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Iron chelation in the treatment of neurodegenerative diseases

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ABSTRACT

Disturbance of cerebral iron regulation is almost universal in neurodegenerative disorders. There is a growing body of evidence that increased iron deposits may contribute to degenerative changes. Thus, the effect of iron chelation therapy has been investigated in many neurological disorders including rare genetic syndromes with neurodegeneration with brain iron accumulation as well as common sporadic disorders such as Parkinson's disease, Alzheimer's disease, and multiple sclerosis. This review summarizes recent advances in understanding the role of iron in the etiology of neurodegeneration. Outcomes of studies investigating the effect of iron chelation therapy in neurodegenerative disorders are systematically presented in tables. Iron chelators, particularly the blood brain barrier-crossing compound deferiprone, are capable of decreasing cerebral iron in areas with abnormally high concentrations as documented by MRI. Yet, currently, there is no compelling evidence of the clinical effect of iron removal therapy on any neurological disorder. However, several studies indicate that it may prevent or slow down disease progression of several disorders such as aceruloplasminemia, pantothenate kinase-associated neurodegeneration or Parkinson's disease.

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Contents

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1. Introduction

Disease-modifying treatment strategies with proven efficacy for neurodegenerative disorders are currently lacking. Among other factors, this is because our understanding of the pathophysiology of neurodegeneration remains limited. One of the mechanisms that can contribute to neurodegenerative changes is accumulation of redox-active metals. The connection between metal accumulation and neurodegeneration has been strengthened by the successful use of copper chelators in Wilson disease (WD) and manganese chelation in SLC30A10 manganese transporter deficiency [1]. A growing body of data supports the view that disruption of cerebral iron regulation plays a role in the etiology of Parkinson's disease (PD), Alzheimer's disease (AD), Friedreich's ataxia (FRDA), and other neurological disorders [2,3]. The development of orally administered-iron chelating agents such as deferiprone and deferasirox along with advances in non-invasive MRI techniques to quantify iron content in specific brain regions facilitated clinical trials examining the effect of iron removal therapy [4]. This article reviews recent advances in understanding the role of iron in the etiology of neurodegeneration and gives a summary about the clinical experience with iron chelating drugs in neurodegenerative disorders.

2. Causes and consequences of cerebral iron accumulation

Despite cerebral iron accumulation in aging and neurodegenerative disorders has been appreciated for a century, its mechanisms are still poorly understood [5]. In theory, several possible sources of increased brain iron deposits may be involved, (1) bleeding, (2) influx of iron-containing macrophages from the bloodstream or (3) dysregulation of iron transport across the blood-brain barrier (BBB). Cerebral hemorrhage can undoubtedly supply large amounts of iron from the degraded heme prosthetic group. Repetitive subarachnoid bleeding may lead to iron deposition in the pial surface and cause superficial siderosis of the central nervous system (CNS) [6]. Microbleeding due to microangiopathies may be a source of parenchymal iron deposition. It has been documented that extravasated erythrocytes may propagate along perivascular spaces, trigger inflammatory response and contribute to iron deposition in areas distant from the actual bleeding site [7]. Demyelinating lesions in multiple sclerosis are typically formed around a central vein, and extravasation of erythrocytes through venous walls damaged by perivascular inflammation may participate in iron deposition observed in some lesions [8].

Iron-containing phagocytic cells are frequently present in brain areas affected by neurodegenerative changes [9]. Macrophages may be attracted to phagocyte iron accumulated due to damage of iron-rich oligodendrocytes and neurons. Alternatively, iron-containing activated phagocytic cells that migrate into the CNS as part of the inflammatory response may be themselves the source of abnormal iron deposits [10]. This view has been supported by a study employing a rat model of substantia nigra degeneration induced by ibotenic acid where the neurodegeneration was accompanied by an influx of iron-laden macrophages [11].

Abnormal cellular iron homeostasis in the CNS can lead to an increased cerebral iron uptake. This notion is witnessed by an increased brain iron content in aceruloplasminemia and neuroferritinopathy which are hereditary disorders caused by dysfunction of proteins involved in the transport and storage of iron, namely in ceruloplasmin [12] and ferritin light chain (FTL) [13]. Iron is essential for many cellular functions, including energy production, DNA synthesis and repair, phospholipid metabolism, myelination and neurotransmitter synthesis [5]. Impairment or upregulation of any of these functions in brain cells may thus increase the

need for iron. Increased myelin turnover in demyelinating disorders or compromised cellular energy metabolism in ischemic or mitochondrial disorders may enhance the cell iron uptake through the upregulation of transferrin receptors or activation of hypoxia-inducible-factor-1α (HIF-1α) [14,15]. It can be assumed that under normal circumstances cerebral iron can be recycled through lysosomal degradation of iron-rich proteins and organelles. Impairment of this recycling, *e.g.* in lysosomal dysfunction, is another potential source of enhanced cerebral iron uptake [16,17].

