



## Review

## Iron dysregulation in movement disorders

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## ABSTRACT

Iron is an essential element necessary for energy production, DNA and neurotransmitter synthesis, myelination and phospholipid metabolism. Neurodegeneration with brain iron accumulation (NBIA) involves several genetic disorders, two of which, aceruloplasminemia and neuroferritinopathy, are caused by mutations in genes directly involved in iron metabolic pathway, and others, such as pantothenate-kinase 2, phospholipase-A2 and fatty acid 2-hydroxylase associated neurodegeneration, are caused by mutations in genes coding for proteins involved in phospholipid metabolism. Phospholipids are major constituents of myelin and iron accumulation has been linked to myelin derangements. Another group of NBIA is caused by mutations in lysosomal enzymes or transporters such as ATP13A2, mucopolip-1 and possibly also  $\beta$ -galactosidase and  $\alpha$ -fucosidase. Increased cellular iron uptake in these diseases may be caused by impaired recycling of iron which normally involves lysosomes. Abnormal iron utilization by mitochondria, as has been proposed in Friedreich's ataxia, is another possible mechanism of iron accumulation. Other, more common degenerative movement disorders, such as Parkinson's disease, Huntington's disease, multiple system atrophy and progressive supranuclear palsy also exhibit increased brain iron content. Finally, brain iron deficiency has been implicated in restless legs syndrome. This review provides an update on recent findings related to genetics, pathogenic mechanisms, diagnosis, and treatment of movement disorders associated with dysregulation of brain iron. We also propose a new classification of NBIA.

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## Introduction

Several neurologic disorders are associated with dysregulation of brain iron metabolism. There are several reasons why delicate regulation of brain iron is important for normal neurologic function. First, iron is an essential element for many brain functions, namely energy production, DNA synthesis and repair, phospholipid metabolism, myelination and neurotransmitter synthesis (Crichton et al., 2011). Second, excess iron leads to oxidative stress-mediated neurotoxicity (Ke and Qian, 2007). Third, excess or deficiency of iron has been documented to cause central nervous system (CNS) abnormality in various genetic (Gregory and Hayflick, 2011) and sporadic disorders, many of which are manifested as paucity of movement (hypokinesias) or abnormal involuntary movements (hyperkinesias) (Crichton et al., 2011).

There are huge differences in iron content among various cell types and brain regions. Found particularly in oligodendrocytes, iron content is much lower in neurons and astrocytes (Connor et al., 1990). Microglia probably serve as brain iron capacitor with an ability to promptly accumulate and release iron and, therefore, microglia iron levels vary considerably (Connor and Menzies, 1990). Brain iron levels change with age, from nearly non-detectable levels at birth to a relatively rapid accumulation within the first three decades of life (Schenck and Zimmerman, 2004; Taylor and Morgan, 1990; Zecca et al., 2001). In the developing brain, iron co-localizes with the myelinogenic foci and the highest period of iron uptake in the brain coincides with peak myelination and plateaus in the third decade (Todorich et al., 2009). The key role of iron in myelination is probably linked to high energy needs for myelin synthesis (Todorich et al., 2009). Iron content is not identical in oligodendrocytes throughout the brain, but seems to be particularly high in intracortical compared to white-matter myelin (Fukunaga et al., 2010). In adulthood and old age, slow gradual iron accumulation is observed mostly in microglia and astrocytes (Connor et al., 1990).

Age-related increase in iron content is not homogenous throughout the brain. It involves primarily globus pallidus (GP), red nucleus, substantia nigra (SN) pars reticulata, dentate nucleus, and putamen but to a lesser degree also the caudate, thalamus and frontal gray matter (Hallgren and Sourander, 1958; Schenck and Zimmerman, 2004). Predominant iron accumulation in these regions has been documented by histochemistry (Hallgren and Sourander, 1958; Morris et al., 1992) to correlate with iron content measured by magnetic resonance imaging (MRI) (Drayer et al., 1986; Yao et al., 2009). With the advent of high-field scanners and of iron-sensitive sequences such as T2\* weighted imaging (T2\*WI), susceptibility weighted imaging or field-dependent relaxivity increase, MRI has become an indispensable diagnostic and research tool in the study of disorders with iron dysregulation (Schipper, 2011).

The reason, why brain iron content increases with aging, is not well understood. One hypothesis suggests that iron accumulation is a passive phenomenon caused by dysfunction of the blood brain barrier (BBB) (Faucheux et al., 1999). Alteration in BBB efficiency and selectivity (Farrall and Wardlaw, 2009) may allow uncontrolled entry of iron to predisposed areas. Regional age-related decrease of the p-glycoprotein efflux pump activity, the marker of BBB function, has been observed in the internal capsule, corona radiata and orbitofrontal cortex (Bartels et al., 2009). However, these regions do not match areas with age-related iron accumulation. Another possibility is that iron accumulation is an active process triggered by regulatory pathways. It has been shown that iron is involved in mediation of apoptosis and that decreased availability of antioxidant compounds observed during aging leads to

increased oxidative stress, triggers apoptotic pathways and degenerative changes and may thus result in an increase of reactive iron pool (Kaur et al., 2009). Apoptosis and iron accumulation may be also triggered in deafferented neurons which have lost its trophic support (Sastry and Arendash, 1995). Age-related vascular changes may also cause hypoxic–ischemic tissue injury with consequent compensatory increase in mitochondria biogenesis and activation of hypoxic pathway, both of which may facilitate iron uptake (Williams et al., 2012). In demyelinating or vascular white matter lesions, iron released from damaged oligodendrocytes apparently can not be reused for myelination and instead is translocated and ultimately may be stored in the subcortical gray matter regions (Dwork et al., 1990). Altered iron trafficking caused by disruption of neural pathways may hypothetically contribute to this failure of iron recycling. Thus, white-matter changes with loss of myelinated fibers during aging and subsequent need of re-myelination along with impaired iron recycling may create a potential for abnormal iron accumulation (Berlet and Volk, 1980).

Many sporadic and genetic disorders with increased brain iron load manifest as movement disorders, possibly due to the propensity of basal ganglia to accumulate iron. This review summarizes recent advances in our knowledge of the clinical manifestations, genetics, pathogenesis, and treatment of these disorders. It also attempts to elucidate the relationship between iron and neurodegeneration and address the question whether iron accumulation is a direct cause of neurodegeneration, a secondary event in a pathophysiologic cascade, or a harmless nonspecific marker of neurodegeneration.

## Metabolism of iron

While brain and systemic iron metabolism are separated by the BBB and blood–cerebrospinal fluid barrier, body iron homeostasis is precisely controlled by hepcidin antimicrobial peptide (HAMP) (Table 1) (Ganz and Nemeth, 2011). Systemic iron preferentially enters endothelial cells bound to transferrin (TF) and its influx into CNS is regulated through transferrin receptor (TFRC) expression on capillary endothelial cells of the brain parenchyma and choroid plexus (Fishman et al., 1987; Taylor and Morgan, 1991). Brain conserves acquired iron very well and its content decreases only minimally during systemic iron deficiency. The mechanisms by which brain disposes of excess iron are largely unknown. Supposedly, iron may be recaptured from the ventricular cerebrospinal fluid by the choroidal epithelia and transported into the blood (Zheng and Monnot, 2011). Interestingly, endothelial cells forming the BBB express the iron storage protein ferritin and thus may serve not only as a barrier but also as an iron buffer for CNS (Connor et al., 2011).

Iron can either cross the BBB by transcytosis or enter the endosomal/lysosomal compartment of endothelial cells where it can be stored and transferred into CNS when needed. Iron is released from the endothelial cells in the ferrous state ( $\text{Fe}^{2+}$ ) and ceruloplasmin (CP) localized at astrocytic perivascular foot processes facilitates its oxidation to ferric state ( $\text{Fe}^{3+}$ ) (Attieh et al., 1999). Ferric ions can be thereafter bound to various transporting proteins such as TF, lactotransferrin (LTF) or ferritin heavy polypeptide and distributed throughout the brain.

Small amount of absorbed iron is allowed to stay unbound forming the labile iron pool (Fig. 1). It is because redox active metal ions can react with hydrogen peroxide via the Fenton's reaction leading to excess production of reactive oxygen species (ROS) and consequent peroxidation of polyunsaturated fatty acids (PUFA) in membrane phospholipids (Goldstein et al., 1993). Intracellular storage and detoxification of free iron is mediated by the ferritin complex, composed of

**Table 1**

Proteins involved in the iron homeostasis (according to HUGO Gene Nomenclature Committee).

Protein symbol	Protein name	Synonym (name/abbreviation)
<i>Iron uptake</i>		
TFRC	Transferrin receptor	CD71, p90
TF	Transferrin	
LTF	Lactotransferrin	
MFI2	Antigen p97 (melanoma associated)	Melanotransferrin
SLC11A2	Solute carrier family 11, member 2	Divalent metal transporter 1/DMT1
<i>Iron storage</i>		
FTH1	Ferritin, heavy polypeptide 1	FTH
FTL	Ferritin, light polypeptide	
<i>Mitochondrial iron metabolism</i>		
SLC25A37	Solute carrier family 25, member 37	Mitoferrin/MFRN
TFR2	Transferrin receptor 2	
ABCB7	ATP-binding cassette, sub-family B, member 7	
FTMT	Ferritin mitochondrial	MtF
FXN	Frataxin	
<i>Iron export</i>		
SLC40A1	Solute carrier family 40, member 1	Ferroportin 1/FPN1
HEPH	Hephaestin	Hp
CP	Ceruloplasmin	
<i>Iron regulation</i>		
HAMP	Hepcidin antimicrobial peptide	
HFE	Hemochromatosis	Hemochromatosis protein
ACO1	Aconitase 1, soluble	Iron regulatory protein 1/IRP1, iron-responsive element binding protein 1/IREB1
IREB2	Iron-responsive element binding protein 2	Iron regulatory protein 2/IRP2
HIF1A	Hypoxia inducible factor 1, alpha subunit	

two subunits, ferritin heavy polypeptide 1 (FTH1) and ferritin light polypeptide (FTL). In catecholaminergic neurons of SN and locus coeruleus, the major iron storage molecule is neuromelanin, an aggregate derived from oxidized excess catechols contained in organelles of the lysosomal type (Tribl et al., 2006; Zecca et al., 2001).

