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Review

Neurodegeneration with brain iron accumulation — Clinical syndromes and neuroimaging ☆

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ABSTRACT

Iron participates in a wide array of cellular functions and is essential for normal neural development and physiology. However, if inappropriately managed, the transition metal is capable of generating neurotoxic reactive oxygen species. A number of hereditary conditions perturb body iron homeostasis and some, collectively referred to as neurodegeneration with brain iron accumulation (NBIA), promote pathological deposition of the metal predominantly or exclusively within the central nervous system (CNS). In this article, we discuss seven NBIA disorders with emphasis on the clinical syndromes and neuroimaging. The latter primarily entails magnetic resonance scanning using iron-sensitive sequences. The conditions considered are Friedreich ataxia (FA), pantothenate kinase 2-associated neurodegeneration (PKAN), PLA2G6-associated neurodegeneration (PLAN), FA2H-associated neurodegeneration (FAHN), Kufor-Rakeb disease (KRD), aceruloplasminemia, and neuroferritinopathy. An approach to differential diagnosis and the status of iron chelation therapy for several of these entities are presented. This article is part of a Special Issue entitled: Imaging Brain Aging and Neurodegenerative disease.

1. Brain iron

Iron is critical for normal neuroembryogenesis and physiology and participates in a wide spectrum of cellular functions including cytokinesis, myelination, electron transport, antioxidant enzyme activity and biogenic amine metabolism [1]. While allowing for this bioversatility, the electronic properties of this transition metal enable iron to take part in chemical reactions that may be injurious to neural and other cellular substrates. Iron plays a pivotal role in cellular redox chemistry by reducing H_2O_2 to the highly-cytotoxic hydroxyl ($OH^{\bullet}$) radical (Fenton catalysis) or by behaving as pseudoperoxidase activity that bio-activates benign compounds (e.g. catechols) into toxic free radical intermediates. Various biochemical and physiological characteristics of the mammalian CNS render it particularly vulnerable to iron- and redox-related damages. Some of the more important of these are (i) the robust flux of molecular oxygen in normally-respiring neural tissues, (ii) excessive generation of reactive oxygen species (ROS) by effete mitochondria in aging post-mitotic neurons, (iii) susceptibility of the CNS to lipid peroxidation accruing from its high cholesterol and unsaturated fat ($C_{20:5}$, $C_{22:6}$) content, (iv) the abundance of oxidizable (e.g. dopamine, kynurenine) and potentially-excitotoxic (glutamate) neurotransmitters, and (v) a relative dearth of certain antioxidant defenses [2]. Iron homeostasis in peripheral and neural tissues is tightly regulated by a panoply of proteins controlling its absorption, extracellular transport, cellular flux, signaling activities, valence configuration, and intracellular storage [3–8]. The CNS maintains strict and fairly autonomous control of its chemical microenvironment and the blood–brain barrier (BBB) precludes free flux of transferrin, ferritin, ceruloplasmin and other iron-regulating proteins from the systemic circulation to the CNS. Cerebrovascular endothelial cells at the BBB bind circulating diferric transferrin and the resulting complexes are internalized. After dissolution of the complexes within endothelial endosomes, apotransferrin is recycled to the blood and iron is exported across the abluminal membrane, likely via ferroportin, to the interstitial space [8,9]. Despite this meticulous control, iron progressively accumulates in the mammalian CNS as a function of advancing age, and a portion of the metal in the brain parenchyma and cerebrospinal fluid (CSF) remains redox-active. Within the normal human CNS, the iron is preferentially sequestered in the basal ganglia, hippocampus, certain cerebellar nuclei and other, largely subcortical, brain regions. Within the diseased CNS, iron-derived ROS may facilitate pro-toxin bioactivation; aberrant cell signaling, bioenergetic failure; proteosomal dysfunction, protein aggregation and inclusion formation; electrophysiological derangements; and synaptolysis, apoptosis and necrosis [10].

Pathological iron deposition and attendant oxidative stress (OS) occur and may constitute an important therapeutic target in a host of

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Table 1
Neurodegeneration with brain iron accumulation (NBIA).

Friedreich ataxia (FA)[a]
Pantothenate kinase-associated neurodegeneration (PKAN)
Phospholipase A2G6-associated neurodegeneration (PLAN)
Fatty acid 2-hydroxylase associated neurodegeneration (FAHN)
Kufor-Rakeb disease (KRD)
Aceruloplasminemia
Neuroferritinopathy

[a] Not a classic NBIA syndrome (see text).

genetic and acquired human neurological disorders. This article focuses primarily on the clinical and neuroimaging aspects of a group of heritable conditions known collectively as 'neurodegeneration with brain iron accumulation (NBIA)' (Table 1). Interested readers are referred elsewhere for detailed accounts of the molecular pathology of these entities [8,11] and discussion of the acquired conditions manifesting secondary CNS iron overload (Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, multiple sclerosis, progressive supranuclear palsy, corticobasal degeneration, superficial siderosis, etc. [10,12–15]).

2. Iron neuroimaging

Magnetic resonance imaging (MRI) is sensitive to the presence and concentration of non-heme iron in the living human brain and is currently the modality of choice for the investigation and differential diagnosis of NBIA syndromes. Iron deposits in brain and other tissues cause local magnetic field inhomogeneities with decreased T2 (transverse) relaxation time and as a result appear hypointense (dark or low signal) on T2-weighted and T2* images, particularly at higher field strengths [15–17]. Various pulse sequences have been employed to visualize tissue iron, including spin echo, fast spin echo, and gradient echo (GE) techniques (Fig. 1). Two commonly used and accepted methods for estimating brain iron on MRI are the field dependent relaxivity increase (FDRI) method and calculations based on susceptibility weighted imaging (SWI). The FDRI method is based on the increase in the transverse relaxivity rate ($R2 = 1/T2$) with increasing field strength. Spin echo acquisitions are performed at two different field strengths (originally, 0.5 T and 1.5 T and more recently 1.5 T and 3.0 T). The repeated measurements obtained across two magnetic field strengths are then used for calculation of FDRI which has been shown to correlate with tissue iron stores [18–20]. SWI is based on the determination of local field inhomogeneities resulting from the influences of ferritin iron and other paramagnetic substances on the product of signal amplitude and a filtered version of the signal phase at a given field strength and echo time [20]. SWI obviates the requirement for scanning at multiple field strengths, an advantage over FDRI [21,22]. On the other hand, although heme iron (deoxygenated hemoglobin) affects both R2 and phase and can confound precise ascertainment of non-heme iron (ferritin, hemosiderin) levels, the impact on SWI is substantially stronger. Indeed, the robust contrast between gray and white matter on GE imaging of cerebral cortex may be due, at least in part, to the greater blood volume of gray matter. SWI is also more prone to distortion by air/bone/tissue interfaces and structural topography relative to the magnetic field [23].