Impaired cellular homeostasis of metals may initiate neurodegeneration through various mechanisms. Of these, oxidative stress induced by the formation of free radicals is the one best established. Increased amounts of 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde which are products of lipid peroxidation [18] have been found on post-mortem analysis of human brains from aceruloplasminemia patients [19]. Protein carbonyl groups and 8-oxo-7,8-dihydro-2-deoxyguanosine (8-oxdG) as markers of oxidative damage to proteins and DNA can be detected in tissue of various neurodegenerative disorders including AD [20–23]. Also, depletion of endogenous antioxidants such as glutathione has been documented in the substantia nigra of PD patients further supporting the role of oxidative stress in neurodegeneration [24].

Other possible mechanisms of iron toxicity are impaired production of metalloproteins, altered expression of proteins containing the regulatory iron responsive element (IRE) on their RNA [2], activation of microglial cells leading to inflammation [25], promotion of protein misfolding and aggregation [26–28] and triggering cell death by the novel iron-dependent pathway termed 'ferroptosis' [29–31]. Even though these processes were convincingly demonstrated *in vitro* and in animal studies, there is currently little direct evidence that they are causally involved in neurodegenerative processes as it occurs in humans. Several studies indicated that iron may co-localize with α-synuclein aggregates in Lewy bodies suggesting that iron may be involved in the protein misfolding process [32]. Accordingly, clinical severity was associated with the cerebral iron concentration estimated by MRI in several disorders. In PD, iron concentration in the SN correlated with disease severity assessed according to the Hoehn and Yahr Scale [33]. In multiple sclerosis, the striatal iron concentration was associated with clinical severity measured by the Expanded Disability Status Scale (EDSS) [34] and predicted clinical worsening over time [35]. Several cross-sectional MRI studies in healthy aging indicated that pallidal and putaminal iron concentrations were correlated with executive dysfunction and impairment of manual dexterity [36–38]. In this regard, a longitudinal MRI study showed that higher putaminal iron concentration in healthy older adults predicted faster shrinkage of this structure on follow-up examination strengthening the connection between iron content and degeneration in the putamen [39,40].

3. Iron chelation in neurodegenerative diseases

3.1. Aceruloplasminemia

Aceruloplasminemia is caused by a mutation in the gene coding for ceruloplasmin protein [12]. Systemic iron accumulation is a consequence of the lack of ceruloplasmin ferroxidase activity preventing the cellular iron efflux. Among the neurodegeneration with brain iron accumulation (NBIA) group of disorders, aceruloplasminemia is associated with the highest iron accumulation affecting liver, pancreas, retina and many brain regions including basal ganglia and cortex [41,42]. Brain iron accumulation, reaching values 5–10 times higher than normal levels [42], can frequently be detected even in presymptomatic subjects [43]. Since aceruloplasminemia is a rare orphan disease, effects of chelation therapy

Table 1
Studies examining effect of chelation therapy in aceruloplasminemia.

Study (year)	Duration of neurologic symptoms (yrs)	Age (yrs)	Medication (dose)	Treatment duration	Radiologic outcome	Clinical outcome
Miyajima et al. [48]	10	61	DFO-B (500 mg/twice wk)	10 mo	T2* increase in striatum/thalamus	Moderate improvement of blepharospasm and rigidity, no change of dysarthria and spasticity
Yonekawa et al. [55]	5	54	DFO-B (1000 mg/d)	6 wk	No change	Mild improvement of chorea and ataxia
Loreal et al. [56]	3	62	DFO-B (2000 mg/5 × wk)	12 mo	No change	n.a.
Haemers et al. [57]	2	59	DFO-B (2400 mg/d 5 × wk)	6 mo	n.a.	No improvement of cranial dystonia and gait instability
Mariani et al. [58]	asymptomatic	40	DFP (75 mg/kg/d) + DFO-B (20 mg/kg/d 5 × wk)	6 + 8 mo	No change	Remains asymptomatic
Skidmore et al. [50]	4	54	DFS (1000 mg/d)	3 mo	n.a.	Moderate improvement of gait and cognition, no change of spasticity
Finkenstedt et al. [45]	4; n.a.	47; 39	DFO-B (15–20 mg/kg/day)	3;5 mo	No change	No improvement of ataxia and parkinsonism
Hida et al. [54]	7	58	DFO-B (dose n.a.)	12 mo	n.a.	Mild improvement of gait and dyskinesias, no change in cognition
Pan et al. [49]	6	52	DFO-B (500 mg/wk)	4 yrs	10–30% R2* reduction in BG/SN	No improvement of cervical dystonia, tremor and cognitive disorder
Roberti et al. [52]	1; asymptomatic	57; 61	DFS (5–20 mg/kg/d)	16; 9 mo	No change	Improvement of behavioral changes; remains asymptomatic
Tai et al. [64]	asymptomatic	35	DFS (500–1000 mg/d)	2 yrs	No change	Remains asymptomatic
Suzuki et al. [51]	6	59	DFS (500 mg/d)	10 d	n.a.	Improvement of chorea and gait instability, no change of cognitive disorder
Lindner et al. [46]	asymptomatic	24; 39;43	DFS (4–15 mg/kg/d)	4 yrs	No change	All remain asymptomatic
Rusticeanu et al. [63]	asymptomatic	39	DFS (500 mg/d)	2 yrs	No change	Remains asymptomatic
Badat et al. [44]	asymptomatic	28	DFP (75 mg/kg/d) DFO-B 45 mg/kg/d	6 yrs	No change	Remains asymptomatic
Doyle et al. [61]	asymptomatic	20	DFS (dose n.a.)	18 mo	n.a.	Remains asymptomatic
Fasano et al. [62], Bove et al. [58]	asymptomatic	58	DFO-B (500 mg/d) DFP 2500 mg 2–7 d/wk)	10 yrs	No change	Remains asymptomatic