Most of the cellular iron is not localized in the cytosol, but is dispatched to mitochondria and endosomal/lysosomal compartment (Fig. 1). Solute carriers (SLCs) are proteins transporting iron across membranes (Table 1). SLC family 25, member 37 (SLC25A37), previously known as mitoferrin (MFRN) is involved in iron transport into mitochondria, where it is incorporated into iron–sulfur (Fe–S) clusters by the action of a complex of multiple enzymes (Gille and Reichmann, 2011). In SN, iron can enter mitochondria also through TFR2 receptor (Mastroberardino et al., 2009). Iron can exit mitochondria only in the form of heme or Fe–S clusters that are supposedly transported to cytosol by ATP-binding cassette, sub-family-B, member-7 (ABCB7) transporter. Mitochondrial iron may be stored in the mitochondrial ferritin (FTMT), which is expressed in metabolically highly active cells in order to protect mitochondria from oxidative damage (Levi and Rovida, 2009; Li et al., 2011). Iron-rich substances such as cytochrome c, ferritin or mitochondria are degraded by lysosomes (Johansson et al., 2010). Iron can be partially recycled after exiting endosomal/lysosomal compartment via SLC11A2, previously known as divalent metal transporter 1 (DMT1) (Burdo et al., 2001). Agglomerates of ferritin molecules processed by lysosome form an insoluble compound

called hemosiderin (Schenck and Zimmerman, 2004). Iron can exit the cell only via SLC40A1, previously known as ferroportin 1 (FPN1). Intracellular iron homeostasis is maintained by several proteins, iron regulatory protein 1 (IRP1), also known as aconitase 1 (ACO1), iron-responsive element binding protein 2 (IREB2) and hypoxia inducible factor 1, alpha subunit (HIF1A) through regulation of expression of iron regulatory proteins. In the case of high cellular iron, expression of TFRC and DMT1 is decreased and expression of FPN1 and ferritin is increased (Crichton et al., 2011; Wu et al., 2010). Expression of DMT1 may be also upregulated by hypoxic conditions or inflammatory stress regardless of the cellular iron status (Huang et al., 2006; Qian et al., 2011).

Gene mutations (Table 2) or other dysregulation of proteins involved in iron metabolic pathway may ultimately lead to iron accumulation in certain brain regions (Table 3) and cause their dysfunction.

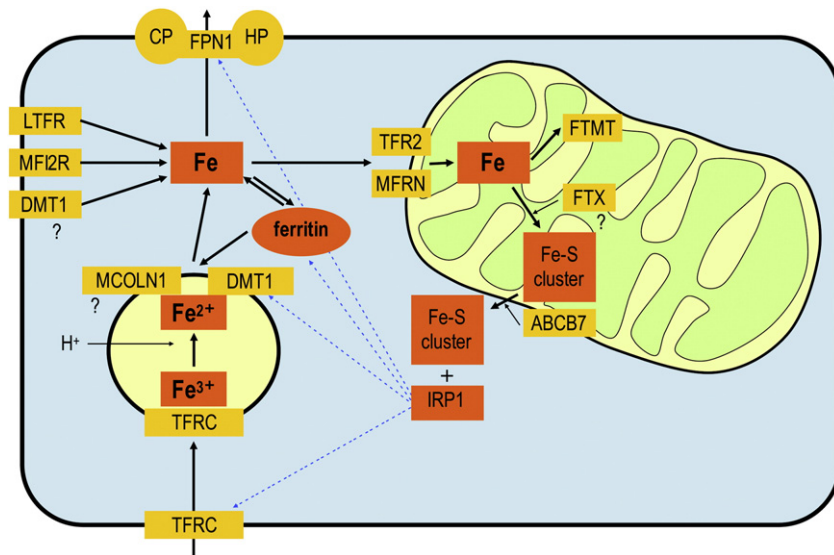
### Neurodegeneration with brain iron accumulation (NBIA)

A large group of heterogeneous neurologic disorders with markedly excessive, regional brain iron stores, far surpassing the levels observed during normal aging, have been labeled as NBIA (for review see Gregory and Hayflick, 2011; Kurian et al., 2011; McNeill and Chinnery, 2011; Schneider et al., 2011). A distinctive feature of NBIAs is a prominent accumulation of iron recognizable on routine MRI, usually as a decreased signal on T2WI. Since the clinical presentation is not specific and wide variety of phenotypes may arise from a single gene defect, MRI examination frequently leads to the diagnosis of NBIA (Kruer et al., 2011a; McNeill et al., 2008a). Specific pattern of iron accumulation (Table 3) may further direct genetic testing, which ultimately confirms the diagnosis.

There are two disorders caused by dysfunction of proteins directly involved in iron metabolism and storage: hereditary ferritinopathy and aceruloplasminemia. Importantly, overt iron deposition is an invariable feature of these diseases which has been documented even in the presymptomatic stage, implying its direct role in the pathogenesis (Fasano et al., 2008; Maciel et al., 2005). There is good evidence that its toxic effect is the primary cause of tissue injury and these diseases are models of iron-mediated oxidative cell damage (Cozzi et al., 2010; Deng et al., 2010; Gonzalez-Cuyar et al., 2008; Kono and Miyajima, 2006). Another typical feature of these disorders is that clinical symptoms often begin relatively late, when already a profound iron accumulation is present, suggesting that brain initially possesses a good compensatory functional reserve in handling the iron-mediated injury.

Interestingly, other NBIAs, such as PKAN or PLAN (Table 2) are caused by a mutation in genes not directly involved in the iron metabolic pathway and the reason for iron accumulation in these disorders is less clear. These disorders generally begin in childhood or adolescence and iron accumulation may not be apparent at the time of first symptoms and may not be documented until later stages (Gregory and Hayflick, 2011; Hayflick et al., 2006). There are even patients with well documented PKAN or PLAN without evidence of increased brain iron content a long time after symptom onset (Aggarwal et al., 2010; Paisan-Ruiz et al., 2009; Yoshino et al., 2010). Thus, iron accumulation, though profound in some patients, is likely not the primary cause of neurodegeneration.

Interestingly, products of respective genes are directly or indirectly engaged in ceramide, phospholipid or lysosomal metabolism. It was hypothesized that dysfunctional ceramide pathway underlies the pathophysiology of some NBIAs and other neurodegenerative disorders (Bras et al., 2008). Ceramides are a bioactive group of sphingolipids involved in the regulation of cell cycle. They can induce apoptosis by changing properties of phospholipid membranes, inducing pore formation and thus increasing membrane permeability leading to an efflux of lysosomal proteases and inhibition of the mitochondrial respiratory chain (Chan et al., 2007; Jana et al., 2009; Posse de Chaves and



**Fig. 1.** A hypothetical scheme of iron regulation in a brain cell. TF-bound iron enters the cellular endosomal compartment through TFRC and subsequently effluxes to the cytosol through DMT1 or perhaps MCOLN1 channels. Iron can also possibly enter directly the cellular cytosolic compartment through DMT1. Iron bound to LTF or MFI2 can also enter specific neuronal cells through LTFR and MFI2R. Cytosolic iron can be stored in the form of ferritin or enter the mitochondrial compartment through MFRN or TFR2. There is a continuous exchange between the labile iron pool, ferritin-iron and iron stored in lysosomes. Iron in mitochondria is used for Fe-S cluster biosynthesis and iron exits mitochondria in the form of Fe-S clusters. Among others, chaperone FXN and transporter ABCB7 are necessary for this process. Mitochondria may store iron in the form of FTMT. Cytosolic Fe-S clusters interact with IRP and help to regulate iron homeostasis through transcription regulation of involved proteins (dashed blue lines). Excess iron can exit the cell through FPN1. Ferrooxidase activity of HP or CP is necessary for iron efflux. Abbreviations: TF—transferrin, TFRC/TFR2—transferrin receptor type 1/2, DMT1—divalent metal transporter type 1, MCOLN1—mucolipin 1, LTF—lactotransferrin (receptor), MFI2(R)—serum melanotransferrin (receptor), MFRN—mittoferin, FXN—frataxin, FTMT—mitochondrial ferritin, ABCB7—ATP-binding cassette, sub-family-B, member-7, IRP1—iron regulatory protein 1, FPN1—ferroportin 1, HP—hephestin, CP—ceruloplasmin.

Sipione, 2010) (Fig. 3). The mechanism by which ceramide signaling pathway is related to iron metabolism is, however, less clear. Study on endothelial cell culture showed that high concentrations of ceramide led to ROS generation and cell apoptosis. These oxidative features and apoptosis were dependent on the TFRC upregulation and cellular iron uptake, since iron-chelating agents and anti-TFRC antibodies mitigated this effect (Matsunaga et al., 2004). Neurons and oligodendrocytes are prone to ceramide mediated apoptosis since their membranes are rich in PUFA that can easily react with peroxides, triggering ceramide synthesis and enhancing iron uptake through TFRC and DMT1 upregulation (Schonfeld et al., 2007). Whether this is the case in NBAs is currently unknown, since the expression of iron regulatory proteins has not been studied in these disorders. It is, however, unlikely that increased ceramide signaling plays a pivotal role as enzymes afflicted in these disorders are involved in ceramide synthesis and their defects are more likely to decrease its levels (Fig. 3).

Besides its role in cell signaling, ceramide is also a basic element of lipid membranes and dysregulation of its metabolism may change their properties. Altered membrane properties could affect the function of iron transporting proteins (Jana et al., 2009). Proper lipid membrane function is fundamental for cell homeostasis and its instability would likely cause a dysfunction of lysosomes, mitochondria and also myelin sheath derangement. Lysosomes are intimately connected with iron metabolism since lysosomal proteolysis is the primary degradation pathway of the cytosolic ferritin (Zhang et al., 2010) and its disruption may impair cellular iron recycling. Dysfunctional iron recycling would cause its increased uptake from the blood and in postmitotic cells as neurons lead to its gradual accumulation. Increased phagocytosis and decreased disposal of iron-rich substances further increases lysosomal vulnerability by peroxidation of the membrane. This may, especially in the case of membranes' increased fragility, eventually cause leakage of lysosomal enzymes, impair autophagic activity and trigger apoptosis (Johansson et al., 2010; Kurz et al., 2011).

Oligodendrocytes are cells with the highest iron content and enormous energy and lipid metabolism demands for the myelin sheath synthesis. It has been shown that oligodendrogenesis, which is necessary for myelin renewal, begins with iron accumulation in macrophages

that consequently provide iron to maturing oligodendroglial progenitors (Schonberg and McTigue, 2009). Higher myelin breakdown and remyelination may lead to increased iron requirement and iron accumulation in this regard may be a marker of an increased myelin turnover.

Dysfunctional cellular membrane would create increased demands on the energy production through tedious myelin synthesis, membrane potential maintenance and action potential propagation. Both iron accumulation and neurodegeneration may thus be consequences of long-lasting upregulation of the mitochondrial iron-dependent energy producing apparatus. Interestingly, in many NBAs iron accumulates preferentially in GP, which is known for its high vulnerability to various insults compromising energy production such as hypoxic-ischemic injury or genetic mitochondrial disorders (Feve et al., 1993; Johnston and Hoon, 2000).

