike Wilson's disease, the reduction in brain iron on serial MRI scans is often not associated with clinical improvement. The difference in the clinico-radiological improvement with copper chelation in Wilson's disease and none so with iron chelation in the neurodegenerative disorders is difficult to interpret at this point of time. Also, it makes us wonder as to how much the accumulated iron in certain brain regions is directly contributing to disease progression. There are reported PKAN cases where clinical manifestations started prior to the appearance of the classic "eye of the tiger" sign on brain MRI.[56] Is PANK 2 deficiency primarily responsible for the biochemical perturbation with iron accumulation being a secondary effect? Or, as the data from other neurodegenerative disorders suggest, high levels of free iron lead to oxidative stress, ROS production, and subsequent pathological cascade of neurodegeneration in PKAN? If the basis for pathogenesis of PKAN is the latter, long-term iron chelation might be effective in the following group of PKAN patients – i) who are early in the disease course, ii) in adult-onset phenotypes, and iii) in whom the disease progression itself is slow (e.g., atypical PKAN). Further studies are needed with a larger cohort to address this issue. Chelation therapy with deferiprone has failed in BPAN. Parkinsonian symptoms rather worsened after 4 months of 1000 mg twice a day therapy.[57] In another study, the patient could not tolerate the recommended dose. With low dose of 250 mg/day for a year, no clinical benefit was noted.[58] Theoretically, chelation therapy is rather targeting the secondary outcome, that is, intracellular iron overload. In a rat model, it has been shown that oral iron chelation therapy can reduce dopamine (DA) and serotonin (5-HT) levels in striatum. It inhibits tyrosine and tryptophan hydroxylase likely by interacting with the iron bound to these enzymes.[59] This might explain the aggravation of hypokinetic symptoms of the BPAN patient after deferiprone therapy. Iron chelation therapy in aceruloplasminemia has varying results. While systemic iron load has been managed more effectively in most of the trials, clinical and radiological reduction in brain iron load is not that efficient. In aceruloplasminemia, the basic problem is defective iron export from astrocytes and subsequent iron sequestration. Due to absence of CP activity, the ferrous iron entering the brain cannot be oxidized to be exported out and thus accumulates in large amount, through transferrin-independent, non-regulated

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Table 1: Studies on iron chelation in movement disorders

