

A diagnostic approach for neurodegeneration with brain iron accumulation: clinical features, genetics and brain imaging

Uma orientação diagnóstica para neurodegeneração com acúmulo cerebral de ferro: aspectos clínicos, genéticos e de neuroimagem

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ABSTRACT

Neurodegeneration with brain iron accumulation (NBIA) represents a heterogeneous and complex group of inherited neurodegenerative diseases, characterized by excessive iron accumulation, particularly in the basal ganglia. Common clinical features of NBIA include movement disorders, particularly parkinsonism and dystonia, cognitive dysfunction, pyramidal signs, and retinal abnormalities. The forms of NBIA described to date include pantothenase kinase-associated neurodegeneration (PKAN), phospholipase A2 associated neurodegeneration (PLAN), neuroferritinopathy, aceruloplasminemia, beta-propeller protein-associated neurodegeneration (BPAN), Kufor-Rakeb syndrome, mitochondrial membrane protein-associated neurodegeneration (MPAN), fatty acid hydroxylase-associated neurodegeneration (FAHN), coenzyme A synthase protein-associated neurodegeneration (CoPAN) and Woodhouse-Sakati syndrome. This review is a diagnostic approach for NBIA cases, from clinical features and brain imaging findings to the genetic etiology.

Keywords: neurodegeneration with brain iron accumulation; NBIA; clinical features; brain imaging; genetics.

RESUMO

A neurodegeneração com acúmulo cerebral de ferro (sigla em inglês NBIA) representa um grupo heterogêneo e complexo de doenças neurodegenerativas hereditárias, caracterizada pelo acúmulo cerebral de ferro, especialmente nos núcleos da base. O quadro clínico das NBIA em geral inclui distúrbios do movimento, particularmente parkinsonismo e distonia, disfunção cognitiva, sinais piramidais e anormalidades da retina. As formas de NBIA descritas até o momento incluem neurodegeneração associada a pantothenase kinase (PKAN), neurodegeneração associada a phospholipase A2 (PLAN), neuroferritinopatia, aceruloplasminemia, neurodegeneração associada a beta-propeller protein (BPAN), síndrome de Kufor-Rakeb, neurodegeneração associada a mitochondrial membrane protein (MPAN), neurodegeneração associada a "fatty acid hydroxylase" (FAHN), neurodegeneração associada a coenzyme A synthase protein (CoPAN) e síndrome de Woodhouse-Sakati. Esta revisão é uma orientação para o diagnóstico das NBIA, partindo das características clínicas e achados de neuroimagem, até a etiologia genética.

Palavras-chave: Neurodegeneração com acúmulo cerebral de ferro; NBIA; sinais clínicos; neuroimagem; genética.

Neurodegeneration with brain iron accumulation (NBIA) represents a heterogeneous group of inherited neurodegenerative diseases, characterized by excess iron accumulation, particularly in the basal ganglia, and to a lesser degree in substantia nigra and adjacent areas¹. NBIA is considered to be a very rare disease group, with a prevalence of less than 1/1,000,000 in general

population¹. Common clinical features of NBIA include movement disorders, particularly parkinsonism and dystonia, cognitive dysfunction, pyramidal signs, and retinal abnormalities^{1,2,3}.

Hunt in 1917 described a case report of juvenile parkinsonism associated with progressive atrophy of globus pallidus⁴. In 1922, Hallervorden and Spatz reported a family with five affected sisters