Abbreviations: d—day, wk—week, mo—month, yrs—years, n.a.—not available, BG—basal ganglia, SN— substantia nigra, DFP—deferiprone, DFO-B—deferoxamine, DFS—deferasirox.

were reported only in several case studies (Table 1). Deferasirox and deferoxamine treatments lead to serum ferritin normalization, decrease of hepatic and cardiac iron loading, and symptomatic improvement of anemia and diabetes in the majority of patients [44–47]. However, neurological outcomes of iron removal therapy are variable. Only two studies reported neuroimaging outcomes of chelation therapy based on quantitative MRI; both reported 20–30% decrease in iron concentration in the basal ganglia [48,49].

Several weeks to months treatment with deferasirox at a dose of 500–1000 mg/day led to neurological improvement in two cases [50,51] while no improvement after treatment lasting up to 48 months was reported in the majority of patients [45,52,53]. Similarly, treatment with intravenous deferoxamine up to 1000 mg daily led to partial improvement in several case studies [48,54,55] whereas other reports did not find any clinical improvement on doses up to 2400 mg given 2–5 times weekly [49,56,57]. Deferiprone at a dose of 75 mg/kg/day administered for six months failed to remove iron from tissues in one case study [58] while it prevented neurological symptoms from occurring in a long-term treatment of an asymptomatic case [59].

Even without a known family history, the majority of aceruloplasminemia patients can be diagnosed before the onset of neurological symptoms since type 1 diabetes mellitus and anemia typically precede the neurological manifestation by a median of 12 years [60]. This early identification of aceruloplasminemia

subjects enabled the exploration of effect of chelation therapy in the pre-neuro-symptomatic phase. Importantly, studies reported that these still asymptomatic individuals remained free of neurologic symptoms during follow-up lasting up to 10 years [44,46,58,59,61–64]. Lifelong iron chelation therapy may thus potentially prevent neurologic symptoms. However, no strong conclusions can yet be drawn, since several of the reported cases have not reached the expected age of neurologic symptoms.

3.2. Pantothenate kinase-associated neurodegeneration

Pantothenate kinase-associated neurodegeneration (PKAN) caused by a mutation in the *PANK2* gene is the most prevalent disorder from the NBIA group [5]. The affected gene codes for pantothenate kinase 2, a regulatory enzyme in coenzyme A synthesis, which is involved in cellular energy and lipid metabolism [65]. The underlying mechanism of iron accumulation as well as its role in the patophysiology are unknown [66]. In PKAN patients, iron is deposited focally in the globus pallidus (GP) reaching 3–4 times higher concentration compared to healthy subjects [67,68]. Iron deposits in the GP may be related to impaired energy metabolism. Specific neuropathological findings comprising ubiquitin and apolipoprotein-E enriched lesions in the GP were identified in PKAN patients and penumbrae of chronic lacunar infarcts of elderly subjects pointing towards a common pathophys-

iology of ischemia and PKAN [69]. Iron accumulation, neuronal death involving the accumulation of apolipoprotein-E, and cystic degeneration may thus be an unspecific consequence of chronic energy production impairment in the GP.

A phase-II pilot study with 25 mg/kg/day deferiprone treatment lasting six months showed no clinical benefit in nine PKAN patients despite 30% reduction of iron content in the GP as detected on MR imaging [70] (Table 2). Successful iron removal from the GP without concomitant clinical improvement may indicate either that irreversible damage has already occurred, or that iron is not the causative agent in PKAN. In another study 30 mg/kg/day deferiprone treatment led to clinical stabilization in four of five PKAN patients, persistent at a 4-year follow-up [71,72]. However, clinical stabilization may be a misleading outcome measure in PKAN patients since the clinical progression in the atypical (late onset) form is nonlinear with rapid deterioration in the first five years and relative stabilization after that [73]. Another case study reported a beneficial effect of 1000 mg/day deferiprone given in combination with baclofen (i.e. via a pump) in a PKAN patient [74]. Taken together, chelation therapy using deferiprone convincingly removes iron from GP; and, provided that early and long-term therapy is given, chelation may even be a promising approach to slow down or halt the progression of neurological symptoms in PKAN.

3.3. Other NBIA disorders

The clinical experience with chelation therapy in other forms of NBIA yielded mixed results so far (Table 3). Probably the first reported case of – at that time molecularly unspecified – NBIA did not improve after six months of deferoxamine treatment [75].