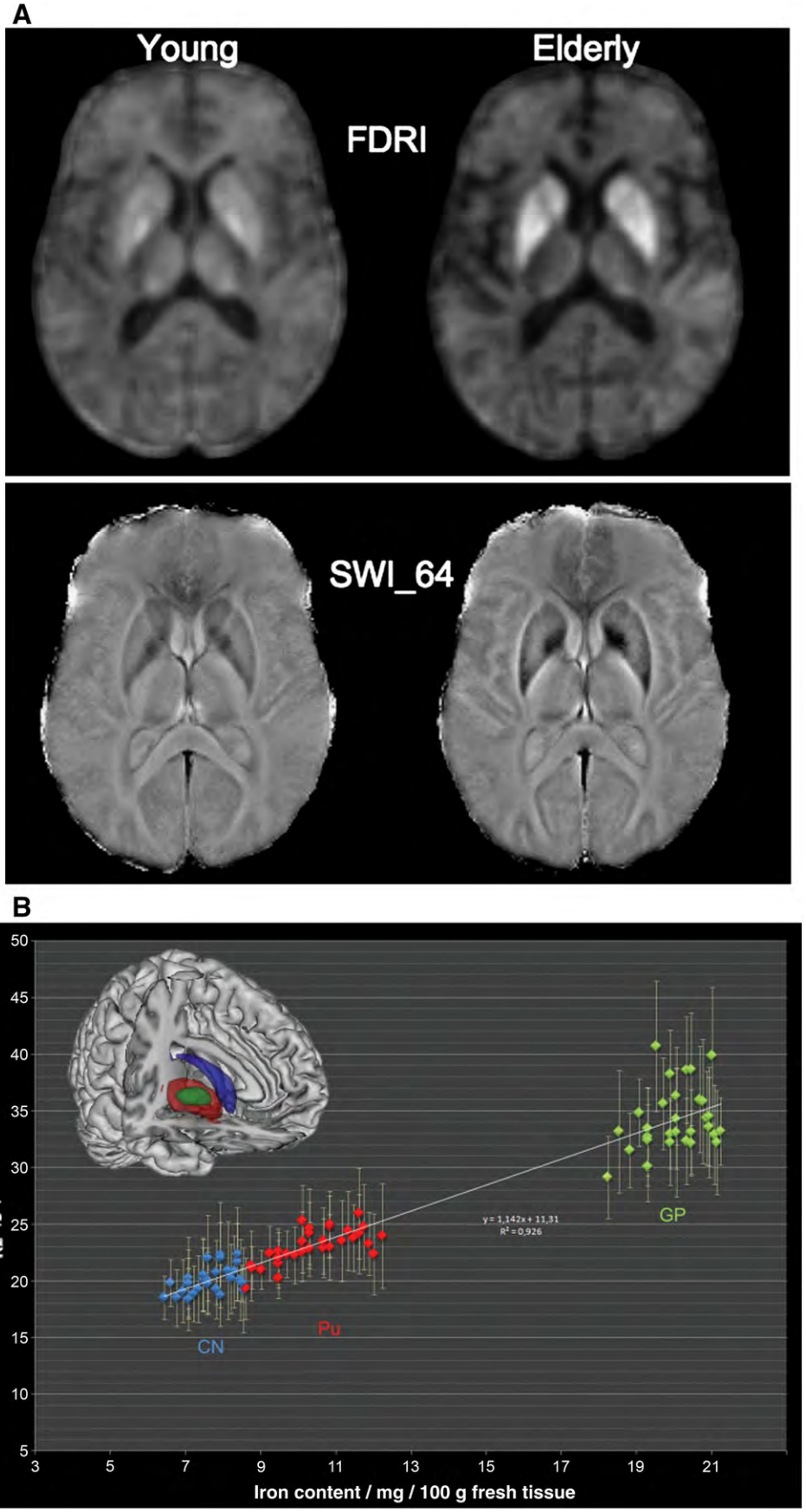
Importantly, studies of healthy volunteers and subjects with PD have revealed linear relationships between the relaxation rates, R2 and R2* ($R2^* = 1/T2^*$) and regional brain iron concentrations [19,20,24,25] estimated from earlier postmortem studies [26] (Fig. 1). In a recent study of normal aging [20], high concentrations of iron in the globus pallidus were detected at all ages and putaminal iron proved to be reliable biomarker of advancing age by both FDRI and SWI. Overall, FDRI appeared more sensitive than SWI for measurement of tissue iron across multiple brain regions. On the other hand, the high spatial resolution afforded by SWI may render this technique particularly appropriate for determination of subtle intra-regional variations (e.g. hemosiderin deposits within small infarcts) in given individuals followed longitudinally with serial scans [20,27]. In a second report [28], the mean relaxation time (T2*) of the putamen (along with thalamic volume and mean diffusivity) was found to be the best predictor of physiological aging in healthy human brain. Importantly, aging-related calcification of basal ganglia and other neural structures may also generate T2/T2* hypointensities and thereby confound iron measurements. However, MRI signals attributed to these minerals can be differentiated because calcifications similarly impact T1 (longitudinal) relaxation times whereas iron deposits do not [29].

Further refinements in MRI techniques to assess brain iron, e.g. measurement of the relaxometry parameter, T2 rho and magnetic field correlation (MFC) imaging, are largely experimental [15] and beyond the scope of this review.

Brain iron stores may also be interrogated using non-MRI modalities, such as transcranial sonography (TS) which yields hyperechoic signals in regions of tissue metal sequestration. TS has been systematically applied to detect excess midbrain iron in Parkinson disease and dementia with Lewy bodies [30,31]. However, this approach suffers from several shortcomings including relatively poor spatial resolution, confinement of imaging to certain brain regions, inadequate insonation of temporal bone windows in a proportion of subjects, and the possibility that factors other than iron, e.g. gliosis [32], may contribute to the observed hyperechogenicity. The use of TS in NBIA is briefly alluded to in Section 3.5. Examples of pathological MR neuroimaging in patients with NBIA are presented throughout the remainder of this article, and the importance of this technology in the clinical investigation and differential diagnosis of the NBIA syndromes is emphasized.