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with neuropathological confirmation of lesions of globus pallidus and substantia nigra⁵. Davidson described in 1954, a case series of five patients presenting with progressive parkinsonism, dystonia, and spasticity, associated with pyramidal and pallidal lesions, and created the term pallidopyramidal degeneration (PPD)⁶. However, this disease was worldwide known as Hallervorden-Spatz syndrome (HSS)³. Julius Hallervorden and Hugo Spatz were German physicians, who performed several neuropathological studies on brain specimens of mental retardation persons, executed during the Third Reich euthanasia program (Aktion-T-4)^{1,2,3}. After confirmation of Hallervorden and Spatz's involvement in the euthanasia program of the Nazi regime in Germany, and the recent neuroimaging and genetic discoveries, this syndrome was renamed NBIA^{1,2}. In 2010, Horstink et al. suggested that PPD was a misnomer and conclude that the existence of PPD as a distinct nosological entity is doubtful⁷. In 2013, Kara et al. argued that the use of the term NBIA is not ideal and suggested the term pallidopyramidal syndromes (PPS), however NBIA is the most known worldwide term². To date ten forms of NBIA has been described, eight with autosomal recessive inheritance, one autosomal dominant form, and one with X-linked dominant inheritance^{1,2}. The most common forms are pantothenase kinase-associated neurodegeneration (PKAN) (30-50% of NBIA cases), due to mutations in the *PANK2* gene, followed by phospholipase A2 associated neurodegeneration (PLAN) due to *PLA2G6* gene mutations, mitochondrial membrane protein-associated neurodegeneration (MPAN) due to *c19orf12* mutations, and beta-propeller protein-associated neurodegeneration (BPAN) causing SENDA syndrome (static encephalopathy of childhood with neurodegeneration in adulthood) (gene *WDR45*, chromosome Xp11.23). Probably most of the case published in the literature as HSS were PKAN¹. Other less common forms are fatty acid hydroxylase-associated neurodegeneration (FAHN), coenzyme A synthase protein-associated neurodegeneration (CoPAN), Kufor-Rakeb syndrome (PARK9), Woodhouse-Sakati syndrome, neuroferritinopathy and aceruloplasminemia^{1,2}. The forms of NBIA described to date and the respective gene mutations are listed in Table 1.

Table 1. Forms of NBIA described to date and the respective gene mutations.

| NBIA subtype | Gene mutation |
|---------------------------|------------------------|
| PKAN | <i>PANK2</i> |
| PLAN | <i>PLA2G6</i> |
| Neuroferritinopathy | <i>FTL1</i> |
| Aceruloplasminemia | <i>Ceruloplasmin</i> |
| BPAN | <i>WDR45</i> |
| Kufor-Rakeb syndrome | <i>ATP13A2</i> (PARK9) |
| MPAN | <i>C19orf12</i> |
| FAHN | <i>FA2H</i> |
| CoPAN | <i>CoASY</i> |
| Woodhouse-Sakati syndrome | <i>C2orf37</i> |

Pantothenase kinase-associated neurodegeneration (PKAN)

PKAN is an autosomal recessive disorder characterized by mutations in the gene encoding a mitochondrial pantothenate kinase (*PANK2*) at locus 20p13-p12.3⁸. It is the most common disorder of the NBIA group^{9,10,11}. The classic clinical presentation of PKAN is characterized by early-onset (mean age is 14 years - range from 1 to 28y) and rapidly progressive course. The affected child presents gait impairment and movement disorders (particularly dystonia and parkinsonism). Spasticity and brisk tendon reflexes are common. Cognition is frequently impaired^{1,12,13,14}. Retinitis pigmentosa may occur, associated or not with acanthocytes in blood cells^{15,16}. The majority of individuals (85%) become wheelchairbound within 15 years after the beginning of symptoms^{13,14}. Speech and swallowing are affected with disease progression. Death is usually secondary to respiratory infections, cardiorespiratory complications, malnutrition state and, rarely, *status dystonicus*. Atypical phenotypes with slowly progressive course have a late onset. Neuropsychiatric symptoms are common and may be early signs. They include mood lability, impulsivity, non-specific behavioral changes, and obsessive-compulsive features^{1,14}.

Brain magnetic resonance imaging (MRI) plays an important role in the investigation of PKAN since it shows the 'eye-of-the-tiger' sign, defined as a medial area of hyperintense signal within hypointense signal in globus pallidus bilaterally and best demonstrated on T2WI and SWI (Figure 1). Hypointense signal may also be observed in the substantia nigra¹⁵.

There is no current specific therapy to stop disease progression. Treatment is supportive and intend to relief associated symptoms^{1,13,14}. Dystonia and spasticity are usually managed with anticholinergic drugs, benzodiazepines, botulinum toxin, oral baclofen and intrathecal baclofen in severe cases. The role of the brain iron accumulation in the pathophysiology of the disease remains under discussion, and iron chelation therapy has been investigated as a disease modifying approach^{1,14,17}.