#### Hereditary ferritinopathy

Hereditary ferritinopathy, also known as neuroferritinopathy (OMIM 606159), is a rare autosomal dominant disorder caused by mutations in the *FTL* gene. It is manifested by low serum ferritin along with pathological iron deposits and ferritin inclusions localized extracellularly and intracellularly in various brain regions respecting the pattern observed in normal aging (Curtis et al., 2001). Autopsy revealed also neuroaxonal spheroids immunoreactive for neurofilaments, ubiquitin and tau in GP, putamen and diffusely in the white matter (Curtis et al., 2001). Contrary to the original report on patients from northern England carrying the most frequent mutation 460dupA, ferritin inclusions were found also in the skin, muscle, kidney and liver in a large French pedigree carrying mutation 498–499InsTC (Vidal et al., 2004). This implies that hereditary ferritinopathy rather than neuroferritinopathy is a more appropriate designation. The disorder has now been reported to occur also in Asian (Kubota et al., 2009; Ohta et al., 2008) and North American populations (Ondo et al., 2010). At least seven mutations have been described thus far (Ory-Magne et al., 2009). The clinical presentation of the prevalent mutation 460dupA starts in 3rd–6th decade and is quite variable, but in the majority of patients the symptoms begin with focal chorea, stereotypy, or dystonia. A fairly typical symptom is orolingual mandibular



**Table 2**  
Genetic neurodegenerative disorders with increased brain iron content.

Disease	Synonym	Gene	Onset (yrs)	Phenotype	Neurologic symptoms	Other symptoms
Neurodegeneration with brain iron accumulation						
Aceruloplasminemia	familial apo-Cp deficiency	CP	16–71 (mean 45)		Cervical dystonia, Blepharospasm, Dysarthria, Parkinsonism, Chorea, Ataxia	Retinal degeneration, Diabetes, Anemia
Neuroferritinopathy	Hereditary ferritinopathy NBIA-2	FTL	13–63 (mean 45)		Chorea, Orofacial Dystonia, Dysarthria, Cerebellar ataxia, Cognitive decline	
PKAN	NBIA-1 Hallervorden-Spatz disease HARP	PANK2	<6	Classic	Dystonia, Dysarthria, Parkinsonism, Pyramidal lesion	Pigmentary retinopathy, acanthocytosis, hypoprebetalipoproteinemia
			10–40	Atypical	Dystonia, Speech difficulty, Tremor, Parkinsonism Psychiatric symptoms	
PLAN	NBIA-2 PARK14 Karak syndrome	PLA2G6	<2 (even congenital)	Infantile neuroaxonal dystrophy	Hypotonia, Psychomotor retardation, Ataxia, Tetraparesis, Epilepsy	Optic atrophy
			1.5–6.5	Atypical neuroaxonal dystrophy	Dystonia, Dysarthria, Psychiatric disturbance, Tetraparesis, Epilepsy	
			20–30s	PARK14	Dystonia-parkinsonism, Psychiatric disturbance	
FAHN	SPG35	FA2H	3–10		Focal leg dystonia, Tetraparesis, Dysarthria, Ataxia	
ATP13A2 mutation	Kufor Rakeb disease PARK9	ATP13A2	12–22		Parkinsonism, Dystonia, Pyramidal lesion, Dementia, Supranuclear gaze palsy, Visual hallucinations	
Woodhouse-Sakati syndrome		C2orf37	20–30s		Dystonia, Chorea, Dysarthria, Cognitive disorder, Epilepsy, Polyneuropathy	Hypogonadism, Deafness, Alopecia, Diabetes, Syndactyly
GM1 gangliosidosis		$\beta$ -galactosidase	>1	Juvenile/adult	Psychomotor delay, Generalized dystonia, Dysarthria, Spastic paresis	Facial dysmorphism, Skeletal dysostosis, hepatosplenomegaly, Macular cherry red spot
Fucosidosis		$\alpha$ -fucosidase	>1	Type 2	Psychomotor delay, Spastic paresis, Seizures, Generalized dystonia	Angiokeratoma, Anhidrosis, Skeletal dysostosis,
Mucopolipidosis type 4		MCOLN1	Congenital, infancy		Psychomotor retardation, Strabismus	Retinal degeneration, Optic atrophy, Anemia, Achlorhydria
MPAN	C19orf12 mutation	C19orf12	4–20		Spasticity, Dystonia, Parkinsonism, Psychiatric symptoms	Optic atrophy, Axonal neuropathy
Other diseases with increased brain iron content						
Friedreich ataxia		Frataxin	2–25	Classic	Cerebellar ataxia, Sensory neuropathy, Dysarthria	Cardiomyopathy, Diabetes, Scoliosis, Foot deformity Hearing loss
			25–60	Atypical	Spasticity, Chorea, Dystonia, Parkinsonism	
Huntington disease		Huntingtin	35–45	Classic	Chorea, Cognitive decline, Tics, Dystonia, Dysarthria	
			<20	Young onset	Parkinsonism, Dementia, Seizures, Ataxia	
			>60	Late onset	Chorea, Dementia, Psychiatric symptoms	
X-linked sideroblastic anemia with ataxia		ABC7	infancy		Progressive spinocerebellar ataxia	Microcytic anemia

**Table 3**  
Iron accumulation pattern in neurologic disorders.

	GP	SN	Caudate	Putamen	Dentate nuclei	Thalamus	Cerebral cortex	Other
Neuroferritinopathy	+	++	+	+	++	+	++	Red nucleus
Aceruloplasminemia	++	++	++	++	++	++	++	Retina
PKAN	++	+			+/-			Retina
PLAN	+	+			+/-			
FAHN	+							
Kufor-Rakeb disease			+	+				
Woodhouse-Sakati syndrome	+	+						Red nucleus
MPAN	+	+						
GM1 gangliosidosis	+							
Fucosidosis	++	++						
Mucopolidosis type IV	+		+	+		+		
Friedreich's ataxia					+			
Huntington's disease	+		+	+				
Parkinson's disease		+						
Multiple system atrophy	+		+	++				
Progressive supranuclear palsy	+		+	+				
Multiple sclerosis	+		+	+		+/-	+/-	

++ Typically observed finding, MRI hallmark.

+ Common finding, not always visible on routine MRI.

+/- Conflicting reports.

dyskinesia associated with jaw dystonia and blepharospasm during phonation producing dysarthria and tongue biting, features overlapping with those of neuroacanthocytosis. Up to 10% of patients present with parkinsonism (Chinnery et al., 2007). Other, usually faster progressing phenotypes with postural tremor in the upper limbs and resting tremor in the lower limbs along with cerebellar features were described in patients carrying the 498–499InsTC and other less common mutations (Devos et al., 2009; Maciel et al., 2005; Mancuso et al., 2005; Ory-Magne et al., 2009). Cognitive dysfunction, depression and psychosis have also been reported (Chinnery et al., 2007).

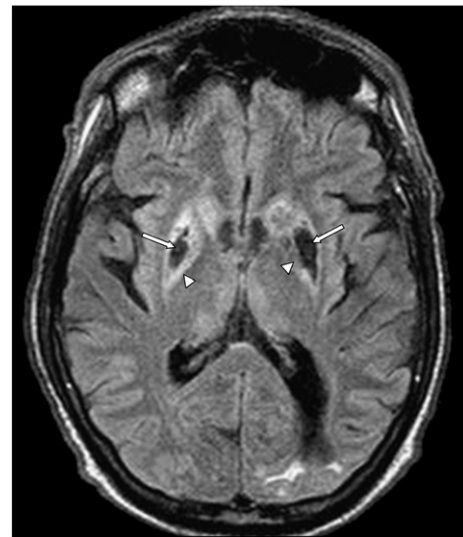
MRI was abnormal in all published cases except one (Mir et al., 2005) and typically showed iron accumulation in the dentate nucleus, GP, SN, caudate nuclei, putamen, thalamus, and cerebral cortex. In later stages, confluent hyperintensity in GP and putamen can be detected in T2WI, corresponding to areas of edema, gliosis and cystic degeneration (McNeill et al., 2008a) (Fig. 2). Generalized brain atrophy and leukoencephalopathy were also described in several patients (Ory-Magne et al., 2009). The single patient with normal MRI presented atypically with generalized dystonia in his early twenties despite having the prevalent mutation 460dupA (Mir et al., 2005). This suggests that another disease process might have played a role in the clinical presentation.

The primary cause of neuropathological changes is reduced iron storage capacity of the structurally changed ferritin and subsequent free iron release triggering oxidative tissue damage, as was documented in a mouse model (Baraibar et al., 2008). Unbound iron may further stimulate FTL synthesis, precipitate its polymerization and together with impaired proteasomal function contributes to ferritin aggregates forming in the cytoplasm and nuclei of neurons, microglia and oligodendrocytes. All known mutations supposedly impair iron storage function of FTL, but the reason for clinical heterogeneity of the disease is not completely clear. It was hypothesised that there is a genotype-phenotype relationship and mutations in the 5' part of the exon 4 disrupt the helical structure necessary for incorporation of the mutated FTL molecule into the ferritin complex and lead to a milder phenotype compared to mutations in the 3' part of the exon 4 which preserve the ability of mutant FTL to incorporate into the ferritin complex severely disturbing its function (Kubota et al., 2009). There is insufficient evidence that low body iron levels may have a beneficial effect on the phenotype. Females were found to have a slightly and insignificantly higher mean age at disease onset (Chinnery et al., 2007) and other authors noted female preponderance in asymptomatic carriers (Kubota et al., 2009; Maciel et al., 2005). Nevertheless, low iron diet and repeated phlebotomies remain a controversial therapy (Chinnery et al., 2007). Tetrabenazine, a monoamine

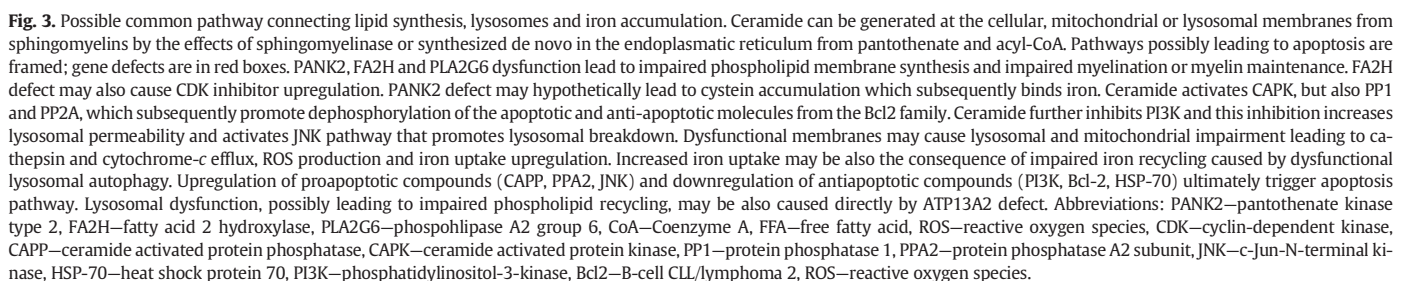
depleting drug, has been shown to improved facial stereotypies and other dyskinesias associated with hereditary ferritinopathy (Ondo et al., 2010).