3. Neurodegeneration with brain iron accumulation

NBIA encompasses a growing constellation of heritable disorders resulting from diverse molecular pathologies. Friedreich ataxia (FA) is not classically grouped with the NBIA. However, we elected to include this important entity here because (i) the exclusion of FA from the NBIA is rather arbitrary and based on historical precedent; as in the case of the 'classical' NBIA, FA is a genetic, progressive neurodegenerative condition featuring prominent iron deposition in brain; (ii) imaging of brain iron is a central theme of this review and several recent reports of *changing* iron signals in FA cerebellum following chelation therapy (see below) are pivotal to the current discussion; and (iii) the reported clinical benefits of iron chelators and antioxidants in FA may inform the management of the notoriously refractory 'classical' NBIA syndromes. Before considering the NBIAs individually, there are some general concepts and characteristics worthy of mention which apply to this group of disorders: (i) in some instances, the implicated mutations directly impact the structure-function of proteins known to participate in tissue iron homeostasis. Prime examples of this are mutant frataxin in Friedreich ataxia (FA) and L-ferritin in neuroferritinopathy. In other cases, as in pantothenate-kinase 2-associated neurodegeneration (PKAN), the link between the protein abnormality and the development of NBIA remains unknown or conjectural. (ii) With the exception of FA, the NBIAs are rare conditions which many practicing pediatric and adult neurologists may encounter infrequently, if at all, outside of a tertiary referral center. On the other hand, the increasing availability of MRI and genetic testing is anticipated to bring more cases of established and novel NBIA syndromes to medical attention. (iii) The vast majority of NBIA cases feature extrapyramidal and/or cerebellar signs (involuntary movements and incoordination) at some point in their natural history and corresponding abnormalities in the basal ganglia and cerebellum on neuroimaging. This may be commensurate with the fact that the basal ganglia, red nuclei and cerebellar dentate nuclei are regions naturally predisposed to the accumulation of iron in the


A
Young
Elderly
FDRI
SWI_64
B
R2* /s-1
Iron content / mg / 100 g fresh tissue
y = 1,142x + 11,31
R² = 0,926
CN
Pu
GP

course of normal development and aging. The regulatory mechanisms governing the remarkably heterogeneous distribution of iron in the normal mammalian neuraxis are enigmatic. (iv). Although a number of NBIA syndromes present in childhood or early adulthood (e.g. FA, PKAN), others may remain asymptomatic until midlife or later (e.g. aceruloplasminemia). The latter suggests that, akin to conditions such as familial Alzheimer disease, normal CNS aging and/or environmental triggers may be required to 'unmask' the primary genetic defect. (v) While some NBIA syndromes target the CNS almost exclusively (e.g. PKAN), others exhibit substantial involvement of peripheral tissues (e.g. aceruloplasminemia). Contrariwise, hereditary hemochromatosis, a systemic disorder of body iron homeostasis, may promote little or no excess iron deposition within the CNS [8] while pathological iron stores in the liver and other organs may be sufficient to trigger airport metal detectors [33]! An appreciation of this clinical variability is vital to the establishment of correct diagnoses and further underscores the fact that the regulation of brain iron metabolism is, in large measure, distinct from that in peripheral tissues. (vi) Even within kindreds, clinical manifestations of NBIA may vary substantially in severity and tempo among affected individuals. Sadly, these diseases tend to be relentlessly progressive and are inevitably fatal. (vii) As a rule, the NBIAs are notoriously refractory to definitive therapy, although certain interventions (e.g. baclofen for spasticity; deep brain stimulation for tremor) may afford significant symptomatic relief in select patients. Treatment with clinically-approved iron chelators (e.g. deferoxamine, which exhibits limited blood–brain barrier penetrability) have rarely yielded significant benefits and may be fraught with complications. There is even the theoretical concern that mobilization of brain iron, even if pharmacologically achievable, might expose hitherto protected neural substrates to the metal's toxic effects and thereby exacerbate the condition. Still, recent advances in the delineation of the molecular mechanisms responsible for the neurodegenerative processes, and the advent of orally-bioavailable, brain-permeant metal chelators (e.g. deferiprone) and antioxidants, offers hope that rational and effective therapy for NBIA may be forthcoming.

3.1. Friedreich ataxia

Friedreich ataxia is an autosomal recessive neurodegenerative condition and the most common of the heritable human ataxias. The pathology is characterized by degeneration within the spinocerebellar and pyramidal tracts, dorsal columns of the spinal cord, dorsal root ganglia, and, to a lesser degree, the cerebellum and medulla [34]. Clinical manifestations generally become apparent before age 25 and include progressive dysarthria, gait and limb ataxia (incoordination), areflexia, loss of proprioception and vibration sense, pes cavus, diabetes mellitus and hypertrophic cardiomyopathy. The latter may give rise to secondary neurological morbidity (e.g. thromboembolic cerebral infarction) and may be the cause of premature death in these patients [32]. Iron accumulates in the brain (cerebellar dentate nuclei; Fig. 2A) and myocardium and can be visualized by MRI and histochemical stains (ferric ferricyanide/Prussian blue) [35–37]. Of note, the restless leg syndrome (RLS) may be over-represented and correlate with low circulating ferritin concentration in FA patients. Evidence of altered brain iron homeostasis in both conditions may suggest intersecting pathophysiologies at the cellular/molecular level [38].

The defective gene in this disease is *FRDA* (encoded by a nuclear gene) which codes for frataxin, a mitochondrial protein. Frataxin is normally highly expressed in mitochondria-rich tissues such as brain, heart, and skeletal muscle where it may assist in the assembly or export of Fe–S clusters from mitochondria, heme biosynthesis and mitochondrial iron storage [32,39]. Cells from FA patients exhibit a marked reduction in frataxin levels usually accruing from an expansion of a GAA trinucleotide repeat in intron 1 [35,40], intramitochondrial iron trapping, and defective aerobic respiration [39]. A detailed account of the pathomolecular effects of mutant frataxin and its yeast homolog, Yfh1p has recently been published [8] and will not be recapitulated here.

3.1.1. Treatment of Friedreich ataxia

Oral administration of the respiratory chain antioxidant, coenzyme Q and its congener, idebenone, has been shown to improve certain cardiac indices in FA, but the impact of these agents on the neurological aspects of the disease has thus far been negligible [41,42]. A ray of optimism emerged in 2007 from a phase 1–2 study in which the orally-active, membrane permeant iron chelator, deferiprone (3-hydroxy-1,2-dimethylpyridin-4-one) was administered to nine adolescent FA patients with no overt cardiomyopathy [43]. Following a 6-month treatment period with 20 to 30 mg/kg/day, MRI revealed a significant reduction in the mean R2* signal in the cerebellar dentate nuclei (Fig. 2B), an index of tissue iron stores (see Section 2). Moreover, the investigators reported a clinically-meaningful amelioration of peripheral neuropathy and ataxic gait in the youngest patients, without evidence of significant adverse hematological or neurological effects. In a more recent study [44], idebenone and deferiprone (each at 20 mg/kg/day) were administered to 20 FA patients (ages 25–81) for 11 months. The therapeutic responses were variable, but significant improvement in kinetic functions and in dentate nucleus iron deposition (determined by MRI T2* values) was observed, respectively, in 13 and 14 subjects.

3.2. Pantothenate kinase-2-associated neurodegeneration

Pantothenate kinase-2-associated neurodegeneration (PKAN; a.k.a. NBIA-1; formerly Hallervorden–Spatz syndrome) is an autosomal recessive disorder characterized by mutations in the gene encoding a mitochondrial pantothenate kinase (*PANK2)* at locus 20p13-p12.3 [45–47]. The prevalence of PKAN is approximately 1–3 per million [48]. Most PKAN patients present in childhood or young adulthood with combinations of dystonia, parkinsonism, dysarthria, spasticity, seizures, mental retardation, dementia, optic atrophy and pigmentary retinopathy [45,49,50]. An onset with clumsiness and gait disturbance around age 3 years followed soon thereafter by asymmetric lower limb dystonia is classic. Atypical cases feature a slowly-progressive neuropsychiatric syndrome in addition to the movement disorder [45]. Psychiatric manifestations include obsessive–compulsive disorder, schizophrenia-like psychosis and depression. Cognitive dysfunction is variable, is generally more severe in patients with earlier–onset disease, may precede motor impairment, and often implicates attention and executive functions [51]. Rare cases of PKAN may present in adulthood and mimic PD or amyotrophic lateral sclerosis [50,52–54]. Another unusual phenotype is HARP (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration). Initially construed as a distinct NBIA syndrome, the original HARP patient was subsequently discovered to harbor a *PANK2* mutation placing this condition squarely within the PKAN disease spectrum [55].