Movement disorder	Author group	Year	No of study participants	Chelation therapy (dose/duration)	Clinical results	Radiological results
PD	Martin Bastida et al.[40]	2017	22 PD patients within 5-year disease onset	20–30 mg/kg/day of deferiprone for 6 months.	No significant improvement or worsening with therapy.	Reduction in iron concentration in dentate nucleus and caudate. No reduction in red nucleus, SN.
Parkinson's disease	Devos et al. (FAIRPARK study)[41]	2014	37 PD patients within 3-year disease onset	30 mg/kg of liquid deferiprone for 12 months (early start took treatment for 12 months, delayed start for 6 months).	Early start group had significant motor improvement than delayed start group. Extension of therapy till 24 months showed waning of the beneficial effects seen initially.	Reduction in iron levels in SN in both early start and delayed start groups. Reduction seen more in early start group.
Parkinson's disease	Devos et al. (FAIRPARK 2)[42]	Estimated study completion on April 2021	372 participants	30 mg/kg of deferiprone for 9 months.	Not yet published.	Not yet published.
NBIA	Koplstock et al.[43]	2019	88 participants with PKAN 58 received deferiprone, 30 placebo	30 mg/kg of deferiprone for 18 months.	Nonsignificant reduction in dystonia scale in treatment arm.	Significant decrease in iron concentration in globus pallidus
NBIA	Abbruzzese et al.[44]	2011	6 participants 4 PKAN and 2 undetermined genetic tests	30 mg/kg of deferiprone for 12 months.	Improvement in motor symptoms observed in 3 patients (2 were PKAN).	Reduction in iron content in globus pallidus in 3 patients at 6-month and 12-month visits.
NBIA	Zorzi et al.[45]	2011	9 PKAN patients	25 mg/kg of deferiprone for 6 months.	No improvement in motor scores.	30 % median reduction in iron content in globus pallidus.
NBIA	Cossus et al.[46]	2014	6 PKAN patients	30 mg/kg of deferiprone for 4 years.	Symptoms stabilized or improved in 3 patients while worsening in 1 patient.	Significant iron reduction in bilateral pallidum in all patients.
NBIA	Miyajima et al.[47]	1997	1 patient of aceruloplasminemia	500 mg of deferoxamine twice weekly for 10 months.	Improvement in blepharospasm and grimacing but dysarthria persisted.	Improvement in the signal intensity in thalamus and striatum suggesting reduction in iron concentration.
NBIA	Poli et al.[48]	2016	1 patient with aceruloplasminemia	1000 mg of deferoxamine for 5 days followed by 6 months deferiprone of 500 mg/day.	Significant improvement in gait instability, truncal ataxia, and myoclonus.	No progression in the levels of iron deposition in striatum and thalamus.
NBIA	Tai et al.[49]	2014	1 patient with aceruloplasminemia	500 mg/day of deferasirox for 6 months and then 1000mg/day for 5 months.	Asymptomatic for any neurological signs and remained asymptomatic.	No change in the MRI hypointensities in basal ganglia, hypothalamus, and dentate nucleus.
NBIA	Finkenstedt et al.[50]	2010	3 siblings with aceruloplasminemia	Deferasirox of 17–20 mg/kg/day for 1 week to 5 months.	Stabilization of neurological symptoms.	No worsening in MRI findings of increased iron overload in basal ganglia and dentate nuclei.
NBIA	Chinner et al.[51]	2007	41 subjects with neuroferritinopathy	3 patients attempted with iron chelation. 4000 mg of deferoxamine weekly in 2 subjects for 14 months and deferiprone of 6 g/day for 2 months in 1 patient.	1 patient with generalized dystonia deteriorated, while other 2 had no response.	Post-chelation MRI results not discussed.

NBIA							
Friedreich ataxia	Casali et al.[52]	2012	1 patient with neuroferritinopathy	15mg/kg/day of deferiprone for 6 months.	No improvement in ataxia, parkinsonism, and upper limb dystonia.	Post-chelation MRI results not discussed.
Friedreich ataxia	Boddaert et al.[53]	2016	9 patients	20–30 mg/kg/day of deferiprone for 6 months.	Improvement in neuropathic symptoms and gait in 7 patients after 4 weeks of treatment.	Significant reduction in iron stores in dentate nuclei.
Friedreich ataxia	Velasco-Sanchez et al.[54]	2010	20 patients	Deferiprone of 20 mg/kg/day and idebenone of 20 mg/kg/day for 11 months.	Postural and gait scores worsened, while kinetic function scores improved on ICARS score.	Significant reduction in dentate nucleus iron concentration.
Huntington's disease	Dorsey et al.[55] Phase 2 trial	2014	109 patients	PBT 2 of 250 mg in 36 patients, PBT 2 of 100 mg in 38, and placebo in 35 patients for 26 weeks.	No significant improvement in cognition scores in drug group.	Not commented.

NBIA = neurodegeneration with brain iron accumulation; PD = Parkinson's disease; SN = substantia nigra; PKAN = pantothenate kinase-associated neurodegeneration; MRI = magnetic resonance imaging; ICARS = International Cooperative Ataxia Rating Scale

pathway. Chelation in the initial phases may decrease excess iron entry into brain astrocytes but once neurodegeneration has started, it is difficult to revert the process only by chelation without making an alternative way of iron export from the cells. Recently, intraperitoneal infusion of ceruloplasmin-enzyme replacement therapy has been demonstrated to reduce brain iron overload and improvement in neurological symptoms in ceruloplasmin-knockout (CpKO) mouse model of aceruloplasminemia.[60] How far can this observation be extended to clinical practice, only time will tell. In neuroferritinopathy, the intracellular vicious cycle of reduction in iron storage capacity of ferritin leading in turn to free iron-induced ferritin aggregation and oxidative stress cannot be targeted by iron chelation. New therapeutic agents targeting this detrimental cascade can be more effective.