Phospholipase A2 associated neurodegeneration (PLAN)

PLAN is an autosomal recessive form of NBIA. The disease is caused by failure in the ubiquitously expressed *PLA2G6* gene, which maps to chromosome 22q13.1^{10,18}. This gene encodes phospholipase A2 group VI, which may disrupt membrane homeostasis, involved in free fatty acids and lysophospholipids synthesis, resulting in neurodegeneration, atrophy, brain iron accumulation, gliosis and degeneration of the optic pathways^{9,19}. The majority of PLAN cases have early-onset of symptoms, with beginning in childhood. *PLA2G6*-associated diseases have variable syndromes and may include: classic infantile neuroaxonal dystrophy (INAD), atypical neuroaxonal dystrophy (aNAD) of childhood-onset and *PLA2G6*-related dystonia-parkinsonism with late onset in adulthood (PARK14)^{1,9,13}.

INAD is characterized by early-onset mental developmental delay, ataxia with cerebellar atrophy, neuropathy and optic atrophy. Patients usually have hypotonia, kyphoscoliosis and limb contractures. The symptoms usually occurs before 2 years old and the progression of the disease is rapid leading to death in the first decade^{9,20}. An estimated 50% of patients have abnormal iron accumulation in brain MRI, evolving globus pallidus, dentate nuclei and substantia nigra (Figure 2)¹⁰. Optic pathway atrophy is a relevant clue for the disease⁹.

aNAD was previously described as Karak syndrome. This disease is less aggressive than classic INAD. The typical clinical presentation of aNAD include early-onset (older than INAD) ataxia and dysarthria, hypotonia, areflexia, dystonia and cognitive impairment^{1,20}. Children with aNAD may develop optic atrophy¹⁹. Brain MRI usually have similar features observed in INAD: abnormal iron accumulation in globus pallidus, dentate nuclei and substantia nigra, and cerebellar atrophy²⁰.

Adult-onset PLAN with dystonia and parkinsonism, described as PARK14, has onset in young adulthood. Clinical

features include parkinsonism-dystonia syndrome with variable response to dopaminergic medications and neuropsychiatric symptoms⁹. Brain MRI may be normal or may disclose iron accumulation in globus pallidus, substantia nigra and striatum²¹.

There is no specific treatment for PLAN. Symptomatic treatment for spasticity, dystonia and parkinsonism should be tried¹. A levodopa course for parkinsonism may improve symptoms¹³.

Neuroferritinopathy

Neuroferritinopathy is a rare autosomal dominant NBIA of adult-onset related to a mutation in the ferritin light chain gene *FTL1*, on chromosome 19q13.3¹⁹. The onset of symptoms is predominantly described in young adulthood or middle age¹. The clinical manifestation includes psychiatric symptoms (psychosis, anxiety and depression), frontal lobe dysfunction, dystonia, choreoathetosis, rigidity and spasticity. Other abnormalities described in patients with neuroferritinopathy include lingual dyskinesia, blepharospasm, cerebellar symptoms,

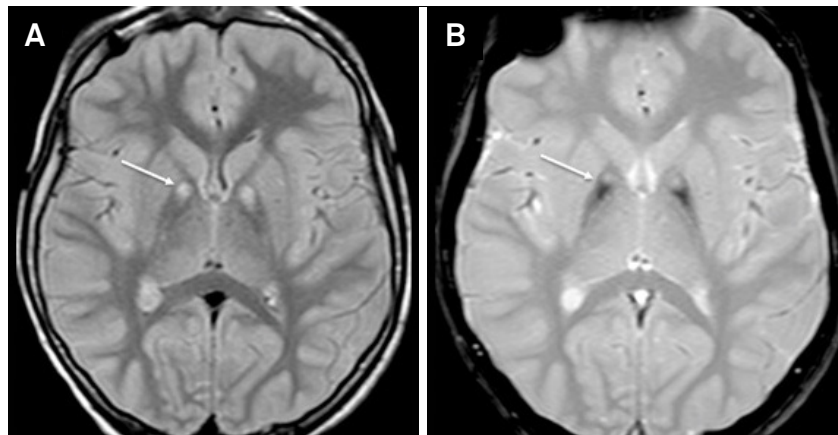


Figure 1. Brain MRI of a patient with pantothenase kinase-associated neurodegeneration (PKAN). Axial FLAIR- (A) and GRE T2-weighted (B) MRI discloses 'eye-of-the-tiger' sign, defined as a medial area of hyperintense signal within an hypointense signal in globus pallidus bilaterally.