The majority of the affected (both classical and atypical) and many pre-symptomatic individuals with PKAN exhibit the "eye-of-the-tiger

Fig. 1. Magnetic resonance imaging (MRI) of iron in human brain. A. Young (left) and elderly (right) group means for FDRI images (acquired at 1.5 T and 3.0 T; top) and SWI images (1.5 T; bottom). Increasing iron concentrations engender higher (brighter) FDRI signals but lower (darker) SWI phase signals. "64" denotes use of 64-pixel kernel Hanning filter. FDRI, Field-Dependent Relaxation Rate (R2) Increase; SWI, susceptibility-weighted imaging. Adapted from [20], with permission. B. Correlation of age-adjusted iron concentrations (X-axis) estimated from published *post-mortem* data [26] and mean R2* values (Y-axis) in human basal ganglia. The subcortical regions examined are depicted in the 3D reconstruction based on T1-weighted images. CN, caudate nucleus (blue): Pu, putamen (red); GP, globus pallidus (green). Adapted from [16], with permission.

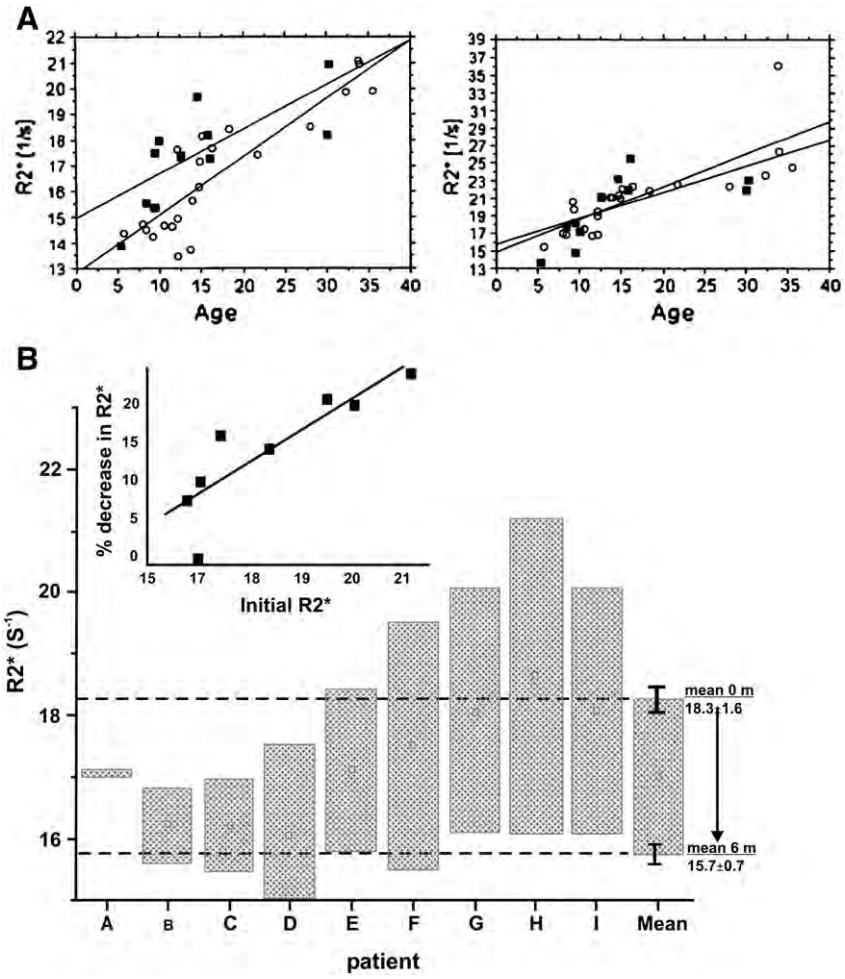


Fig. 2. MRI of brain iron stores in Friedreich ataxia (FA). A. Mean R2* values reflecting tissue iron concentrations are significantly greater in the cerebellar dentate nucleus (i), but not in globus pallidus (ii), of FA patients (squares) relative to controls (circles) and increase with age in both regions (although the rate of increase for the dentate nucleus appears to be lower in the FA subjects). Adapted from [37], with permission. B. Absolute and relative changes in R2* of dentate nucleus in nine FA patients after 6-month oral therapy with the iron chelator, deferiprone (DFP). Mean R2* measurements are significantly lower after treatment (bottom of bars) relative to pre-treatment values (top of bars). Adapted from [43], with permission.

sign" on T2-weighted MRI. This represents a hyperintense signal surrounded by a ring of hypointensity in the globus pallidus attributed to tissue vacuolization/gliosis and pathological iron deposits, respectively (Fig. 3) [56]. Brown discoloration of the basal ganglia due to excessive iron sequestration is noted at autopsy. Histochemical staining with Perls' method reveals granular iron deposits scattered throughout the neuropil and within microglial cells and astrocytes of the globus pallidus and substantia nigra pars reticulata. Similar concretions and spheroid bodies (focal axonal swellings) occur in the subthalamic nucleus of Luys and within cerebral gray and white matter. Although 'Hallervorden–Spatz' cases exhibiting various pathological changes in peripheral blood lymphocytes have been reported [57,58], these have not been documented in genetically-confirmed PKAN.

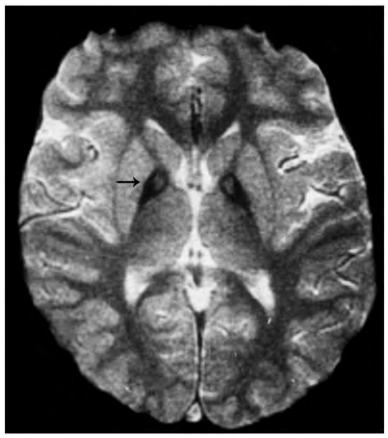


Fig. 3. Brain MRI of subject with pantothenate kinase-2 associated neurodegeneration (PKAN). T2*-weighted echo-planar sequence demonstrates characteristic "eye-of-the-tiger" sign in the globus pallidus (arrow). Modified from [105], with permission.