#### Aceruloplasminemia

Aceruloplasminemia (OMIM 604290) is a rare autosomal recessive disorder caused by the CP gene mutation (Miyajima et al., 1987). Majority of reported patients are of Japanese origin, but several patients were reported in China, America and Europe (McNeill et al., 2008b). The disease prevalence was estimated at 1:2,000,000 in Japan (Miyajima et al., 1999) and remains a rare curiosity in other parts of the world. CP has an indispensable role in oxidation  $Fe^{2+}$  ions, which is a necessary step for iron loading onto TF and ferritin (Van Eden and Aust, 2000). Iron can enter neurons only bound to TF in the oxidized state and this is hampered in aceruloplasminemia. As a consequence of decreased cellular iron uptake, extracellular iron pool increases. Moreover, intracellular iron levels also increase as the iron efflux through FPN1 is dependent on CP. This was documented in a mouse model of aceruloplasminemia in liver,



**Fig. 2.** 1.5 T FLAIR MRI image of a patient with neuroferritinopathy showing hyperintense lesions (arrowheads) reflecting areas of cystic degeneration and hypointense lesions (arrows) reflecting accumulated iron in caudatum, putamen and pallidum.



were described in autopsied brains (Miyajima, 2003). More than 40 mutations which affect either trafficking CP from endoplasmic reticulum to Golgi apparatus, incorporation of copper into apoceruloplasmin or interaction between CP and FPN1 have been described (Kono and Miyajima, 2006; Kono et al., 2010). There seems to be no genotype–phenotype correlation. All known mutations impair the function of both, serum and brain glycosylphosphatidylinositol-anchored form, which are generated by alternative mRNA splicing (McNeill et al., 2008b).

Iron accumulation in retina, liver, pancreas, myocardium and brain leads to retinal degeneration, diabetes mellitus, microcytic anemia and neurological symptoms. The usual onset of neurologic symptoms is in

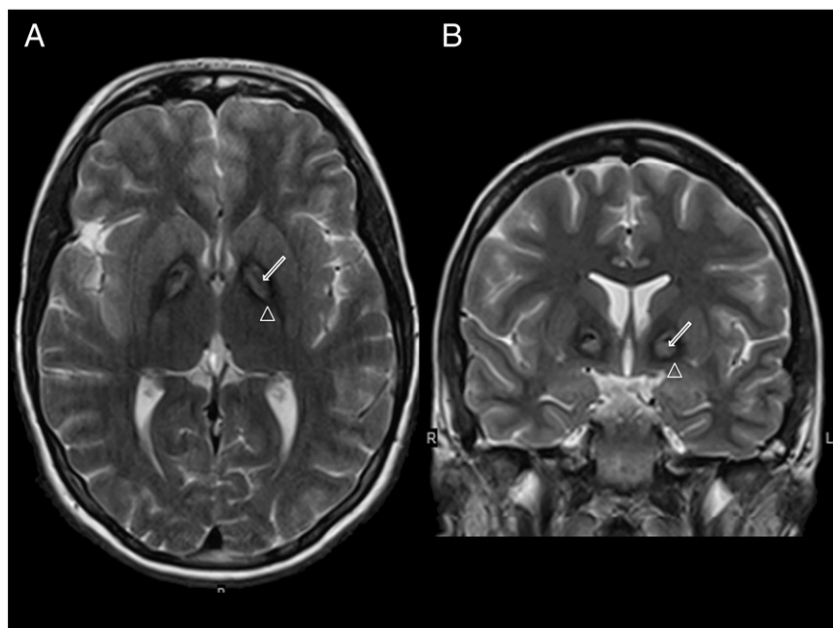
the 5th decade. They are non-specific, often manifested by blepharospasm, facial and cervical dystonia, dysarthria, chorea, parkinsonism, gait ataxia and cognitive decline (Miyajima et al., 2003). Retinal degeneration may histopathologically resemble age-related macular degeneration (Wolkow et al., 2011). Serum iron level is usually decreased, but serum ferritin is elevated. Aceruloplasminemia may be suspected even before the onset of neurologic symptoms in patients with diabetes mellitus and microcytic anemia accompanied by high serum ferritin and not responding to iron supplementation (Ogimoto et al., 2011). Undetectable serum CP and copper, along with typical brain MRI, practically confirms the diagnosis. Brain MRI invariably shows profound iron accumulation in striatum, GP, SN, thalamus, dentate nuclei and cortex (McNeill et al., 2008a). Early diagnosis is imperative since iron supplements should be avoided in the treatment of hypochromic anemia because it may worsen neurological symptoms (Harris et al., 1995). Efficiency of disease screening in every patient with hypochromic anemia is questionable due to very low disease prevalence. The burden of CP mutations may however be higher than initially suspected since neurologic symptoms and iron accumulation were described also in heterozygotes, who may escape correct diagnosis (Chen et al., 2008; Daimon et al., 2000; Kuhn et al., 2007; Miyajima et al., 2001). Several published patients with movement disorders and decreased serum ceruloplasmin might have suffered from heterozygous CP mutations, although this was not documented by genetic testing (Lirong et al., 2009; Walshe, 2005).

#### *Pantothenate kinase associated neurodegeneration (PKAN)*

PKAN (OMIM 606157) is an autosomal recessive disorder caused by mutations in the gene encoding pantothenate kinase 2 (*PANK2*) (Zhou et al., 2001) which is an essential mitochondrial regulatory enzyme in the coenzyme-A (CoA) biosynthesis. CoA is critical to the fatty acid metabolism which is necessary for membrane lipid synthesis and lipid  $\beta$ -oxidation and its deficit is supposedly mostly apparent in cells with the highest energy and myelin maintenance demand, as retinal rods and GP neurons. This is supported by autopsy findings which, despite ubiquitous expression of *PANK2*, revealed neuropathologic abnormalities largely confined to GP. The central region of GP exhibits profound

rarefaction with abundant degenerating neurons staining consistently for ubiquitin (Kruer et al., 2011b). Abundant iron was found in the form of perivascular hemosiderin deposits, iron-laden macrophages and as cytoplasmic ferritin found predominantly in astrocytes, but to a lesser degree also in neurons. This pattern of distribution suggests that overwhelming of the defense mechanism against increased iron ingress from blood vessels is important in the pathogenesis of the disease. Another typical pathologic finding in PKAN is the presence of axonal spheroids likely representing swollen and dystrophic axons. Defects in the axonal transport or membrane integrity possibly arising from insufficient neuronal energy metabolism are supposedly the cause of their formation (Gregory et al., 2009).

PKAN is the most frequent NBIA, accounting for more than 50% of cases (Gregory et al., 2009). The classic form of PKAN was originally referred to as Hallervorden–Spatz disease, but because Julius Hallervorden has been associated with Nazi euthanasia programs of the Third Reich, this eponym has been abandoned (Van Craenenbroeck et al., 2010). The movement disorders, such as dystonia, dysarthria, parkinsonism, ataxia, and spasticity usually begin in the first decade, but they are often preceded by developmental delay, general clumsiness or attention deficit hyperactivity disorder (ADHD). Cognitive impairment and behavioral abnormalities as well as pigmentary retinopathy are common but highly variable (Hayflick et al., 2003). Hypoprebetalipoproteinemia, acanthocytes and retinitis pigmentosa (HARP) phenotype is now recognized as a part of the PKAN spectrum and PKAN can be accompanied by any of these symptoms (Houlden et al., 2003). Clinical symptoms tend to progress rapidly, but periods of rapid decline are often interspersed by periods of relative stability, similarly to mitochondrial disorders. Atypical form of PKAN begins in the second decade or even later, and patients with late adult-onset were also described (Aggarwal et al., 2010; Antonini et al., 2006). Marked clinical variability in neurologic presentation and progression has been reported in many families, so that some family members present with childhood-onset cognitive and behavioral changes, generalized dystonia and chorea, whereas others may have only slowly progressive focal dystonia, such as oromandibular “eating” dystonia, while others may present with adult-onset parkinsonism (Thomas et al., 2004). The clinical heterogeneity in different families has been



**Fig. 4.** Axial (A) and coronal (B) T2WI 3T MRI image of a patient with PKAN showing typical “eye of the tiger” sign with central hyperintensity reflecting gliosis or edema (arrow) surrounded by hypointensity reflecting accumulated iron (arrowhead). Kindly provided by Dr. M. Dezortova (ZRII, IKEM, Prague).



attributed to different genetic mutations, and milder atypical phenotype was initially connected with a partially retained PANK2 function (Hayflick et al., 2003). Later studies, however, found correlation only between PANK2 activity and age at onset, but not the rate of disease progression (Hartig et al., 2006) or any particular genotype–phenotype correlation (Pellecchia et al., 2005).

MRI in patients with PKAN reveals iron accumulation in GP and to a lesser extent also in SN. Susceptibility-weighted MRI demonstrates continuous involvement of nigropallidal pathways (Vinod Desai et al., 2007). A highly specific MRI feature for PKAN is the “eye of the tiger” sign (Fig. 4). It comprises of the central region of hyperintensity with a surrounding hypointensity in GP in T2WI (McNeill et al., 2008a). Once considered pathognomonic for PKAN (Hayflick et al., 2003), it was later shown to be present also in other diseases, such as hereditary ferritinopathy and multiple system atrophy (Erro et al., 2011; Kumar et al., 2006; McNeill et al., 2008a). Although longitudinal follow-up studies are lacking, several observations have suggested that the earlier appearing central hyperintensity in GP represents gliosis and edema, while the surrounding hypointensity represents iron accumulation (Chiapparini et al., 2011; Hayflick et al., 2006; Rossi et al., 2011). This observation suggests that edema and gliosis are consequences of primary tissue insult and iron accumulation may be only a secondary event. Thus, although MRI pattern in PKAN is similar to that in hereditary ferritinopathy, the sequence of iron accumulation and gliosis/edema is opposite. The reason for iron accumulation in PKAN remains unknown. Original hypothesis postulated that iron aggregates with cysteine due to its iron-chelating properties and these aggregates mediate oxidative stress (Perry et al., 1985). After the discovery of other NBIA with similar pattern of iron accumulation but without increased cysteine levels, other theories based on the link between iron and lipid metabolism were proposed instead (Schneider and Bhatia, 2010). Thus, iron accumulation could be a consequence of disturbed ceramide metabolism (Fig. 3). Interestingly, silencing PANK2 in some cell types led to cellular iron deficiency due to increased iron egress caused by FPN1 upregulation (Poli et al., 2010). If this happens in endothelial cells of PKAN patients, it would explain why iron deposits are accumulating in the perivascular space.