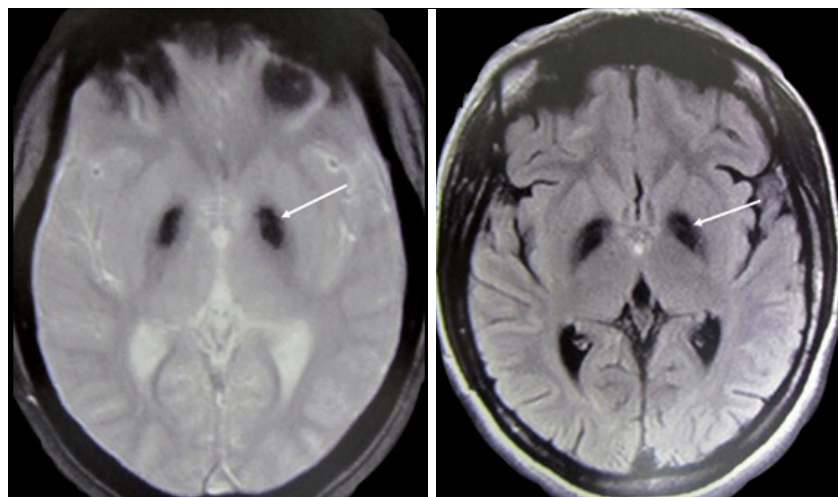


Figure 2. Patient with phospholipase A2 associated neurodegeneration (PLAN) due to *PLA2G6* mutations. Brain MRI shows marked hypointense signal with iron accumulation in globus pallidus.

parkinsonism and palatal tremor^{10,22}. Blood tests show low levels of serum ferritin, typically ≤ 20 $\mu\text{g}/\text{dl}$, which may reinforce the diagnosis²². Brain MRI findings include iron accumulation in globus pallidus, caudate, substantia nigra, red nuclei and putamen. In late stages of the disease cystic necrosis in basal ganglia and globus pallidus may occur²²⁻²⁴. Pathological studies have demonstrated ubiquitin and tau positive neuroaxonal spheroids and neurofilaments, and ferritin-positive inclusions in putamen and cerebellum²³. Treatment is symptomatic and supportive, and dystonia may benefit with botulinum toxin. No curative treatments are available^{22,24}.

Aceruloplasminemia

Aceruloplasminemia is an autosomal recessive disease caused by mutation in the ceruloplasmin gene. Ceruloplasmin is a copper-bound ferroxidase essential to normal iron metabolism, including cell iron efflux and oxidation of ferrous iron to ferric iron²⁵. When ceruloplasmin activity is severely decreased, iron overload occurs and tissue iron deposition and degeneration follows. Iron accumulates primarily in the brain, retina and pancreas, giving rise to the classical presentation of the disease, a triad consisting of neurological symptoms, retinal degeneration and diabetes mellitus. The prevalence of aceruloplasminemia is higher in Japan²⁶.

Symptoms onset in aceruloplasminemia usually occur in the fourth decade. Typically, the first manifestation of the disease is diabetes mellitus accompanied by microcytic anemia with low serum iron, elevated ferritin and hepatic iron deposition without fibrosis or cirrhosis²⁷. Retinal macular degeneration is usually asymptomatic^{28,29}. Neurological symptoms develop later in the disease, around the sixth decade of life. Movement disorders are the most common neurological features in aceruloplasminemia and include ataxia, cranio-facial dyskinesias (torticollis, blepharospasm, facial grimacing and tongue dystonia), parkinsonism and dysarthria^{30,31}. Dementia and other neuropsychiatric symptoms are frequent in aceruloplasminemia^{30,32}.