PANK2 catalyzes the phosphorylation of pantothenate (vitamin B_5) in the coenzyme A biosynthetic pathway. Phosphopantothenate, the product of the PANK2 reaction normally condenses with cysteine in the next step of the pathway. Cysteine has been reported to accumulate in the globus pallidus of persons diagnosed with Hallervorden–Spatz syndrome [59]. Hayflick and colleagues initially posited that the excessive tissue cysteine, an amino acid with iron-chelating properties, may mediate the regional accumulation of iron in these patients. Moreover, in the presence of transition metals, cysteine undergoes rapid autoxidation yielding reactive oxygen and sulfur species [31,60] which may promote oxidative neuronal injury in the basal ganglia of PKAN subjects and associated extrapyramidal symptoms [47,49]. The recent identification of an NBIA syndrome (phospholipase A2G6-associated neurodegeneration (PLAN) — see below) with clinical phenotypes overlapping those of PKAN, but

without anticipated disturbances in brain cysteine metabolism, poses a stiff challenge to the 'cysteine hypothesis' of iron deposition in these disorders.

Unfortunately, there is at present no specific treatment with proven efficacy for persons afflicted with PKAN. Iron chelation therapy with deferoxamine and administration of vitamin B_5 have been attempted without evidence of benefit [61]. Oral or intrathecal baclofen and stereotactic pallidotomy may provide symptomatic relief but have no known disease-modifying effects [62,63].

3.3. Phospholipase A2G6-associated neurodegeneration

As alluded to in the previous section, genetic lesions distinct from mutations in *PANK2* may present a neurological picture virtually identical to that of PKAN. As a case in point, mutations in the gene encoding a calcium-independent group VI phospholipase A_2 (*PLA2G6*) have been implicated in some children with NBIA initially diagnosed as having PKAN [45,64]. Several distinct autosomal recessive syndromes have been reported in patients with phospholipase A2G6-associated neurodegeneration (PLAN; also referred to as NBIA-2). Some present with early psychomotor retardation, cerebellar signs, spasticity and visual disturbances; others display dystonia–parkinsonism and dementia associated with frontotemporal atrophy [65]. Importantly, T2 signal attenuation indicating iron accumulation in the substantia nigra and striatum are seen in many, but not all, of the affected individuals [66]. Moreover, in contradistinction to PKAN, the "eye-of-the-tiger sign" is not characteristic of PLAN (Fig. 4).

The PLA2G6 enzyme has been implicated in arachidonic acid release, prostaglandin and leukotriene synthesis, phospholipid remodeling, and apoptosis [67] and has previously been associated with forms of infantile neuroaxonal dystrophy [68] and Karak syndrome [69]. It is unclear whether pathological brain iron trapping in patients with phospholipase A2G6-associated neurodegeneration (PLAN) accrues from alterations in lipid neurochemistry or from some other unknown action of the mutant enzyme.

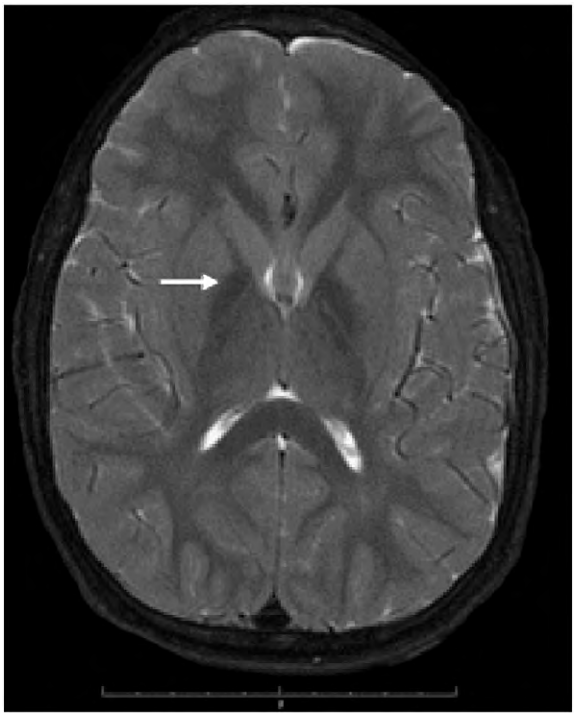


Fig. 4. T2-weighted MRI of a 9-year-old patient with phospholipase A2G6-associated neurodegeneration (PLAN). There is symmetrical signal attenuation in the globus pallidus compatible with excessive iron deposition (arrow).
From [66], with permission.

3.4. Fatty acid hydroxylase-associated neurodegeneration

Autosomal recessive NBIA may result from mutations in the fatty acid hydroxylase gene, *FA2H* [70]. Mutant *FA2H* had previously been linked to types of leukodystrophy and hereditary spastic paraplegia [71]. Subjects with FA2H-associated neurodegeneration (FAHN) and NBIA present with childhood–onset gait disorder, marked ataxia, dystonia and spastic paraparesis, but no optic atrophy, pigmentary retinopathy or cognitive decline. On MRI, FAHN patients exhibit bilateral T2 hypointensities of the globus pallidus compatible with excess iron, severe pontocerebellar atrophy, mild diffuse cortical atrophy, thinning of the corpus callosum and confluent periventricular white matter T2 hyperintensities [70–72] (Fig. 5). The white matter abnormalities in FAHN may represent syndromic overlap with the aforementioned FA2H-related leukodystrophy. FA2H catalyzes the formation of 2-hydroxylated fatty acids that are necessary for the biosynthesis of ceramide, galactosylceramide and sulfatide constituents of normal CNS myelin [73].

3.5. Kufor-Rakeb disease

Kufor-Rakeb Disease (KRD) is an autosomal recessive NBIA disorder first described in 1994 [74] resulting from mutations in the *ATP13A2* gene on chromosome 1p36 [75]. The gene codes for a putative lysosomal P-type transmembrane cation-transporting ATPase of uncertain function [76,77]. Symptoms generally begin in the 2nd or 3rd decade and may be heralded by neuropsychiatric abnormalities such as mania, delusions and insomnia. Characteristic clinical features include parkinsonism (which may be transiently L-dopa-responsive), pyramidal dysfunction (spastic weakness) and supranuclear gaze palsies. Cognitive deterioration and dementia may or may not develop. Elevated CSF kynurenine levels have been reported but are not specific to this condition. The disease is usually slowly progressive, although a subacute course rendering victims bed-bound within the first few years may occur [74,77]. Brain MRI in KRD reveals generalized cortical and subcortical atrophy and hypointensities of the caudate and putamen on T2* sequences (Fig. 6) compatible with augmented iron deposition (but which awaits neuropathological confirmation). In a recently-reported Chilean family [78], a 45 year-old mother with compound heterozygosity for mutant *ATP13A2* exhibited parkinsonism (Hoehn and Yahr stage 2), dementia, symmetrically reduced putaminal tracer uptake on dopamine transporter (DAT) imaging, global brain atrophy, and T2/T2* hypointensities in caudate and putamen consistent with abundant iron. Children heterozygous for mutant *ATP13A2* all manifested subtle signs of parkinsonism (reduced arm swing, limb rigidity, mild postural tremor), but T2/T2* imaging, TS and DAT single photon emission computed tomography scans of the basal ganglia were within normal limits.