There is no effective treatment for PKAN, although iron chelation therapy has been tried in an attempt to slow down the progression of the disease (Zorzi et al., 2011). Deep brain stimulation (DBS) of internal GP has been documented in several series to be effective in the treatment of severe generalized dystonia, but the observed improvement is not as robust as in primary generalized dystonias (Lim et al., 2011; Mahoney et al., 2011; Timmermann et al., 2010). DBS also is a promising symptomatic treatment of dystonia in other NBIA.

#### *PLA2G6 associated neurodegeneration (PLAN)*

PLAN (OMIM 256600) is an autosomal recessive disorder caused by mutations in the gene encoding phospholipase A2G6 (PLA2G6), a type A2 calcium independent group 6 phospholipase catalyzing hydrolysis of glycerophospholipids, generating free fatty acids and lysophospholipids (Khateeb et al., 2006; Morgan et al., 2006). There are three forms of PLAN: infantile neuroaxonal dystrophy (INAD), atypical neuroaxonal dystrophy (ANAD), and adult onset dystonia-parkinsonism (Gregory and Hayflick, 2011). The infantile form, which begins within the first 2 years of life, is characterized by a regression in the psychomotor development, followed by ataxia, gait instability, truncal hypotonia, strabismus, nystagmus and optic atrophy. These symptoms are later accompanied by spastic tetraparesis, polyneuropathy, cognitive decline and seizures. ANAD usually begins later, on average at 4–5 years of age, and is manifested by a slower progression of dystonia, dysarthria and neurobehavioral disturbances such as autism, ADHD and depression. Other symptoms described in the infantile form are also variably present (Gregory et al., 2009). PLA2G6 mutation may also manifest as dystonia-parkinsonism syndrome with the onset in 2nd or 3rd decade and marked initial

response to levodopa. Because of associated parkinsonism, PLAN is also categorized as PARK14 (Paisan-Ruiz et al., 2009). PARK14-linked parkinsonism is frequently accompanied by an early development of psychosis, pyramidal signs and frontotemporal type dementia (Yoshino et al., 2010). MRI reveals early cerebellar atrophy and gliosis in majority of patients and iron accumulation in GP and SN in about 50% of patients with INAD phenotype (Gregory et al., 2008). The proportion of patients with iron accumulation increases with disease progression, but it may be absent in the dystonia-parkinsonism phenotype (Yoshino et al., 2010). White matter changes suggestive of demyelination were also described in a large proportion of patients (Khateeb et al., 2006; Kurian et al., 2008).

Axonal spheroids composed of accumulated aberrant phospholipid membrane are the pathologic hallmark of PLAN, although patients without spheroids found in autopsied brains have been described (Morgan et al., 2006). These spheroids are abundant in distal axons in CNS and peripheral nerve terminals. When found in the peripheral nerve biopsy the spheroids serve as a highly specific diagnostic marker of PLAN (Malik et al., 2008). Autopsy findings are variable with iron deposition severity ranging from absent to small clusters of iron-laden macrophages to widespread iron aggregates in GP. Majority of brains also exhibit tau pathology with neurofibrillary tangles along with diffuse  $\alpha$ -synuclein accumulation and numerous Lewy bodies, similar to end-stage PD (Paisan-Ruiz et al., 2010). This raises the possibility of PLA2G6 abnormality in some sporadic neurodegenerative disorders.

PLA2-knockout mouse model displays slowly progressing, predominantly cerebellar neurodegeneration with age-dependent accumulation of spheroids but without iron accumulation (Malik et al., 2008; Zhao et al., 2011). Interestingly, another mouse model with point mutation in the PLA2G6 gene causing its deactivation led to much earlier disease onset, better resembling the human disease (Wada et al., 2009). The authors hypothesized that the difference might be caused by abnormal intracellular signaling related to the mutated PLA2G6. The pathophysiology is unclear, but two features of PLA2G6 protein may be involved: phospholipid membrane remodeling and cell cycle regulation (Bras et al., 2008). Altered lipid composition of membranes may have far-reaching consequences (Fig. 3). Apoptosis induction caused by PLA2 activation is likely mediated through activation of sphingomyelinase and ceramide production (Johansson et al., 2010). On the other hand, PLA2 dependent membrane repair may be important in restoring the membrane damaged by peroxidation and in preventing apoptosis induction. Thus, both decreased and increased PLA2 enzymatic activity might possibly lead to apoptosis through different pathways (Lei et al., 2010). Initial reports described PLA2G6-inactivating null mutations in patients with INAD phenotype and missense mutations in patients with later-onset PLAN (Gregory et al., 2009). Recent study confirmed that distinct PLAN phenotypes may arise from different mutation effects on the enzyme function. In INAD, catalytic activity of PLA2G6 *in vitro* was found to be decreased, whereas in the dystonia-parkinsonism phenotype it was normal or even increased (Engel et al., 2010). Interestingly, several patients with clinically typical INAD possessed only a single heterozygous mutation suggesting either the presence of an undetected mutation or a pathogenic potential of some heterozygous mutations caused by dominant-negative mechanism (Paisan-Ruiz et al., 2010; Wu et al., 2009). These observations along with the differences in animal models imply alteration of the PLA2-mediated regulation of the cell cycle caused by some mutations.

#### *Fatty acid hydroxylase associated neurodegeneration (FAHN)*

FAHN (OMIM 611026) is an autosomal recessive disease with multiple phenotypes caused by mutations in the gene encoding fatty acid 2-hydroxylase (FA2H) (Kruer et al., 2010). Mutations in FA2H were initially discovered in patients with familial leukodystrophy complicated by spastic paraparesis and dystonia (Edvardson et al., 2008). The gene

was shown to be the same as in a previously described locus designated as spastic paraplegia 35 (SPG35) (Dick et al., 2010). Patients with FAHN, however, have been found to also exhibit profoundly decreased signal in GP in T2WI suggestive of iron accumulation in addition to other MRI features such as dystrophic white matter changes, thinning of the corpus callosum and ponto-cerebellar atrophy (Kruer et al., 2010). Subsequently, other patients with mild signal decrease in GP were described (Garone et al., 2011). Although the connection between myelination and iron metabolism has been appreciated for some time, FAHN is first direct evidence that iron accumulation and abnormal myelin metabolism may have common cause. Nevertheless, iron tends to occur later in the course of the disease or may not be evident at all in some patients (Kruer et al., 2010).

Patients typically develop normally up to 3–10 years of age at which time they begin to develop various combinations of gait impairment, dystonia, dysarthria, ataxia, spastic paraparesis, optic nerve atrophy, nystagmus, cognitive decline and seizures (Kruer et al., 2010). Autopsy findings are not yet available and the pathophysiology is largely unknown. FA2H has a role in the synthesis of 2-hydroxylated fatty acids (2-HFA) that are important components of sphingolipids, phospholipid membrane and myelin sheaths. It has been estimated, that more than 15% of myelin lipids contain 2-HFA (Hama, 2010). The known disease causing mutations are inactivating and may thus cause impaired myelin maintenance. It was suggested that FA2H is dispensable during the early phases of myelination, but it is necessary for long term stability of myelin during life (Hama, 2010). Indeed, young FA2H-null mice are indistinguishable from the wild type, but aged mice developed scattered demyelination and axonal degeneration in central and peripheral nervous system (Zoller et al., 2008). However, the pathologic effects are not confined to abnormal myelination since mice with FA2H deleted only in oligodendrocytes had milder symptoms compared to FA2H-knockout mice (Potter et al., 2011). Indeed, FA2H also has a role in the lipid signal transduction and its defects may lead to apoptosis by upregulating expression of cyclin-dependent kinase (CDK) inhibitors (Hama, 2010).

#### *Kufor–Rakeb disease and other lysosomal disorders*

Kufor–Rakeb disease, also designated as PARK9, first described in a Jordanian family, is an autosomal recessive disorder caused by mutations in the gene encoding ATPase type 13A2 (ATP13A2) (OMIM 606693) (Najim al-Din et al., 1994). Symptoms usually present between 10 and 20 years of age and include fatigue, apathy and behavioral disturbances. During the progression other symptoms such as dystonia-parkinsonism, supranuclear gaze palsy, dysarthria, facial–finger myoclonus and pyramidal signs may develop. Initially responding well to levodopa, the beneficial effects gradually diminish as dyskinesias or psychotic side effects emerge (Lees and Singleton, 2007; Ramirez et al., 2006). Clinical symptoms and disease course resemble those in PARK14, but brain MRI is different and usually shows severe generalized brain atrophy.

Although T2\* hypointense MRI signal has been described in putamen and caudate in two patients (Bruggemann et al., 2010; Schneider et al., 2010), iron accumulation in ATP13A2 mutations has not been definitely established based on histochemistry of autopsied cases (Chien et al., 2011; Eiberg et al., 2011; Santoro et al., 2011). It was suggested that only mutations causing complete dysfunction of the ATP13A2 protein lead to iron dysregulation (Santoro et al., 2011). The ATP13A2 gene which codes for the lysosomal transport protein is expressed chiefly in SN, thought to be responsible for lysosomal cation influx and optimal pH maintenance. Acid environment is necessary for iron efflux from lysosome and suboptimal pH may result in the retention of iron and other materials causing lysosomal dysfunction. This may consequently lead to impaired recycling of iron and of membrane lipids (Kruer et al., 2010), as well as abnormal  $\alpha$ -synuclein metabolism (Gitler et al., 2009). The misfolded protein is retained in the endoplasmic reticulum (ER), where it contributes to ER stress (Park et al., 2011). It was also suggested that

dysfunctional ATP13A2 loses its protective function against manganese toxicity (Tan et al., 2011).

Apart from above mentioned disorders, T2 hypointensities in GP, SN and thalamus suggestive of iron deposits have been reported in other metabolic diseases including GM1 gangliosidosis (OMIM 611458) (De Grandis et al., 2009), fucosidosis (OMIM 612280) (Galluzzi et al., 2001; Ismail et al., 1999; Oner et al., 2007; Provenzale et al., 1995; Steenweg et al., 2010) and mucopolisidosis type 4 (MLIV) (OMIM 252650) (Frei et al., 1998; Wakabayashi et al., 2011). Although excessive brain iron deposits were not confirmed by histochemistry so far, these lysosomal storage disorders share some common features with the classic NBIA. They may present as a developmental delay or as a juvenile/adult onset disorder with combined pyramidal/extrapyramidal symptoms (Caciotti et al., 2011; Wakabayashi et al., 2011; Willems et al., 1991). Interestingly, the most striking abnormality is the impairment of myelination. Two of the involved enzymes,  $\beta$ -galactosidase and  $\alpha$ -L-fucosidase, cleave saccharides from various glycoproteins and glycolipids. Their defects thus lead primarily to impaired phospholipid membrane recycling likely responsible for hypomyelination and secondarily possibly to iron pathway dysregulation. Interestingly, in a mouse model of gangliosidosis, progressive brain iron depletion, rather than accumulation, was observed (Jeyakumar et al., 2009). Mucopolin 1 (MCOLN1) is a putative lysosomal ion channel supposedly responsible for iron release from lysosomes. Beside accumulation of lipids, increased lysosomal iron levels and low cytosolic iron levels were observed in MLIV patients' fibroblasts (Dong et al., 2008). Despite the improving knowledge about the role of lysosomes in iron metabolism and neurodegenerative disorders (Kurz et al., 2011; Shachar et al., 2011), it is still unclear why iron accumulation occurs in some but not other lysosomal disorders and why only subset of patients is affected.