Diagnosis of aceruloplasminemia is based on the absence or very low serum ceruloplasmin. Brain MRI usually discloses severe iron accumulation in caudate, pallidus, putamen, dentate nuclei, red nuclei, substantia nigra, thalamus, inferior and superior colliculi and cortex (Figure 3). This widespread pattern of involvement helps distinguish aceruloplasminemia from other NBIA, in which iron deposition is either more limited (e.g. confined to the pallidus) or associated with other features (e.g. cavitation, cerebellar atrophy or thin corpus callosum)^{30,33}. White matter T2 hyperintensities can also occur³⁴. Heterozygous cases can present with an incomplete picture, generating further diagnostic difficulties^{32,35,36}. Genetic testing confirms the diagnosis.

A number of iron chelating agents have been tried with mixed results and data on efficacy is scarce³⁷. Deferasirox reduces hepatic but not brain iron overload. Sporadic reports have demonstrated that deferasirox and deferiprone may delay neurological symptoms^{36,38,39}.

Beta-propeller protein-associated neurodegeneration (BPAN)

BPAN is a X-linked dominant form of NBIA caused by mutations in *WDR45* gene, a β -propeller scaffolding protein, associated with disruption of autophagosome maturation, accumulation of aberrant autophagic structures and damaged cellular components^{40,41}.

Clinically, BPAN is characterized by two phases of disease: an early neurological disorder with rapid progression and a static encephalopathy of childhood. The early onset phenotype includes neurological symptoms similar to Rett-like syndrome: epilepsy, sleep disorders and global developmental delay, followed by a rapid progressive onset of parkinsonism, dystonia, and dementia^{14,42}. The second form is a static encephalopathy of childhood with neurodegeneration in adulthood (SENDA syndrome), which typically presents with hyperintense signal of the substantia nigra with a central band of hypointense signal in brain MRI (Figure 4)⁴³.

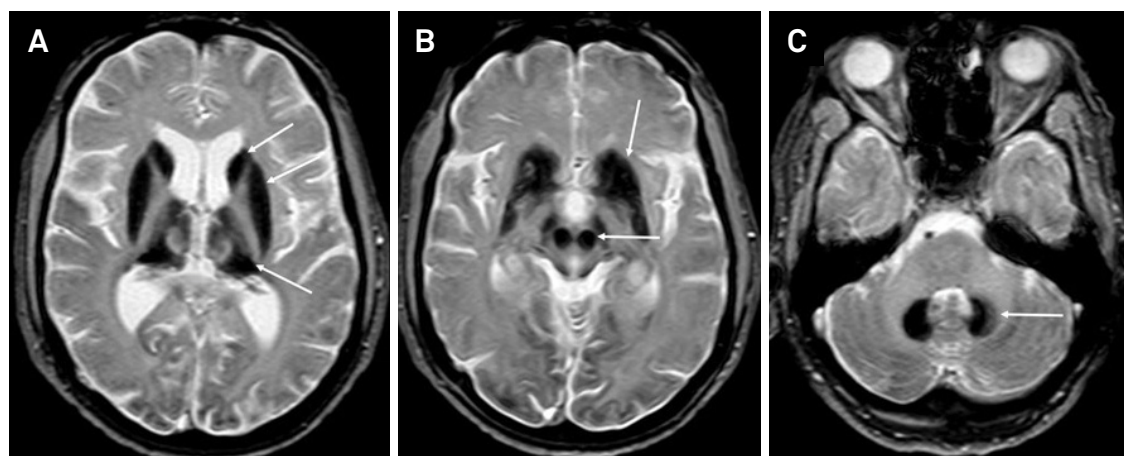


Figure 3. Brain MRI of a patient with aceruloplasminemia MRI discloses global and severe iron accumulation in caudate, pallidus, thalamus, putamen (A), red nuclei, substantia nigra (B) and dentate nuclei (C).

Neuropathological studies have disclosed large axonal spheroids, siderophages, reactive astrocytes, severe neuronal loss and abundant tau-positive neurofibrillary tangles, suggesting the occurrence of a tauopathy^{40,43}.