Neuroferritinopathy is a rare autosomal dominant disorder caused by a mutation in the _FTL_ gene [13]. It is characterized by low serum ferritin along with pathological iron deposits localized in various brain regions, namely GP, substantia nigra, putamen, caudate, dentate nucleus, and the cerebral cortex [76,77]. Brain iron deposition can be documented long before neurological symptoms appear [78]. In symptomatic patients with neuroferritinopathy, 4000 mg deferoxamine weekly over a period of 14 months, 2000 mg deferiprone for two months or regular monthly venesections for six months did not result in clinical improvement [79]. Monthly venesections also showed no effect in another case study [80]. Analogically to aceruloplasminemia, chelation therapy in neuroferritinopathy is advocated already in the presymptomatic phase given that iron deposition can be detected in the basal ganglia decades before the onset of clinical symptoms [81].

Mitochondrial protein-associated neurodegeneration (MPAN) is another disorder from the NBIA group caused by a mutation in the _C19orf12_ gene. Its physiological function and the mechanism of iron accumulation located into GP and SN are not entirely understood [82]. A case study reported no change in clinical status after chelation therapy with 30 mg/kg/day deferiprone lasting two years [83].

Patients with MRI-documented brain iron accumulation without mutations in genes known to cause NBIA are diagnosed as "idiopathic NBIA". Typically, the age-at-onset is later compared to other NBIA forms and focal siderosis is observed in the GP. Mild to moderate clinical benefit and stabilization during follow-up lasting 6–48 months was observed in 3 out of 4 documented idiopathic NBIA patients treated with 30 mg/kg/day deferiprone [71,72,84,85].

3.4. Friedreich's _ataxia_

FRDA is caused by a trinucleotide repeat extension or point mutations in a gene coding for the iron chaperone frataxin which is necessary for mitochondrial iron metabolism [86]. Pathological amounts of iron supposedly accumulate in the mitochondria

in FRDA, apparently leading to a deficiency of mitochondrial iron-sulphur cluster-containing proteins such as aconitase [87–90]. The respiratory chain electron transporters involving complex I–III are inhibited, resulting in decreased energy production and increased free radical formation [91] which may ultimately lead to oxidative stress-induced activation of the intrinsic apoptotic pathway [92]. Frataxin-deficient flies are hypersensitive to increased dietary iron uptake, but their mitochondrial function can be restored by inhibiting the mitochondrial iron uptake _via_ mitoferrin [93]. The most severely affected organs are heart, cerebellum, and spinal cord, especially dorsal root ganglia [94]. Abnormal iron granules were detected in cardiomyocytes in FRDA while the total iron concentration was not different from that of control cases [95]. Other post-mortem studies in fixed and frozen heart tissue documented increased iron concentration along with iron-reactive inclusions in cardiomyocytes of the ventricular septum and left ventricular wall [96,97]. Abnormal iron deposits were detected in the cerebellar dentate nuclei by some groups [98] while others could not confirm this finding [99] suggesting that iron quantification in dentate nuclei may not be a reliable biomarker in FRDA. Accordingly, no net iron increase was observed in dorsal root ganglia and cerebellar dentate nucleus, but microscopic evaluation suggested shifts in cellular iron localization in both structures [100,101].

The first open-label investigations on the efficacy of iron chelation in FRDA indicated that treatment with deferiprone 20 or 30 mg/kg/day may be beneficial (Table 4). Six month-treatment in nine adolescent patients reduced the iron content of the dentate nuclei. Iron removal was accompanied by moderate neurological improvement in speech fluency, hand dexterity, and ataxic gait. However, as little as 10% improvement in the International Cooperative Ataxia Rating Scale (ICARS) total score was documented, with best effects in the youngest patients. This normalization of iron concentration occurred relatively quickly, within two months after commencing deferiprone treatment. Iron removal was limited to the dentate nuclei, whereas other brain regions showed no significant change in iron accumulation over the period of chelation therapy, as detected by T2* relaxation time measurements [102]. In another open-label study, the effect of deferiprone 20 mg/kg/day together with the antioxidant idebenone was examined in 20 adolescent patients. While cardiac hypertrophy improved and iron concentration in the dentate nucleus significantly decreased after 11 months of treatment, as assessed by T2* relaxation time measurement, again no difference in the total ICARS score was observed. Examining individual items of the ICARS scale, significant recovery of kinetic functions occurred, although gait and postural scores worsened [103]. In a randomized controlled trial comparing deferiprone dosage ranging from 20 to 60 mg/kg/day for 6 months, those patients receiving the highest dose (60 mg/kg/day) had to be discontinued due to worsening of ataxia while the lower dose (40 mg/kg/day) improved cardiac parameters but also led to mild clinical worsening of ataxia. The lowest dose (20 mg/kg/day) improved cardiac parameters and had no effect on neurological symptoms as measured by Friedreichís Ataxia Rating Scale (FARS) and ICARS. Post-hoc subgroup analyses in patients with less severe disease suggested a possible benefit of deferiprone 20 mg/kg/day on ataxia and neurological function [104]. Yet another study examined the effect of a triple therapy comprised of 5–25 mg/kg/day deferiprone, idebenone, and riboflavin in 13 patients. There was no clinical improvement on the Scale for the Assessment and Rating of Ataxia (SARA), however a possible positive effect on disease progression was suggested [105]. To conclude, higher doses of deferiprone seem to worsen neurologic symptoms in FRDA; lower doses might be beneficial in younger patients with less severe disease. However, more evidence is needed.