#### *Woodhouse–Sakati syndrome (WSS)*

WSS (OMIM 241080) is a rare autosomal recessive disorder caused by a mutation in the *c2orf37* gene (Alazami et al., 2010). Initially described in patients from Saudi Arabia, this disorder is manifested with hypogonadism, deafness, alopecia, diabetes mellitus and progressive dysarthria, dystonia, chorea and cognitive decline (Woodhouse and Sakati, 1983). Other symptoms including seizures, syndactyly, keratoconus and polyneuropathy were later reported (Schneider and Bhatia, 2008). MRI reveals T2 hypointensities in SN, GP and red nucleus suggestive of iron deposits with, often profound, white matter disease (Al-Semari and Bohlega, 2007). The product of this gene is expressed in nucleoli (Alazami et al., 2010), however, little is known about its function.

#### *Neurodegeneration associated with c19orf12 mutation*

A recent paper described a novel homozygous mutation in an orphan gene *c19orf12* encoding a mitochondrial protein of unknown function in a substantial group of patients with a central European descent suffering from previously unknown NBIA (Hartig et al., 2011). On the basis of the mitochondrial localization of the protein, it was proposed to name this disorder as mitochondrial membrane protein associated neurodegeneration (MPAN). Brain MRI in these patients uniformly showed T2 hypointensities in GP and SN. Both, the clinical presentation with spastic paraparesis, dystonia, parkinsonism, psychiatric symptoms, motor axonal neuropathy and optic atrophy and autopsy findings with Lewy bodies, axonal spheroids and tau pathology resembles PKAN. However, the average age at onset of 9 years was higher and the rate of progression was slower. Interestingly, one of these patients with later onset presented with parkinsonism and was initially diagnosed as PD. Future studies should be directed towards elucidation of this protein's function. This knowledge may improve our understanding of mechanisms involved in iron accumulation and possibly also in the pathophysiology of sporadic neurodegenerative disorders.

## Idiopathic NBIA

There is a heterogeneous group of patients with a variable age at onset and negative screening for mutations in known genes and they are given the diagnosis of idiopathic NBIA (Aggarwal et al., 2010; Bruggemann et al., 2011). The proportion of idiopathic NBIA is gradually decreasing with rapid advances in the genetics of neurodegenerative disorders, but there are still patients suffering from genetic forms of NBIA in whom specific mutations have not yet been identified for various reasons. For example, large deletions and duplications of genes are not identifiable by sequencing and part of the idiopathic NBIA population may thus be composed of not properly diagnosed patients with known NBIA. It is also possible, that some NBIA cases are not genetic in nature. Nevertheless, further genes causing NBIA are awaiting their discovery (Gregory et al., 2009), which will be accelerated with the wider use of whole exome and genome sequencing (Naidoo et al., 2011).

A specific subgroup of idiopathic NBIA is formed by patients with a distinct phenotype, static encephalopathy of childhood with neurodegeneration in adulthood (SENDA). These patients have a psychomotor impairment in the early childhood which remains stable until adulthood, when a relatively sudden onset and fast deterioration of dystonia-parkinsonism and spasticity develops. MRI shows iron accumulation in GP and SN with mild cerebellar atrophy and a specific T1 pattern: SN hyperintensity with a central band of hypointensity (Gregory and Hayflick, 2011; Kruer et al., 2011a).

## Other diseases with increased brain iron content

Knowledge of brain iron metabolism and pathogenesis of NBIA can help in understanding other more common neurodegenerative disorders with increased brain iron content. Iron accumulation is not a hallmark of these disorders and usually is not apparent on routine MRI.

### Friedreich's ataxia (FRDA) and mitochondrial disorders

FRDA (OMIM 229300) is an autosomal recessive disorder caused in 97% of cases by expansions of a GAA repeat in the first intron of both *frataxin* (FXN) alleles, which interfere with its transcription. The remaining 3% are compound heterozygotes who carry one allele with a loss-of-function mutation (Cossee et al., 1999). Similar to other triplet-repeat disorders, the age of onset and the rate of disease progression are negatively correlated with the number of GAA repeats (Marmolino, 2011). Usually starting before 25 years of age, FRDA typically manifests with progressive limb ataxia, dysarthria, sensory neuropathy and signs of pyramidal pathway dysfunction (Schols et al., 1997). However, atypical cases with later onset, dominant spasticity, chorea, dystonia or tremor have been described (Hou and Jankovic, 2003). Other symptoms of FRDA are cardiomyopathy, diabetes mellitus and scoliosis.

Mitochondrial iron accumulation was suggested to underlie the disease pathophysiology and it was documented by histochemical stains in yeast and animal models (Marmolino, 2011) as well as in fibroblasts and cardiomyocytes of FRDA patients (Delatycki et al., 1999; Michael et al., 2006). On the other hand, there are controversies whether mitochondrial iron accumulation occurs in the human nervous tissue. Autopsy studies have shown degeneration with loss of myelinated fibers and gliosis in spinocerebellar and pyramidal tracts, dorsal root ganglia and dorsal columns of the spinal cord. In the brain, cerebellar dentate nuclei typically showed the most severe degenerative changes (Koeppen et al., 2011). Accordingly, routine MRI shows atrophy of cerebellum, brainstem and cervical spinal cord (Pagani et al., 2010). Increased mitochondrial iron deposits in dentate nucleus were not found by histochemistry in a postmortem study. However, ferritin iron was shown to relocate from oligodendrocytes to microglia and astrocytic processes in the late stage FRDA. It was accompanied by a marked upregulation of FPN1 in the Purkinje cell terminals. Upregulation of FPN1 may enable iron efflux from cellular regions near iron-laden mitochondria and it was

hypothesized to be a defense mechanism (Koeppen et al., 2007). Contrary to autopsy findings, a slightly increased iron content in cerebellar dentate nuclei was detected by the T2\*WI MRI (Boddaert et al., 2007; Waldevogel et al., 1999). There are several alternative explanations for this finding such as an increased deoxyhemoglobin content due to altered blood flow or higher condensation of iron containing proteins (Boddaert et al., 2007). Nevertheless, the increase of T2\* signal after the iron chelating treatment supports the iron accumulation possibility. The reason for discrepant results of autopsy and MRI studies is unclear but it is important to note that the autopsy study examined brains from patients in the late stage of the disease, possibly harboring other pathological features such as atrophy and microglial cleaning reaction.

FXN supposedly has a direct role in the mitochondrial iron trafficking, namely the incorporation into Fe-S complexes and its detoxification through ferrooxidation (Marmolino, 2011). FXN defects may thus cause a dysfunction of proteins dependent on Fe-S prosthetic group, intramitochondrial iron accumulation and increased cellular iron uptake. Indeed, decreased activities of respiratory complexes I–III and lower maximal rate of ATP production have been documented in FRDA (Ristow et al., 2000). Intramitochondrial iron accumulation results possibly from its impaired egress since iron can exit mitochondria only in the form of complex molecules. Moreover, cytosolic Fe-S complexes have a role in the cellular iron homeostasis and their deficiency cause IRP1-mediated upregulation of TFRC (Lobmayr et al., 2005). Another interesting possibility is that dysfunction of frataxin leads to an upregulation of FTMT which effectively binds iron but can not readily release it. This may ultimately cause lack of iron available for the metalloprotein synthesis further promoting mitochondrial dysfunction (Popescu et al., 2007). In the mouse model, iron accumulation followed occurrence of neurological symptoms and the inactivation of mitochondrial Fe-S dependent enzymes (Puccio et al., 2001) implying its secondary role in the pathogenesis (Bayot et al., 2011).

Other mitochondrial iron accumulation disorder with a phenotype resembling FRDA has been described in patients with the *ABCB7* gene mutation, which codes a mitochondrial Fe-S cluster exporter. It manifests as a slowly progressive spinocerebellar ataxia, profound cerebellar hypoplasia and microcytic anemia (Fleming, 2011). The disease was named X-linked sideroblastic anemia with ataxia (OMIM 301310) (Shimada et al., 1998). Iron-laden mitochondria were found in patients' erythroid cells, but it is unclear whether iron dysregulation occurs in neuronal cells and underlies neurological symptoms (Hellier et al., 2001).

### Neurodegenerative movement disorders

Aging is the main risk factor for most neurodegenerative disorders (Rhodes and Ritz, 2008) and it was suggested that age-related iron accumulation is one of the factors connecting aging and neurodegeneration (Bartzokis et al., 2007b). Along this line, it was suggested that the lower incidence of neurodegenerative disorders in females might be explained by higher life-long body iron losses through menstruation. However, lower brain iron level in females was not supported by other studies (Burgetova et al., 2010; Xu et al., 2008). Interestingly, higher iron content was documented in the left hemisphere suggesting a relationship with motor lateralization (Xu et al., 2008). Altogether these findings indicate that the intrinsic brain metabolism variation between hemispheres rather than global gender-related iron metabolism differences influence the brain iron content. This leads to speculations that lateralized brain iron content is related to the asymmetry of symptoms in PD. This is supported by a recent meta-analysis showing that motor lateralization impacts the side of onset in PD (van der Hoorn et al., 2011). Iron accumulation has been reported in almost every neurodegenerative disorder suggesting that iron may be involved in some essential process involved in neurodegeneration such as apoptosis (Sian-Hulsmann et al., 2011). On the other hand, it is not possible to exclude that iron increase is just a consequence of cellular loss (Sasthy and Arendash, 1995).



### Parkinson's disease

Several autopsy studies have found increased total iron content in the SN of PD patients compared to age-matched controls but other studies did not confirm this finding (for review see (Friedman et al., 2009)). These inconsistencies were explained in part by different histochemical methods employed (Friedman et al., 2009) or pathophysiological heterogeneity of PD (Sian-Hulsmann et al., 2011). Another study indicated that iron content in the SN was not elevated in mildly affected but only in advanced PD patients (Riederer et al., 1989). This suggests that iron increase is not involved in the early disease development and introduces the disease stage as another source of variability in SN iron content.