3.6. Aceruloplasminemia

Ceruloplasmin is an abundant plasma α_2-glycoprotein that is synthesized primarily, but not exclusively, in the liver. In the presence of ceruloplasmin, ferrous ion (Fe^{2+}) becomes oxidized to ferric ion (Fe^{3+}) with concomitant complete reduction of molecular oxygen. To date, the only clearly defined physiological function of ceruloplasmin is its ferroxidase activity [79,80]. The holoprotein contains six copper atoms, three of which form a trinuclear cluster that activates oxygen required for catalytic activity. The ferroxidase activity of ceruloplasmin facilitates iron efflux from cells. Ceruloplasmin oxidizes ferrous ions following their transfer to the cell surface via ferroportin and may foster shedding and delivery of ferric iron to transferrin in the extracellular milieu. A glycosylphosphatidylinositol (GPI)-anchored ceruloplasmin bound to astroglial cell membranes was found to be the major isoform of this protein in the CNS. Moreover, the ability of astrocytes isolated from ceruloplasmin-deficient mice to purge

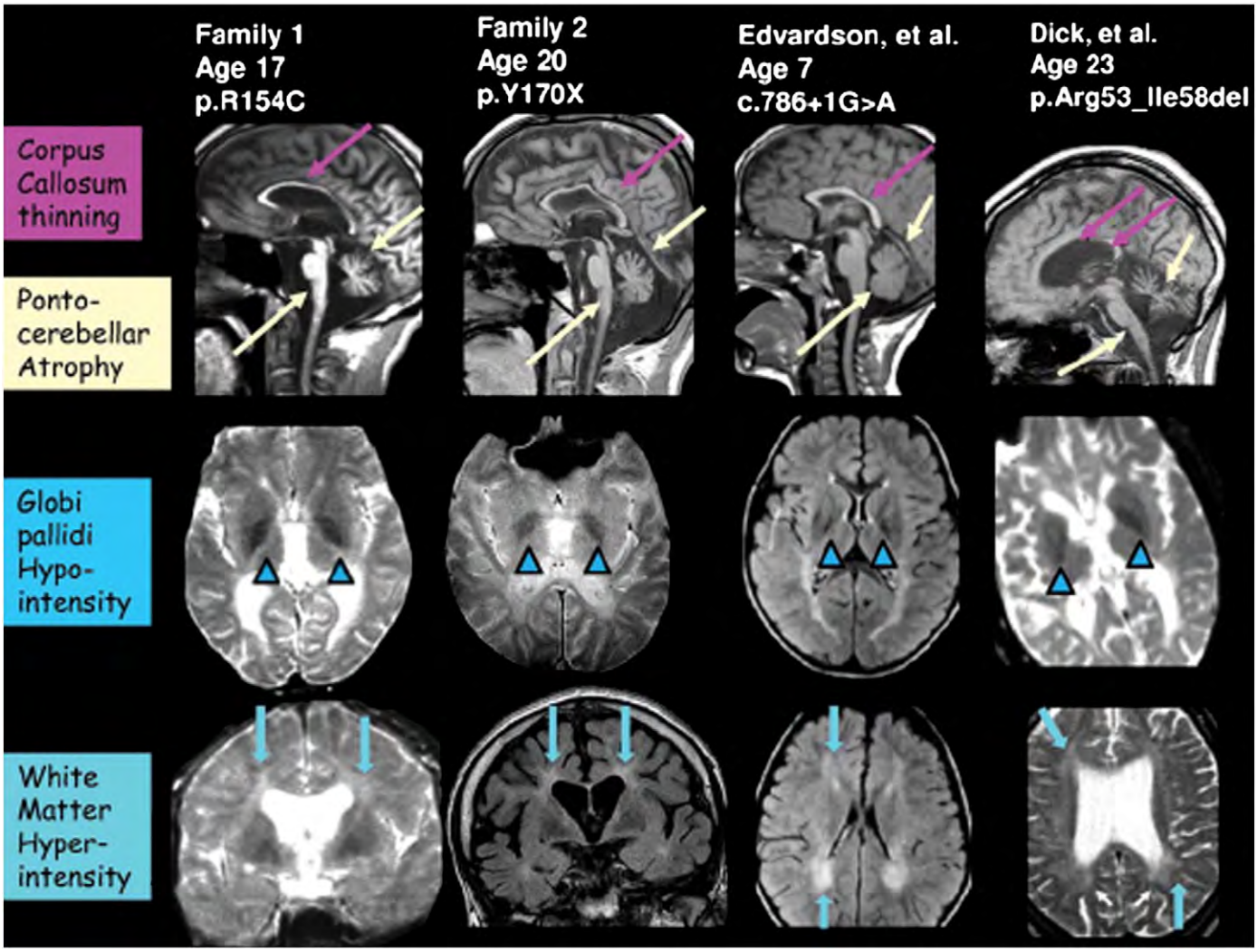


Fig. 5. Fatty acid 2-hydroxylase associated neurodegeneration (FAHN). MR images of the brain from four published cases are depicted [70–72]. There is marked pontocerebellar atrophy (yellow arrows), mild cerebral atrophy, and thinning of the corpus callosum (magenta arrows) in all cases. T2-weighted images indicate hypointensities of the globus pallidus (arrowheads) consistent with iron deposition, and subcortical/periventricular white matter hyperintensities (blue arrows).
Adapted from [70], with permission.

themselves of iron was compromised, implicating GPI-anchored ceruloplasmin as an important component of the iron-regulatory machinery in the mammalian CNS [81].

In 1987, Miyajima and colleagues [82] described a 52-year-old Japanese woman who presented with extrapyramidal symptoms associated with signal hypointensities of the basal ganglia and cerebellum on MRI compatible with excessive iron sequestration. There was also retinal degeneration, diabetes mellitus, mild anemia, low plasma iron concentrations, elevated plasma ferritin levels, severe hepatic iron overload and undetectable serum ceruloplasmin. A loss-of-function mutation in the ceruloplasmin gene (chromosome 3q25) was discovered on nucleotide sequence analysis [83]. Additional cases bearing distinct point mutations and splice-variants in the ceruloplasmin gene have since come to light, with most causing defective assembly of the trinuclear copper cluster [84–86]. Neuroimaging features have been consistent with pathological iron deposition in basal ganglia, thalamus and cerebellum (Fig. 7). Patients homozygous for this defect manifest serious parenchymal iron overload affecting the liver, pancreas and CNS. CNS involvement is often diagnosed at midlife, is progressive, and targets the basal ganglia (choreathetosis, dystonia, dysarthria, dementia), the cerebellum (ataxia) and retina (pigmentary degeneration with visual loss). Circulating ceruloplasmin levels and attendant ferroxidase activity in the homozygous condition are nil or negligible. Subjects heterozygous for mutant ceruloplasmin exhibit ~50% reduction in circulating protein levels ("hypoceruloplasminemia") and display subtle signs of cerebellar dysfunction on careful testing [87].