The variable efficacy of the iron chelators on neurological symptoms is related to the ability of chelators to cross the BBB, time of onset of the treatment, and the therapeutic protocol administered. Most of the trials have evaluated the clinical efficacy on a short-term basis. Even for those patients that were evaluated prior to the onset of neurological manifestations, no long-term data are available. Another important consideration is the associated side effects that lead to early discontinuation of the chelation therapy. Also, due to the ubiquitous profile of iron, a cellular specificity is required to target regional siderosis without causing any changes in the systemic iron homeostasis.

Can we identify PD patients who can benefit from iron chelation therapy? Newer imaging techniques like QSM and 7-Tesla MRI can quantify nigral iron content.[61] Hence, there is an immense scope of utilizing these newer imaging modalities to identify PD patients in whom iron chelation therapy can be more effective.

Can we have a definite threshold value of nigral iron content differentiating pathological from physiological deposition and hence, selecting patients in whom iron chelation can be tried? Can chelation revert neurodegeneration at all? Recent studies have highlighted that early axonal pathology and defective axonal transport leads to synucleinopathies like PD. "Dying back" degeneration of dopaminergic and serotonergic axonal projections with late involvement of cell bodies in nigra has been noted in different PD models.[62] There can be a role of neuritogenic stimuli to salvage the dysfunctional neurons which have not yet degenerated and become nonfunctional.[63] In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model, such neurorestorative action of a multitarget iron chelator and brain-selective monoamine oxidase-AB inhibitor M30 has been demonstrated. M30 inhibits degradation of hypoxia-inducible factor-1α (HIF-1α) by prolyl hydroxylase (the activity depends on iron and oxygen). Stabilization of HIF-1α induce neurotrophic factors (brain-derived neurotrophic factor and glial cell-derived neurotrophic factor) and survival signaling factors (protein kinase C, serine/threonine kinase, and glycogen synthase kinase-3β).[64] So, if we can quantify nigral iron overload and start iron chelation early in disease course in selective PD patient population, there may be a therapeutic window within which we can mitigate, if not revert, excess iron-induced neurodegeneration. Newer iron-sensitive brain imaging techniques can be further utilized in patients with NBIA and Friedrich's ataxia to select patients in whom large-scale therapeutic trials with iron chelators can be performed. The co-relation of regional iron quantification and

https://doi.org/10.1017/cjn.2020.279 Published online by Cambridge University Press

therapeutic effect of iron chelation in these conditions will be of immense therapeutic importance.

Finally, the studies on iron chelation in movement disorders have not mentioned how to assess the effectiveness of chelation. Reduction in the brain iron content as seen on imaging may not match the clinical profile and cannot be relied upon. While Wilson's disease management has established guidelines for assessing the effectiveness of chelation by determining 24-hour urinary copper and serum copper levels, it is not so with iron chelation.[65]

Conclusions

Iron accumulation has an important contribution in the pathophysiology of neurodegenerative diseases, with dismal results on attempted chelation therapy. It is not the chronic exposure and resultant toxicity of iron, nor a single carrier protein-mediated defect in iron toxicity, but a complex array of physiological and biochemical alterations that has been proposed to have a causative role in PD, HD, NBIA, or Friedrich's ataxia. Whether brain iron accumulation in selective areas in these diseases is indeed pathogenic or just an innocent bystander effect of different pathological mechanisms is still a matter of debate. Newer sensitive imaging techniques like QSM can detect and quantify brain iron in these diseases, but how much is the iron contributing to the disease pathogenesis is still unknown. Newer and more selective chelating agents or combination chelation therapy can be considered in future clinical trials with the aim to slow the progression of diseases with abnormal brain iron accumulation.

Conflict of Interest

None.

Statement of Authorship

MJ planned the study and edited the final version. DK did the literature search, manuscript writing, and final formatting. JG did the literature search and manuscript writing.

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