Kufor-Rakeb syndrome - PARK 9

The mutation of the gene *ATP13A2* (PARK9) results in a rare autosomal recessive form of juvenile parkinsonism, previously known as Kufor-Rakeb syndrome⁴⁴. The first cases described presented early parkinsonism, pyramidal signs, upgaze palsy and mental retardation⁴⁵. However, it is recognized that the wide-ranging abnormalities in the gene leads to loss of function mutations, which impact the pathophysiological function of *ATP13A2* protein resulting in considerable clinical heterogeneity⁴⁶. Moreover, the mutations in heterozygous state have been found in parkinsonian patients suggesting that heterozygous carriers may increase risk for development of the disease⁴⁵.

The onset of Kufor-Rakeb syndrome is mostly before the age of 20, with variable disease progression. The clinical manifestations comprise levodopa-responsive parkinsonism, dystonia, pyramidal signs, facial-finger mini-myoclonus, supranuclear gaze palsy and cognitive impairment⁴⁷. Brain MRI usually shows global atrophy. The disease is included in NBLA

group since T2* weighted sequence discloses iron accumulation in basal ganglia in some patients⁴⁸.

Mitochondrial membrane protein-associated neurodegeneration (MPAN)

MPAN is an autosomal recessive disease caused by mutations in *C19orf12* gene. Pathological studies have demonstrated increased iron accumulation in the globus pallidus and substantia nigra, gliosis, neuronal loss, and eosinophilic spheroidal structures in the globus pallidus. The characteristic peripheral axonal spheroids of PLAN may be seen in some patients. MPAN is considered a synucleinopathy, with Lewy bodies and Lewy neurites in basal ganglia and neocortex^{19,49}.

The disease may manifest from the first decade of life (3-16 years) to adulthood (until 30 years). The most common features are early lower limb spasticity with extensor plantar response, dysarthria, dystonia (involving hands and feet), optic atrophy, neuropsychiatric abnormalities and cognitive decline. The presentation in adults is more variable, with prominent neuropsychiatric symptoms, parkinsonism and gait disorders. Others clinical findings that support the diagnosis of MPAN are dysphagia, axonal motor neuropathy and bladder and/or