It was also suggested that total iron is not increased in PD, but its distribution is altered. Indeed, contrary to normal subjects where more iron is deposited in the SN pars reticulata, in PD iron is deposited abundantly in the SN pars compacta containing pigmented neurons, which are mostly afflicted by the neurodegenerative process (Sian-Hulsmann et al., 2011). Compared to aged matched controls, inappropriately low concentrations of ferritin in the SN of PD patients and even in the incidental Lewy body cases were reported (Friedman et al., 2011). Normal upregulation of ferritin associated with increased iron content during aging was absent in PD patients due to sustained activity of IRP1 in an autopsy study (Faucheux et al., 2002). It is however not clear whether decreased levels of ferritin pertain to glia, where ferritin is the main iron storage protein, or also to neurons where neuromelanin stores most of the iron (Zecca et al., 2001). Interestingly, FTL was shown to be a component of neuromelanin granules documenting its iron-regulatory function in neurons (Tribl et al., 2009). Tissue concentration of neuromelanin is dramatically decreased in PD because pigmented neurons in SN pars compacta are preferentially lost in PD, but spared neurons contain large amounts of neuromelanin (Kastner et al., 1992). In fact, accumulated iron in the SN is deposited within neuromelanin granules (Good et al., 1992). A higher level of redox activity of neuromelanin–iron aggregates was demonstrated in PD caused by their iron overload (Faucheux et al., 2003). Despite the protective role of neuromelanin in dopaminergic neurons, extracellular neuromelanin–iron complexes released from dying neurons can activate microglia which produce neurotoxic compounds and thus exacerbate neurodegeneration (Zecca et al., 2008). Altogether, these studies suggest that disruption of the ferritin-complex along with other disturbances of iron regulation eventually overwhelm the storage capacity of neuromelanin system, which may lead to increased labile iron pool and promote the neurodegenerative process.

Detection of increased iron content in SN may be of clinical significance since it can help in the diagnosis of PD. Combination of several MRI parameters can discriminate between PD patients and controls with an excellent accuracy. SN of PD patients exhibits decreased fractional anisotropy reflecting microstructural disintegration and decreased T2\* transverse relaxation rate reflecting tissue iron stores (Du et al., 2011; Peran et al., 2010). Moreover, according to several MRI studies, iron deposition in the SN correlates with the disease severity as well as with the motor score in the contralateral body side (Gorell et al., 1995; Jin et al., 2011) but not with the disease duration (Wallis et al., 2008). Correlation between disease severity and SN iron content suggest direct relationship between neurodegeneration and iron accumulation. T2\*WI obtained by a 7-Tesla MRI scanner offers an excellent contrast of the SN pars compacta and may enable radiological diagnosis of PD by the “naked eye” (Cho et al., 2011).

Recognition of increased iron content in the SN of PD patients and connection between monogenic parkinsonism and NBIA's led to extensive genetic examinations in PD. However, based on studies in large populations, polymorphisms or mutations in genes encoding FTL, FTH1, IREB2, TF, LTF, TRFC or FXN (for review see Rhodes and Ritz, 2008) as well as HAMP (Castiglioni et al., 2010b), FTMT (Castiglioni et al., 2010a), PANK2 (Klopstock et al., 2005), ATP13A2 (Rakovic et al., 2009), and PLA2G6 (Kauther et al., 2011; Tan et al., 2010; Tomiyama et al., 2011) were not recognized as a common

cause of PD. On the other hand, a specific haplotype of the *DMT1* gene was found to occur at greater frequencies in Chinese PD patients compared with controls suggesting that alterations in *DMT1* function may predispose to PD (He et al., 2011), however this result requires confirmation. There was a higher frequency of the G258S *TF* gene polymorphism found in a cohort of French PD patients (Borie et al., 2002), but it was not replicated by a subsequent study with a different population (Ezquerria et al., 2005). It is possible that heterozygous mutations in several of these genes play a role in small subsets of adult-onset PD patients as was documented in a family study with the *ATP13A2* gene mutation (Bruggemann et al., 2010) and individual cases of a population study investigating the *PLA2G6* gene (Tan et al., 2010). The association between mutations in *CP* gene and PD is controversial. One study found several *CP* gene variants in a group of PD patients (Hochstrasser et al., 2004), but frequencies of these variants in PD seem to be not different from healthy population (Castiglioni et al., 2010b). In a recent study iron deposition in SN inversely correlated with the plasma CP level. In fact, only patients with low CP exhibited abnormal SN iron accumulation (Jin et al., 2011).

Other studies showed abnormal expression of iron regulation proteins. Nigral cells behave as if they were iron deficient, expression of proteins involved in iron uptake as *DMT1*, *TFR2* and *LTFR* is upregulated (Faucheux et al., 1995; Ke and Qian, 2007), whereas expression of those involved in iron efflux as *FPN1* is downregulated (Wang et al., 2007). SN areas with the most severe cell degeneration showed an increased *LTFR* expression (Faucheux et al., 1995). Upregulation of iron uptake may have similar reasons as in *FRDA* since mitochondrial dysfunction, which was documented in nigral cells in PD, may lead to decreased Fe–S cluster synthesis (Gille and Reichmann, 2011). Upregulation of *DMT1* in PD may possibly be also caused by the activation of the ceramide signaling pathway (Jana et al., 2009).

Evidence for a potential role of iron in the process of neurodegeneration comes also from animal studies. Its toxic effect was evidenced by a selective dopaminergic loss elicited by an intranigral infusion of iron (Wesemann et al., 1994) and even by repeated high-doses of intravenous iron (Jiang et al., 2007). Chelator pretreatment reduced degeneration of SN neurons in various toxin-induced animal PD models (Berg and Hochstrasser, 2006). Mice with dysfunctional *DMT1* have been also partially protected against PD-inducing toxins, stressing the role of this protein in iron mediated degeneration (Salazar et al., 2008).

Beside causing oxidative stress, iron was also suggested to enhance the expression of  $\alpha$ -synuclein (Rhodes and Ritz, 2008) as well as to induce fibril formation and may thus promote the formation of Lewy bodies (Uversky et al., 2001). Recent *in vitro* study confirmed that iron and mutant  $\alpha$ -synuclein may interact and that iron aggravates the toxicity caused by the  $\alpha$ -synuclein alone (Chew et al., 2011). Lewy bodies containing reactive iron and oxidized lipid material were also found in lipid metabolism disorders and lysosomal storage diseases suggesting a connection between PD and these metabolic diseases (Shachar et al., 2011).

### Other neurodegenerative disorders

Brain iron accumulation has been documented in other sporadic and genetic degenerative movement disorders (Berg and Hochstrasser, 2006). In multiple system atrophy (MSA) and progressive supranuclear palsy (PSP), increase of the total iron content with a different pattern compared to PD has been described. An autopsy study showed iron accumulation in putamen and SN in both PSP and MSA (Dexter et al., 1991). Increased putaminal iron is the most consistent finding in MRI studies and its visualization may thus be helpful in the differential diagnosis between PD and MSA or PSP (Gupta et al., 2010; Vymazal et al., 1999; Wang et al., 2011). T2 hypointensities in putamen have low sensitivity but high specificity for atypical parkinsonism (Arabia et al., 2010). Interestingly, the eye-of-the-tiger sign has been described in several patients with clinically probable MSA (Chang et al., 2009; Strecker et al., 2007), but the diagnosis was not confirmed by autopsy. The reason for the iron accumulation in MSA and PSP is not clear,



although hypoceruloplasminemia has been implicated in some cases of MSA (Kurisaki et al., 2002). Another hypothetical possibility is that the increased iron deposition comes from dysfunctional oligodendrocytes. The neuropathological hallmark of MSA are glial cytoplasmic inclusion bodies, which are aggregates of misfolded proteins such as  $\alpha$ -synuclein and transferrin located in oligodendroglial cells (Papp et al., 1989). Thus, MSA may be viewed as a primary myelin disorder with a secondary axonal and neuronal degeneration (Wenning et al., 2008). Microglial activation with iron accumulation likely promotes the degenerative process (Schwarz et al., 1996) similarly to Huntington's disease (HD) (Simmons et al., 2007). Interestingly, a similar pattern of iron accumulation associated with myelin disruption has been also described in multiple sclerosis (Burgetova et al., 2010; Drayer et al., 1987) and HD (Bartzokis et al., 2007a).

In the brains of HD (OMIM 143100) patients, increased striatal and cortical iron levels have been reported in autopsy studies (Dexter et al., 1991; Simmons et al., 2007). Increased iron was detected also by MRI in putamen, caudatum and GP, even early in the disease process (Bartzokis et al., 1999). In another study, iron content correlated with the number of CAG triplets but not with disease duration or motor impairment suggesting that genetic load rather than disease progression is related to iron accumulation (Vymazal et al., 2007). The reason for iron accumulation in HD is unclear. In accordance with the previous study, the connection between the disease-causing dysfunctional protein huntingtin and iron metabolism has been suggested since it was shown to be upregulated during cellular iron depletion (Hilditch-Maguire et al., 2000). This was supported by a finding that a chelating agent clioquinol slowed progression in an animal model of HD (Nguyen et al., 2005). The exact function of huntingtin is however not entirely understood and it was suggested to have a role in axonal vesicular transport and brain-derived neuronal growth factor metabolism which are necessary for myelin synthesis and maintenance (Bartzokis et al., 2007a). Abnormal myelin composition with decreased levels of the GM1 ganglioside was described in various cells in HD brains (Posse de Chaves and Sipione, 2010). Myelin disruption accompanied by an increase of the number of oligodendrocytes was described in early disease phases. Thus, myelin breakdown and continuous iron-demanding remyelination has been suggested as another potential cause of iron accumulation in HD (Bartzokis et al., 2007a). Nevertheless, the accumulated iron was not observed in oligodendrocytes but in activated microglia (Simmons et al., 2007). This still may be in agreement with the previous theory since activated microglia serve as an iron donor for oligodendrocyte progenitors during myelination (Schonberg and McTigue, 2009). Increased microglial iron content may thus be a consequence of increased and aberrant remyelination or defective iron transfer between microglia and oligodendrocytes.