Table 2
Studies examining effect of chelation therapy in PKAN.

Study (year)	Disease duration (yrs)	Number of patients (age- yrs)	Medication (dose)	Duration of treatment (months)	Radiologic outcome	Clinical outcome
Zorzi et al. [70]	4–25, median 11	9 (7–39, median 26)	DFP (25 mg/kg/d)	6	30% T2* increase in GP	No improvement
Pratini et al. [74]	10	1 (15)	DFP (1000 mg/d) + i.t. baclofen	12	n.a.	Moderate improvement of dystonia
Cossu et al. [71] Abbruzzese et al. [72]	6–27	5 (22–40)	DFP (30 mg/kg/d)	36–48	20–50% T2* increase in GP	Clinical stabilization of dystonia in 4 pts

Abbreviations: d—day, pts—patients, n.a.—not available, GP—globus pallidus, DFP—deferiprone.

Table 3
Studies examining effect of chelation therapy in other disorders from the NBIA group.

Study (year)	Type of NBIA	Disease duration (yrs)	Age (yrs)	Medication (dose)	Duration of treatment (months)	Radiologic outcome	Clinical outcome
Gallyas and Kornyey [75]	NBIA not specified	2	14	DFO-B (250 mg/d)	6	n.a.	No improvement
Chinnery et al. [79]	NFP	n.a.	n.a.	DFO-B (4 g/wk) DFP (2000 mg tid)	<14 2	n.a.	No improvement
Loebel et al. [83]	MPAN	6	13	DFP (15–30 mg/kg/d)	24	T2* increase in SN, no change in GP	No improvement
Abbruzzese et al. [72]	Idiopathic NBIA	9	65	DFP (30 mg/kg/d)	12	n.a.	No improvement
Cossu et al. [71] Abbruzzese et al. [72]	Idiopathic NBIA	7	52	DFP (30 mg/kg/d)	48	n.a.	Moderate improvement of dystonia and parkinsonism
Forni et al. [84]	Idiopathic NBIA	5	61	DFP (30 mg/kg/d)	6	Reduced T2 hypointensities in BG	Moderate improvement of chorea and gait instability
Kwiatkowski et al. [85]	Idiopathic NBIA	5	52	DFP (30 mg/kg/d)	32	T2* increase in SN/dentate nuclei	Moderate improvement of ataxia, dystonia and dysarthria

Abbreviations: d—day, n.a.—not available, BG—basal ganglia, GP—globus pallidus, SN—substantia nigra, MPAN—mitochondrial protein-associated neurodegeneration, NFP—neuroferritinopathy, NBIA—neurodegeneration with brain iron accumulation.

Table 4
Studies examining effect of chelation therapy in Friedreich's ataxia.

Study (year)	Number of patients	Medication (dose)	Duration of treatment (months)	Radiologic outcome	Clinical outcome
Boddaert et al. [102]	9	DFP (20–30 mg/kg/d)	6	T2* increase in ND	Improvement in ICARS, worsening of gait and balance
Velasco-Sánchez et al. [103]	20	DFP (20 mg/kg/d) + idebenone (20 mg/kg/d)	11	T2* increase in ND	Improvement in ICARS, worsening of gait and balance
Pandolfo et al. [104]	72	DFP (20,40,60 mg/kg/d)	6	n.a.	No change of FARS in the 20 mg/kg/d arm, worsening in FARS and ICARS in the 40 mg/kg/d arm
Arpa et al. [105]	13	DFP (5–25 mg/kg/d) + idebenone (10–20 mg/kg/d) + riboflavin (10–15 mg/kg/d)	15–45	n.a.	No improvement in SARA, possible slowing of disease progression

Abbreviations: d—day, n.a.—not available, DFP—deferiprone, ND—nucleus dentatus, ICARS—International Cooperative Ataxia Rating Scale, FARS—Friedreichís Ataxia Rating Scale, SARA—Scale for the Assessment and Rating of Ataxia.

3.5. Superficial siderosis

Superficial siderosis (SupSid) of the CNS is a progressive neurodegenerative disease caused by consecutive subarachnoid extravasation of blood leading to hemosiderin deposition on pial surfaces of the CNS. The concentration of iron in siderotic tissue may be increased by a factor of 2–14 and ferritin protein by a factor 20–30, particularly in the cerebellar cortex [6]. Increased iron and ferritin levels are detectable also in the cerebrospinal fluid (CSF) [106] and may be thus helpful for monitoring the chelation therapy [107]. The most common etiologies underlying SupSid include trauma, previous surgical procedures, dural tears, and CNS tumors [108]. The preferred treatment option is the elimination of the bleeding source, which, however, sometimes cannot be identified. Notably, even after the bleeding source has been ablated progressive worsening of symptoms may continue. Among cases without apparent bleeding source a proportion was associated with cerebral amyloid angiopathy pointing towards an interesting connection between AD and iron accumulation [109,110].