3.6.1. Treatment of aceruloplasminemia

A few clinical reports suggest that treatment with the Fe^{3+} chelator, deferoxamine may have some role in preventing iron accumulation and related symptoms in individuals with aceruloplasminemia [88]. However, most initial attempts to purge brain and body iron with deferoxamine in these patients have proved unsuccessful, possibly because the iron burden in these individuals favors the Fe^{2+} state in the absence of normal ferroxidase activity [89]. To circumvent this conundrum, Yonekawa and colleagues [89] first administered fresh frozen plasma (450 mL i.v./week) for 6 weeks to replenish blood ceruloplasmin levels and restore ferroxidase activity. Thereafter, deferoxamine (1 g i.v./day) was administered for an additional 6 weeks to deplete *ferric* iron stores. Although MR images of the brain in this test case remained unchanged following treatment, there was unprecedented improvement in choreoathetosis and ataxia and resolution of abnormal high-voltage sharp activity on electroencephalography. Neurological improvements have also been reported after administration of oral zinc sulfate and the iron chelator, deferasirox [90].

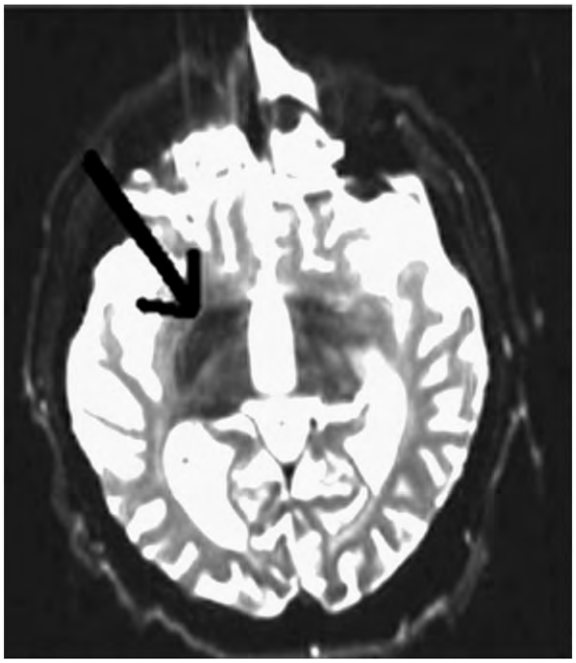


Fig. 6. Kufor-Rakeb disease (KRD). T2*-weighted MRI demonstrating bilateral caudate and putaminal hypointensities (arrow) suggestive of augmented iron deposition. From [77], with permission.

3.7. Neuroferritinopathy

The primary (possibly sole) function of ferritin is the sequestration and storage of metabolically-inert iron. Mammalian ferritin can accommodate up to 4500 iron atoms in its internal cavity. The apoprotein shell is comprised of 24 subunits of two types, a 19 kDa light subunit (L-subunit) and a 21 kDa heavy subunit (H-subunit) [3,91]. Fe^{2+} incorporated into the ferritin shell is oxidized to Fe^{3+} by the ferroxidase activity of the H-subunit, while the L-subunit largely mediates iron-core nucleation. In 2001, Curtis et al. [92] reported a novel, dominantly-inherited neurodegenerative disorder characterized by extrapyramidal signs and excessive iron deposition in the basal ganglia. Initially, all those affected originated from Northern England (Cumbrian region) and presented at ages 40–55 with choreoathetosis, rigidity, dystonia and spasticity, but no cerebellar involvement or cognitive decline [93,94]. MRI of the brain in patients with this condition, termed neuroferritinopathy (or NBIA-3), reveals extensive mixed-signal abnormalities in the basal ganglia, thalami and red nuclei (Fig. 8) which may correlate with disease progression [92,94,95].

In the Cumbrian cohort, the genetic defect was mapped by linkage analysis to locus 19q13.3 containing the gene for ferritin L-chain [92]. The same mutation appears to have arisen independently in France [96] and at least three additional families with neuroferritinopathy have been recognized [97]. In the French family, notable neurological signs included dystonic dysarthrophonia, blepharospasm, and cerebellar dysfunction. Variations in the molecular pathology of the mutant L-ferritin genes in these families were recently reviewed [8]. It has been postulated that disruption of the C-terminus of L-ferritin compromises protein stability and function and that "unshielded" cytosolic iron resulting from the assembly of incompetent holoferritin might facilitate oxidative tissue damage in patients with neuroferritinopathy [98].

Neuropathological examination of the brains in these cases revealed cystic necrosis of the globus pallidus with variable involvement of surrounding structures. There was prominent accumulation of stainable iron and ferritin, often in the form of discrete inclusions, in neurons of the globus pallidus and within microglia and oligodendrocytes of the forebrain and cerebellum. Importantly, the Cumbrian patients showed no evidence of systemic iron overload or diabetes, and their serum ferritin levels were surprisingly low (hypoferritinemia). Although liver function tests in these subjects were normal [92], unique hepatocytic concretions have been

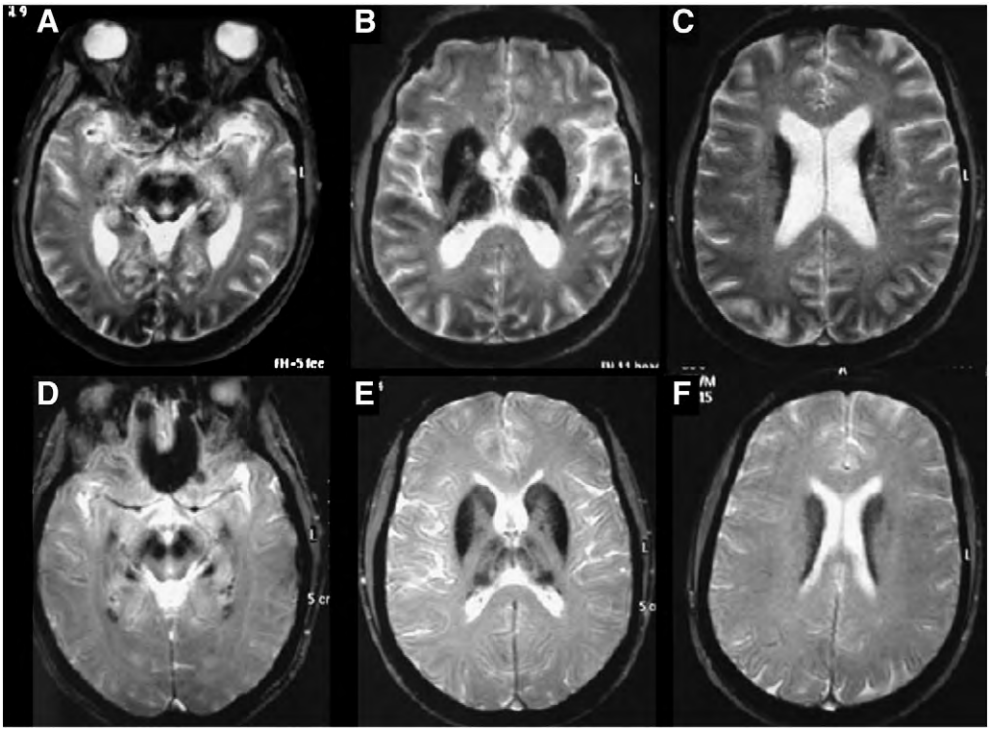


Fig. 7. Aceruloplasminemia. Gradient echo (GE) T2*-weighted images reveal profound hypointensities (iron deposition) in the caudate nucleus, putamen, globus pallidus, thalamus and midbrain with ventriculomegaly in a 56 year-old male proband (A–C). Similar, but less florid, lesions of the basal ganglia and thalamus are demonstrable on neuroimaging of the proband's sister (D–F).
From [88], with permission.