## Hemochromatosis

It is not yet clear whether hematochromatosis (OMIM 235200), predominantly caused by the *HFE* gene mutation (Feder et al., 1996), is a risk factor for degenerative diseases. Although several epidemiological studies support the role of the *HFE* mutations in PD and other neurodegenerative disorders, others do not (for review see (Nandar and Connor, 2011)). *HFE* gene mutation is the prevalent cause of systemic iron overload leading to iron deposits in several organs including liver, heart and endocrine tissue (Adams and Barton, 2007). Brain is believed to be protected from the systemic iron overload by BBB. However, *HFE* protein has been shown to be expressed in brain vessels and choroid plexus and its mutation may thus influence brain iron uptake (Connor et al., 2001). Moreover, impaired function of the BBB has been described during aging potentially allowing increased amounts of iron to enter the brain. Accordingly, increased iron content in basal ganglia and dentate nucleus ascertained by MRI has been described in several

hemochromatosis patients (Berg et al., 2000). It is thus conceivable that impaired BBB function may be responsible for iron permeability and consequent development of neurological symptoms such as parkinsonism, tremor, cognitive decline, psychiatric symptoms or cerebellar signs in individual patients (Costello et al., 2004; Nielsen et al., 1995; Russo et al., 2004; Serata et al., 2012). A recent MRI study showed increased brain iron content in men but not women with *HFE* mutations (Bartzokis et al., 2010). If only men have a higher risk of neurodegeneration associated with *HFE* mutations, then previous studies might have been biased. Another reason for inconclusive results of genetic studies may be the fact, that movement disorders seen in patients with hemochromatosis are variable and may not conform to standard definitions for established nosological entities. Aggressive treatment by repeated phlebotomies may also alter the risk of developing the neurological disease. Since movement disorders are rare in association with hemochromatosis, it has been suggested that such patients should be thoroughly investigated for another neurological disease (Russo et al., 2004).

## Restless legs syndrome (RLS)

There is a growing body of evidence that iron dysregulation plays a role in RLS as suggested by the observation that iron deficiency exacerbates RLS and iron replacement improves the symptoms (Allen and Earley, 2007; Ondo, 2010). It is also well documented that dopaminergic transmission, which is disturbed in RLS, is critically dependent on iron. Several autopsy, MRI and sonography studies have documented iron deficiency in SN and other brain areas in RLS patients (Allen and Earley, 2007; Allen et al., 2001; Godau et al., 2008). Furthermore, serum and CSF ferritin levels correlate negatively with the risk of development of RLS. Recent study found that expression of *MEIS1*, which is a RLS-predisposing gene, is regulated by cellular iron status (Catoire et al., 2011).

**Table 4**

Classification of movement disorders with abnormal iron metabolism.

1. Metabolic disorders associated with brain iron accumulation
  - 1.1. Disorders of the iron metabolic pathway
    - 1.1.1. Neuroferritinopathy
    - 1.1.2. Aceruloplasminemia
  - 1.2. Disorders of the ceramide/phospholipid metabolism
    - 1.2.1. Panthotenate kinase associated neurodegeneration (PKAN, NBIA-1)
      - Classic PKAN
      - Atypical PKAN
    - 1.2.2. PLA2G6 associated neurodegeneration (PLAN, NBIA-2)
      - Infantile neuroaxonal dystrophy (INAD)
      - Atypical neuroaxonal dystrophy (ANAD)
      - Adult-onset dystonia-parkinsonism syndrome (PARK 14)
    - 1.2.3. Fatty acid hydroxylase associated neurodegeneration (FAHN)
  - 1.3. Lysosomal disorders
    - 1.3.1. ATP13A2 mutation (Kufor-Rakeb disease, PARK 9)
    - 1.3.2. GM1 gangliosidosis
    - 1.3.3. Fucosidosis
    - 1.3.4. Mucopolipidosis type IV
  - 1.4. Disorders of the mitochondrial iron regulation
    - 1.4.1. Friedreich's ataxia
    - 1.4.2. X-linked sideroblastic anemia with ataxia
  - 1.5. Disorders with unknown gene function
    - 1.5.1. Woodhouse-Sakati syndrome (c2orf37 gene mutation)
    - 1.5.2. Neurodegeneration associated with c19orf12 mutation (MPAN)
    - 1.5.3. Idiopathic NBIA
      - Static encephalopathy with neurodegeneration in adulthood (SENDIA)
2. Other movement disorders associated with abnormal iron metabolism
  - 2.1 Parkinson's disease
  - 2.2 Multiple system atrophy
  - 2.3 Progressive supranuclear palsy
  - 2.4 Corticobasal degeneration
  - 2.5 Lewy body disease
  - 2.6 Restless legs syndrome
  - 2.7 Huntington's disease

Interestingly, TFRC and IRP1 were found to be downregulated in the SN dopaminergic cells, despite having low levels of iron. Levels of DMT1, FPN1 and FTH1 were also markedly decreased (Allen and Earley, 2007; Connor et al., 2004). Similar changes, decreased FTH1, TFRC and increased IRP1, were found also in microvessels isolated from RLS brains (Connor et al., 2011). Compared to healthy subjects, epithelial cells of the choroid plexus of RLS patients contained less iron and FTH1 while their TFRC, DMT1 and FPN1 were upregulated and FTMT was increased. Another autopsy study found increased FTMT levels and an increased number of mitochondria in the SN but not in the putamen homogenate (Snyder et al., 2009). One possible explanation of these abnormalities is dysregulation of iron transport across BBB (Connor et al., 2011). Indeed, based on the above mentioned data, it seems that the impaired iron uptake found in dopaminergic neurons and endothelial cells in brain microvessels may be partially compensated by an increased iron transport into CSF through the choroid plexus. Another possibility is that RLS is a primary mitochondrial disorder causing cellular energy insufficiency and increase of FTMT with secondary impairment of interaction between Fe-S clusters and IRP1 leading to its decreased activity and cytosolic iron deficiency. Interestingly, RLS prevalence was shown to be increased in FRDA patients, which may be connected to dysfunctional ascending sensory pathways. However, RLS severity in FRDA correlated with serum ferritin levels and SN iron status, suggesting a different mechanism possibly related to mitochondrial iron dysregulation (Frauscher et al., 2011; Synofzik et al., 2011). Surprisingly, men with severe RLS are more likely to develop PD (Gao et al., 2010). This finding is unexpected because the decreased iron content in neuromelanin neurons in SN has been described in RLS and it should be a protective factor against PD (Connor et al., 2003). Abnormal mitochondrial iron handling and subsequent mitochondrial dysfunction may possibly explain the connection between these two conditions, but further studies examining the mitochondrial function in RLS are necessary.

It is beyond the scope of this review to discuss other disorders in which abnormal brain iron accumulation has been implicated, such as stroke, Alzheimer's disease, amyotrophic lateral sclerosis, prion disorders, multiple sclerosis and age-dependent macular degeneration (Crichton et al., 2011; Kell, 2010).

### Treatment possibilities targeting iron accumulation

Considering growing evidence for iron's role in the neurodegenerative process, there is an increasing interest in the development of chelating drugs (Li et al., 2011). The mechanism of their action is not straightforward and neutralization of redox active iron and its subsequent removal from an organism may be just a part of the story. It is possible that iron redistribution between cellular compartments rather than simple removal may underlie their effect. By lowering cytosolic iron levels, chelating drugs also activate the HIF1A mediated pathway inducing expression of various substances with neuroprotective effect (Lee et al., 2009; Wu et al., 2010). It is important to note that the use of chelating agents in patients suffering from neurodegenerative disorders is still controversial and accompanied by significant side effects. Beside iron, these drugs may chelate other divalent ions as zinc and copper and possibly cause their deficit (Bareggi and Cornelli, 2010). The extent of chelation may vary in different tissues according to the specific permeability for a particular chelating agent.

So far, clinical experience with chelating drugs has yielded mixed results. Treatment with desferrioxamine led to an improvement in neurologic symptoms or at least to stabilization in some patients with aceruloplasminemia (Fasano et al., 2008; Hida et al., 2010; Miyajima et al., 1997). Effectiveness of this therapy is, however, not consistent and other authors reported no improvement (Finkstedt et al., 2010; Loreal et al., 2002; Mariani et al., 2004). In a group study even 20% reduction of brain iron content was not accompanied by a clinical improvement (Pan et al., 2011). Short term iron chelating treatment was not

beneficial in neuroferritinopathy (Chinnery et al., 2007). It is possible that clinical symptoms were irreversible in these patients due to a long lasting deleterious effect of accumulated iron. Nevertheless, chelating treatment could possibly be effective if started early in the disease course. Inconsistent results may also arise from the fact that many of currently available chelating agents such as desferrioxamine do not sufficiently cross the BBB (Finkstedt et al., 2010). Treatment with deferiprone, a BBB crossing compound, led to a radiological and clinical improvement in two idiopathic NBIA patients (Forni et al., 2008; Kwiatkowski et al., 2012) but a clinical benefit was not observed in a study with ten PKAN patients despite 30% reduction of iron content in the GP (Zorzi et al., 2011). Deferiprone treatment led to clinical improvement along with reduction of iron content measured by MRI in the dentate nuclei in a group of nine FRDA patients (Boddaert et al., 2007). These results were replicated in an open-label study examining the effect of combined treatment with deferiprone and indebenone in a group of 20 FRDA patients (Velasco-Sanchez et al., 2011). The mechanism of improvement is not clear and the possibility that chelation in fact increased availability of iron for metalloprotein synthesis can not be excluded.

### Conclusions

Dysregulation of iron metabolic pathways has been demonstrated in a large number of neurodegenerative movement disorders. Iron accumulation plays a crucial role in two genetic disorders of the iron pathway, neuroferritinopathy and aceruloplasminemia. Iron accumulation, however, has been demonstrated in many other metabolic disorders affecting the phospholipid/ceramide metabolism, mitochondrial or lysosomal function as well as in a variety of sporadic neurodegenerative diseases. While iron accumulation in these disorders is probably not the primary pathogenic mechanism, it may secondarily contribute the neurodegenerative process. The reason for iron accumulation in these disorders is not completely understood, but it appears to be related to the ceramide/phospholipid metabolism in several diseases, such as PKAN, PLAN and FAHN. Furthermore, iron accumulation and myelin derangements seem to be intimately connected not only in metabolic diseases such as FAHN, PLAN, WSS or lysosomal disorders, but also in other diseases such as MSA, HD and multiple sclerosis. Increased iron uptake may be also caused by its impaired recycling, as in the Kufor–Rakeb disease and possibly also in other lysosomal disorders, GM1-gangliosidosis, fucosidosis and MLIV. Utilization of iron appears to be disturbed in some mitochondrial disorders such as FRDA and possibly in PD. We propose a novel classification of movement disorders with brain iron dysregulation based on the presumed mechanism of iron accumulation (Table 4). We anticipate that NBIAs caused by genes with a hitherto unknown function, such as MPAN or WSS, will be included within the suggested categories in the future.

Despite improved understanding of the role of iron in cellular metabolism, there are still many unanswered questions, such as why iron tends to accumulate predominantly in certain deep brain nuclei and what is the nature of the relationship between age-related white matter abnormalities and increased brain iron content. Another intriguing question is whether significant amounts of iron can be transferred via the axonal transport and transsynaptically along neuronal pathways. Future research should also focus on the function of iron regulatory proteins in rare metabolic disorders. Development in the field will likely lead to discovery of safer and more effective iron-chelating drugs along with pre-symptomatic biomarkers and an improved identification of NBIA patients in early stages of the disease who would then be targeted as potential candidates for the novel, neuroprotective therapies.

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