Ineffectiveness of deferoxamine was mentioned in several pioneering case reports [111,112]. In a 65 year-old patient with SupSid from an unknown source, who was followed for more than three years after initiation of deferiprone, a significant reduction of hemosiderin deposits in the cortex and cerebellum was seen,

Table 5
Studies examining effect of chelation therapy in superficial siderosis of the CNS.

Study (year)	Disease duration (yrs)	Number of patients	Medication (dose)	Duration of treatment (months)	Radiologic outcome	Clinical outcome
Levy and Llinas [117]	12 [3–20]	10	DFP (30 mg/kg/d)	3	Reduced T2 hypointensities in 4	Improvement in 4, no change in 4, worsening in 2
Levy and Llinas [113,114]	1	1	DFP (15–30 mg/kg/d)	38	Reduction of hemosiderin deposits in cortex and cerebellum	Improvement of ataxia and hearing loss
Cummins et al. [115]	5	1	DFP (3 g/d)	6	No change	Improvement of ataxia
Huprikar et al. [116]	6	1	DFP (2 g/d 5x/wk)	4	No change	Improvement of ataxia
Schirinzi et al. [107]	5	1	DFP (30 mg/kg/d)	3	No change	Improvement of stance and speech

Abbreviations: d—day, wk—week, DFP—deferiprone.

together with a resolution of hearing loss and ataxia [113,114] (Table 5). Improvement after several months of deferiprone therapy was also documented in two other case reports of SupSid [115,116] while worsening was observed after discontinuation of the chelating drug in another one [107]. A similar beneficial clinical effect was also reported for trientine, which is a copper and iron chelating drug [106]. The safety and neuroradiological outcomes of iron removal treatment in SupSid were studied in an open-label trial of 30 mg/kg/d deferiprone administered for 3 months. Reduction of hemosiderin deposits on follow-up MRI was apparent in four out of 10 patients. In a telephone assessment of the clinical effects, four patients reported subjective improvement, four reported no change, and two reported subjective worsening [117]. Thus, some improvement of neurological symptoms in SupSid seems to occur provided a BBB crossing chelating agent is used over an aedequate time period.

3.6. Parkinson's and Alzheimer's diseases

Disturbances of the cerebral iron metabolism have been documented not only in rare disorders, such as NBIA or SupSid, but also in common sporadic neurodegenerative disorders such as PD and AD. This observation triggered interest in iron chelation therapy for these disorders [118] (Table 6). In PD, iron levels in the substantia nigra pars compacta (SNpc) are increased by a factor of 1.5–2, but are not altered in other brain regions [119]. This increase can clearly be detected in vivo by MRI when the SNpc is segmented. Notably, quantitative susceptibility mapping appears to be more sensitive for iron estimation in the SNpc than R2* transverse relaxivity measurement [120–124]. At the microscopic level, iron deposits in the SNpc are associated with neuromelanin granules in dopaminergic neurons [125], Lewy bodies [32], and activated microglial cells [126]. Enhanced diffuse iron staining is also apparent in the neuropil of the SN [127].

There are many possible interactions between iron dysregulation and neurodegenerative changes in PD. Inhibition of the ubiquitin-proteasome system may lead to dysfunction of the iron regulatory protein 2 (IRP2) and subsequent upregulation of the transferrin receptor (TfR1) and downregulation of ferritin heavy chain as documented in a lactacystin cell model of PD [128]. Iron also interacts with α-synuclein at several levels: (1) it may enhance the translation of α-synuclein mRNA via IRE located at the 5′-untranslated region [129,130], (2) by binding to the α-synuclein protein itself, iron may trigger α-synuclein misfolding and fibril formation, and (3) iron indirectly contributes to α-synuclein aggregation via the triggering of lipid peroxidation. Additionally, α-synuclein is a putative ferrireductase and its overexpression significantly increases cellular ferrous iron possibly enhancing oxidative stress [131]. Iron-laden extracellular neuromelanin released from dying neurons may activate microglia

and trigger chronic neuroinflammation that further stimulates iron accumulation [132,133].

A randomized controlled trial employing the delayed paradigm indicated a possible disease modifying effect of deferiprone 30 mg/kg/day in PD. T2* relaxation time was determined, motor scores were analyzed, and markers of oxidative stress were measured in the CSF. Results indicated that the early start group (who started deferiprone six months earlier) had a slower disease progression on the 18 month-follow up visit as documented by a 2.4 points lower motor score in the Unified PD Rating Scale (UPDRS-III). Additionally, iron content in the SN, as well as malonaldehyde, carbonyl-proteins and 8-oxdG in the CSF were significantly decreased compared to baseline [134]. Patients with lower ceruloplasmin activity in the CSF appeared to respond better to iron chelation suggesting that ceruloplasmin may modify the response to deferiprone treatment in PD [135].