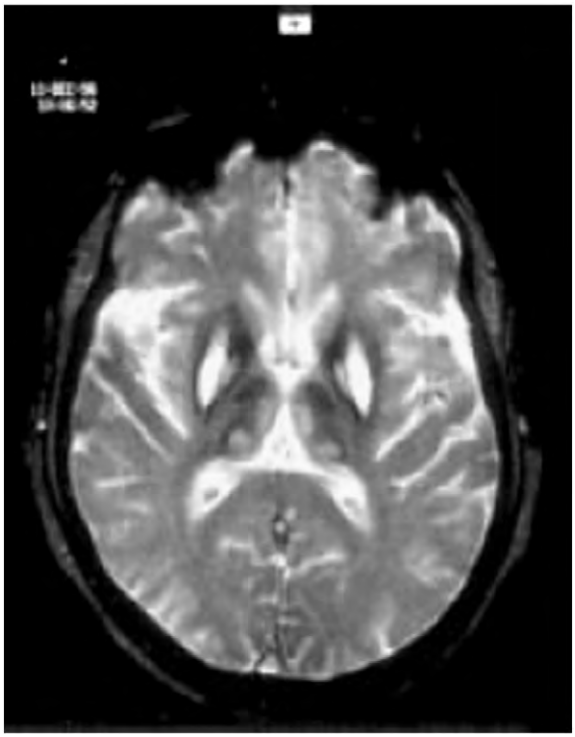


Fig. 8. A case of neuroferritinopathy. T2-weighted MRI of the brain shows mixed hyper- and hypointensities affecting the putamen, globus pallidus and thalamus symmetrically.
From [95], with permission.

observed on biopsy (Professor John Burn, personal communication cited in [8]). In one kindred, there were abundant intranuclear and intracytoplasmic bodies containing ferritin and iron in oligodendroglia, astrocytes, renal tubular epithelium, dermal fibroblasts and muscle capillary endothelial cells [99] prompting one investigator to consider muscle biopsy as a potential diagnostic test for neuroferritinopathy [100]. Attempts at iron chelation in this disease have not yielded any clinical benefits to date [93].

3.8. Differential diagnosis

In subjects with aceruloplasminemia, the systemic abnormalities of iron metabolism may be appreciated prior to the onset of neurological symptoms. Such persons may be misdiagnosed as having type 1 hereditary hemochromatosis and subjected to inappropriate serial phlebotomies that might worsen the anemia. These two diseases can be distinguished by determination of plasma transferrin saturation, which is elevated in hemochromatosis but low in aceruloplasminemia [80]. Patients with Wilson disease may also exhibit symptoms referable to the basal ganglia and subnormal circulating ceruloplasmin levels. However, in contradistinction to Wilson disease, individuals with aceruloplasminemia do not display increased hepatic and urinary copper levels or corneal copper deposition (Kaiser–Fleischer rings) on slit-lamp examination [80]. Cerebellar atrophy/dysfunction and T2 signal loss (iron deposition) in the dentate nuclei may predominate in Friedreich ataxia and hypoceruloplasminemia. These conditions exhibit a similar mode of inheritance (autosomal recessive) but can be readily distinguished by dorsal column and cardiac involvement in the former, and diminished circulating ceruloplasmin in the latter. Low ceruloplasmin levels also complicate acquired copper deficiency [101], but the associated myelopathy is not characteristic of heritable hypoceruloplasminemia. Differentiation of FA from acquired vitamin E deficiency (as might occur with micronutrient malabsorption) or autosomal recessive ataxia with vitamin E deficiency (AVED) may prove challenging on clinical grounds [2,101] and require measurement of blood vitamin E levels or testing for mutant *FRDA* or α-tocopherol transfer protein. PKAN, PLAN, FAHN, KRD and neuroferritinopathy all manifest prominent extrapyramidal dysfunction and iron deposition in basal ganglia. The absence of peripheral iron overload in these conditions, and possible hypoferritinemia in neuroferritinopathy, differentiate these forms of NBIA from aceruloplasminemia [80,92]. Although T2* hypointensities (and other iron-sensitive MRI sequences) of the caudate and/or lenticular nuclei are characteristic of most NBIA disorders, the "eye-of-the-tiger" sign most often denotes PKAN and should prompt molecular testing for *PANK2* mutations. Rarely, this MRI sign may occur in NBIA cases harboring normal *PANK2* genes and has been reported in non-NBIA conditions including Leigh's disease, organic acidurias and acquired dystonias [56,102,103]. In the presence of homogeneous T2 signal attenuation in basal ganglia, but no "eye-of-the-tiger" sign, genetic testing for PLAN or other NBIA may be warranted [45]. Mixed hyper- and hypointense signals in the basal ganglia and thalamus on T2 MRI may favor a diagnosis of neuroferritinopathy, especially in the context of autosomal-dominant inheritance. Not all patients with PLAN show brain iron overload and the absence of basal ganglia hypointensities on MRI does not exclude this diagnosis in cases presenting with infantile neuroaxonal dystrophy [45,65].

4. Conclusions

Heritable perturbations in brain and body iron homeostasis and pathological deposition of this redox-active metal in the CNS have been recognized in a number of pediatric and adult neurodegenerative conditions. In this article, we examined the clinical, pathological and neuroimaging features of FA, PKAN, PLAN, FAHN, KRD, aceruloplasminemia, and neuroferritinopathy. Iron trapping in erythroblast mitochondria and cerebellar hypoplasia occur in X-linked sideroblastic anemia with ataxia [104]. The latter was not reviewed here because, to the author's knowledge, no empirical evidence of brain iron accumulation has thus far been reported in this condition. Similarly, although heterozygosity for common gene (*HFE*) mutations responsible for hereditary hemochromatosis have been promulgated as risk factors for 'acquired' human neurological disorders (Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis, stroke), epidemiological data on this topic are highly conflicting and conjecture regarding the potential impact of the defective alleles on brain iron homeostasis remains unsubstantiated [8]. That being said, it is almost axiomatic that additional, genetically-based NBIA conditions will come to medical attention given the rapid pace of discovery of novel proteins governing diverse aspects of iron metabolism, advances in molecular genetic testing, and the continual refinements (both hardware and software) in MRI and other neuroimaging techniques responsive to tissue iron.

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