AD patients have abnormal iron distribution in cortical and subcortical areas including the hippocampus [136]. While total cortical iron levels may be unaltered in AD [137], post-mortem MRI and histopathological studies showed that increased iron levels are associated with amyloid-beta (Abeta) plaques [138,139], vessel walls, and microglia [140]. One of the possible sources of iron in AD are microbleeds related to cerebral amyloid angiopathy [141]. This hypothesis is supported by increased CSF ferritin in AD patients [142] that is associated with progressive cognitive decline [143]. Iron may upregulate amyloid precursor protein expression; it can also bind to amyloid formations and facilitate their fibrillation. On the other hand, Abeta is capable of reducing ferrihydrite to ferrous ion [144,145].

A single-blind study exploring the efficacy of deferoxamine showed a significant reduction in cognitive decline after 24 months in the active group [146]. Clioquinol (PBT1), a hydroxyquinoline drug with iron, copper, and zinc chelating properties, did not significantly alter the disease progression in a placebo-controlled phase 2 trial. On the other hand, the post-hoc analysis including only the more severely affected patients indicated slowing down of the cognitive deterioration in this subgroup of AD patients [147]. Clioquinol derivative, designated as PBT2, was examined in a 12-week randomized controlled trial with 78 patients. The primary goal was to assess the safety profile and PTB2 was reported to be safe and well-tolerated. Exploratory investigation of clinical effects showed no differences on the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog) and Mini-Mental State Examination (MMSE) between the active and placebo arm. Significant improvement was documented only in two executive function tests, i.e. category fluency test and the trail making test B [148]. However, the post-hoc receiver-operator characteristic analysis indicated that the probability of improvement at any level was significantly higher in the group taking 250 mg PBT2 [149]. In summary, based on the available data there is still insufficient evidence

Table 6
Studies examining effect of chelation therapy in common sporadic disorders.

Study (year)	Type of disease	Number of patients	Medication (dose)	Duration of treatment (months)	Radiologic outcome	Clinical outcome
Devos et al. [134]	PD	40	DFP (30 mg/kg/d)	12	R2* decrease in SN	Slowing of UPDRS progression
McLachlan et al. [146]	AD	48	DFO-B (250 mg/5×/wk)	24	n.a.	Decreased rate of ADL decline
Ritchie et al. [147]	AD	36	PBT1 (250–750 mg/d)	9	n.a.	Decreased rate of ADAS-cog worsening in severely affected group only
Lannfelt et al. [148]	AD	78	PBT2 (50–250 mg/d)	3	n.a.	No difference in ADAS-cog or MMSE; improvement in category fluency test and trail making test B
Norstrand and Craelius [172]	MS	12	DFO-B (20–30 mg/kg/d for 5d/wk)	3	n.a.	5 improved, 6 unchanged, 1 worsened in EDSS
Lynch et al. [173]	MS	18	DFO-B (1–2 g/d)	0.5	n.a.	12 unchanged or improved/6 worsened in EDSS at month 12
Lynch et al. [174]	MS	9	DFO-B (1–2 g/d for 2 wks)	2wk courses repeated á 3 months for 2 yrs	n.a.	1 improved, 3 unchanged, 5 worsened in EDSS

Abbreviations: d – day, wk – week, yrs – years, n.a. – not available, DFP – deferiprone, DFO-B – deferoxamine, PBT1 (clioquinol) – first generation metal protein attenuating compound, PBT2–second generation metal protein attenuating compound based on clioquinol, PD – Parkinson's disease, AD – Alzheimer's disease, MS – multiple sclerosis, SN – substantia nigra, UPDRS – Unified Parkinson's disease rating scale, ADAS-cog – Alzheimer's Disease Assessment Scale- Cognitive Subscale, MMSE – Mini-Mental State Examination, ADL – activities of daily living.

of a disease-modifying effect of iron chelation in AD. Pilot trials in PD are promising, but more evidence is needed at the moment.

3.7. Multiple sclerosis

In multiple sclerosis (MS) patients MRI and histological studies have demonstrated global alterations in brain iron levels. Increased iron concentration was documented in the white matter lesions and deep gray matter structures [150–155]. Iron accumulates in the basal ganglia already in the very early stage of MS, *i.e.* in clinically isolated syndrome [35,156,157]. Iron concentration in the basal ganglia, mostly in the putamen and caudate nucleus was associated with increased disability and cognitive dysfunction [34,158,159]. In MS plaques, increased iron concentration either in the peripheral rim or diffusely within the lesion has been documented in the subacute stage of the lesion evolution. Longitudinal MRI studies show that iron is not present in the acute contrast-enhancing stage, but then iron gradually accumulates over several weeks to months and eventually disappears in the chronic stage, approximately four years after the lesion originated [160–162].

At the microscopic level, iron overload is evident in macrophages in white matter lesions and the basal ganglia [163,164]. Microglia and macrophages may serve as iron donors for oligodendrocytic progenitor cells which are responsible for remyelination [165,166]. On the other hand, excessive iron concentration in macrophages may promote a pro-inflammatory M1 activation state and facilitate inflammation [167]. In an animal model of cerebral iron overload, expression of several NBIA-related proteins involved in phospholipid and myelin metabolism was decreased suggesting that iron accumulation may influence myelin synthesis and maintenance [168]. Several studies showed that chelators ameliorate experimental autoimmune encephalomyelitis which is an animal model of MS. These promising results triggered interest in examining iron removal therapy in MS patients [169–171].

The first chelation study in MS investigated the effect of 20–30 mg/kg/day deferoxamine administered over a period of three months in 12 advanced MS patients; five of whom clinically improved, symptoms in six remained unchanged, and worsened in one [172] (Table 6). A pilot trial examined 19 patients with primary progressive and secondary progressive MS on a two-week course of 1–2 g deferoxamine. Of these at the three month follow-up, symptoms had remained unchanged or slightly improved in 16 patients, while two patients had deteriorated on the EDSS. One patient dropped out of the trial: the drug had to be discontinued due to side effects. On follow-up after 12 months, 12 patients were stable or had improved while six had deteriorated [173]. In another trial with two-week courses of deferoxamine repeatedly given every three months over a total period of two years in nine patients with primary progressive or secondary progressive MS, five patients worsened, three remained stable, and one improved, suggesting that iron chelation may not be very efficient in MS [174]. However, only severely-affected patients were included into these studies and there were no control groups (*i.e.* MS patients not taking chelation therapy). Thus, in the absence of decent comparison to the natural progression of the disease, no definite conclusions can be drawn from the studies with regards to the effect of iron chelation therapy.

4. Concluding remarks

While MRI studies show compelling evidence for the potential of iron chelating drugs to remove accumulated iron in neurodegenerative disorders, their effect on clinical symptoms seems to be behind expectations. At best, only moderate improvement was reported in individual patients, and it was not comparable to the effect of copper chelation therapy seen in WD. In WD, despite cerebral copper concentrations are increased 5–10 fold [175–177], 3–12 months of chelating drug treatment lead to marked improvement of neurological symptoms in 70–80% patients [178]. Even in disorders with extensive diffuse cerebral iron deposits such as aceruloplasminemia, neuroferritinopathy, and SupSid, effects of chelation therapy occur at a much lower level. Only in SupSid, several case studies documented clear improvement suggesting that iron chelation can reverse symptoms in this disorder.

On the other hand, several data indicate that iron chelation may slow down disease progression or even prevent the occurrence of neurological symptoms when initiated in the presymptomatic stage. This disease-modifying effect was indicated by several studies in aceruloplasminemia and other disorders with focal siderosis such as PKAN and PD. Overall, these results suggest that the mechanisms underlying copper and iron toxicity are different. While it seems that copper confers acute but reversible toxicity to the BBB and oligodendrocytes, the brain has better compensatory mechanisms to buffer iron accumulation and deal with its acute toxicity. However, chronic iron deposits may, in the long run, accelerate neuronal degeneration and thus cause delayed neurological symptoms that are already irreversible when they appear. In line with this hypothesis, future trials employing chelating drugs should include young patients with a short disease duration or, ideally, individuals in the presymptomatic stage.

It is unclear in how far different chelating compounds may differ with regards to their efficacy. Deferiprone is currently the drug of the choice in the majority of trials in neurodegenerative disorders since its molecular structure allows crossing lipid membranes and acting intracellularly beyond the BBB [179]. On the other hand, deferoxamine was also shown to reduce abnormal brain iron deposits in aceruloplasminemia despite it does not readily cross the BBB [48,49] suggesting that the capability of crossing biological membranes is not necessary for brain iron removal. It is thus possible that the two agents have different pools of chelation: deferiprone may chelate intracellularly whereas deferoxamine may operate in the extracellular space [180]. In this regard, benefits of combined chelation therapy have been documented in patients with systemic iron accumulation in whom monotherapy may not always attain optimal control. Indeed, combined chelation therapy with deferoxamine and deferiprone at doses lower than normally used, efficiently removed iron from thalassemic patients, indicating a potentiation of the iron chelation efficiency [181]. The oral deferoxamine-deferiprone combination has been reported to be safe and efficacious in thalassemic patients with suboptimal response to monotherapy [182]. Consequently, combined chelation therapy may be beneficial also in several NBIA disorders, especially in heavily iron-loaded patients.

While NBIA syndromes and SupSid are very rare diseases, the possibility of iron chelation therapy is particularly appealing in common sporadic disorders, such as PD, AD or MS. Accounting for only small and focal iron increase in many neurodegenerative disorders, conservative modes of iron chelation and redistribution have been proposed utilizing a low dose regimen of chelators. The aim is to clear focal siderosis from aberrant labile iron pools, redeploying it to physiological cell acceptors or transferrin without interfering with essential local functions or with hematological parameters. Iron chelating drug suitable for this purpose will need to be able to cross cellular membranes and act as a "shuttling" agent [180,183]. Results from large ongoing randomized controlled trials examining disease modifying effects of iron chelation in PKAN (http://tircon.eu) [184] and PD (http://fairpark2.eu) are expected in the next few years. These results may stimulate further development of iron chelators with desired properties.

Conflicts of interest

Authors report no conflicts of interest.

Acknowledgements

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