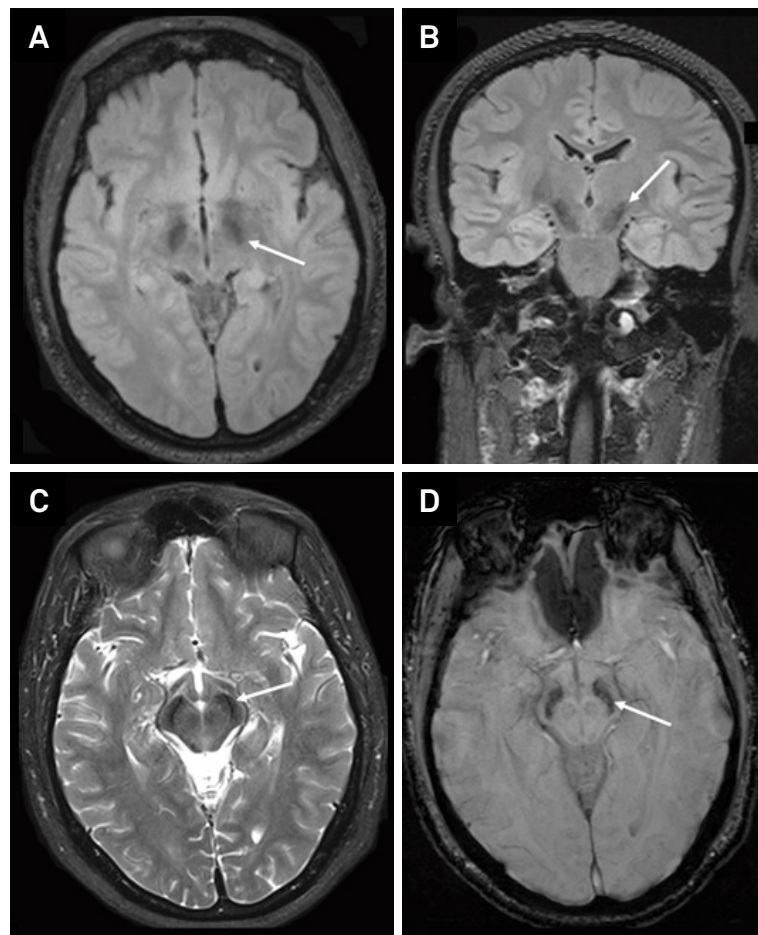


Figure 4. Brain MRI of a patient with beta-propeller protein-associated neurodegeneration (BPAN) or SENDA. There is a marked bilateral hypointense signal in substantia nigra observed in axial and coronal FLAIR (A and B), axial T2 (C) and axial SWI (D) sequences.

bowel dysfunction. The disease progression is slow and the lifespan is long in most of the cases^{19,49}.

The diagnosis of MPAN is made by detection of biallelic pathogenic variants in *C19orf12* gene. Brain MRI shows iron accumulation in substantia nigra and globus pallidus on T2* and GRE sequences, normally without the eye of the tiger sign, which is typically found in PKAN. Cortical and cerebellar atrophy may be seen in advanced disease^{19,49,50}. Similar to others NBIA, there is no curative treatment and the management of patients relies on rehabilitation and symptomatic medications: anti-spastic agents, anticholinergics, dopaminergic agents and botulinum toxin.

Fatty acid hydroxylase-associated neurodegeneration (FAHN)

FA2H mutations were previously known to cause leukodystrophy and a form of hereditary spastic paraplegia (HSP), which was classified as SPG35^{51,52,53}. FA2H produces 2-hydroxylated fatty acids for incorporation into 2-hydroxydihydroceramide and 2-hydroxyceramide. These ceramide species serve as precursors for the synthesis of galactosylceramides and sulfatides, essential lipid components of normal myelin^{54,55}. Phenotypically, affected patients demonstrated features similar to those observed in INAD⁵⁵. The clinical phenotype is characterized by childhood-onset spastic paraplegia, ataxia and dystonia. There are prominent ophthalmologic features such as acquired strabismus, nystagmus and optic atrophy. Intellect is usually spared in FAHN patients. Seizures may be present⁵¹.

Brain MRI in FAHN usually shows bilateral globus pallidus T2 hypointense signal, characterizing iron accumulation, pontocerebellar atrophy and cortical atrophy (Figure 5). Confluent periventricular T2 white matter hyperintense signal were also observed along with thinning of the corpus callosum^{51,55}. It is a matter of discussion if FAHN should be included in one or more of the 3 following groups: NBIA, HSP or leukodystrophy.

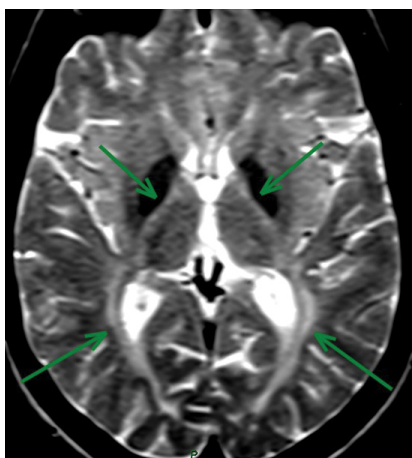


Figure 5. Patient with fatty acid hydroxylase-associated neurodegeneration (FAHN). Brain MRI shows bilateral globus pallidus hypointense signal, characterizing iron accumulation, and confluent periventricular white matter hyperintense signal.

CoA synthase protein associated neurodegeneration (CoPAN)

Coenzyme A synthesis (*CoASY*) is a cofactor in all living organisms and is involved in several enzymatic reactions. Patients with *CoASY* mutations present a clinical picture similar to those with PKAN. CoPAN phenotype is characterized by early-onset spastic-dystonic paraparesis with a later appearance of parkinsonian features, cognitive impairment and pronounced obsessive-compulsive disorder. The disease has a slow progression with loss of ambulation during adolescence and adulthood⁵⁶. Brain MRI usually shows bilateral “eye-of-the-tiger” sign. CT scan shows bilateral calcifications and corresponding to the central spot visible on MRI²¹.

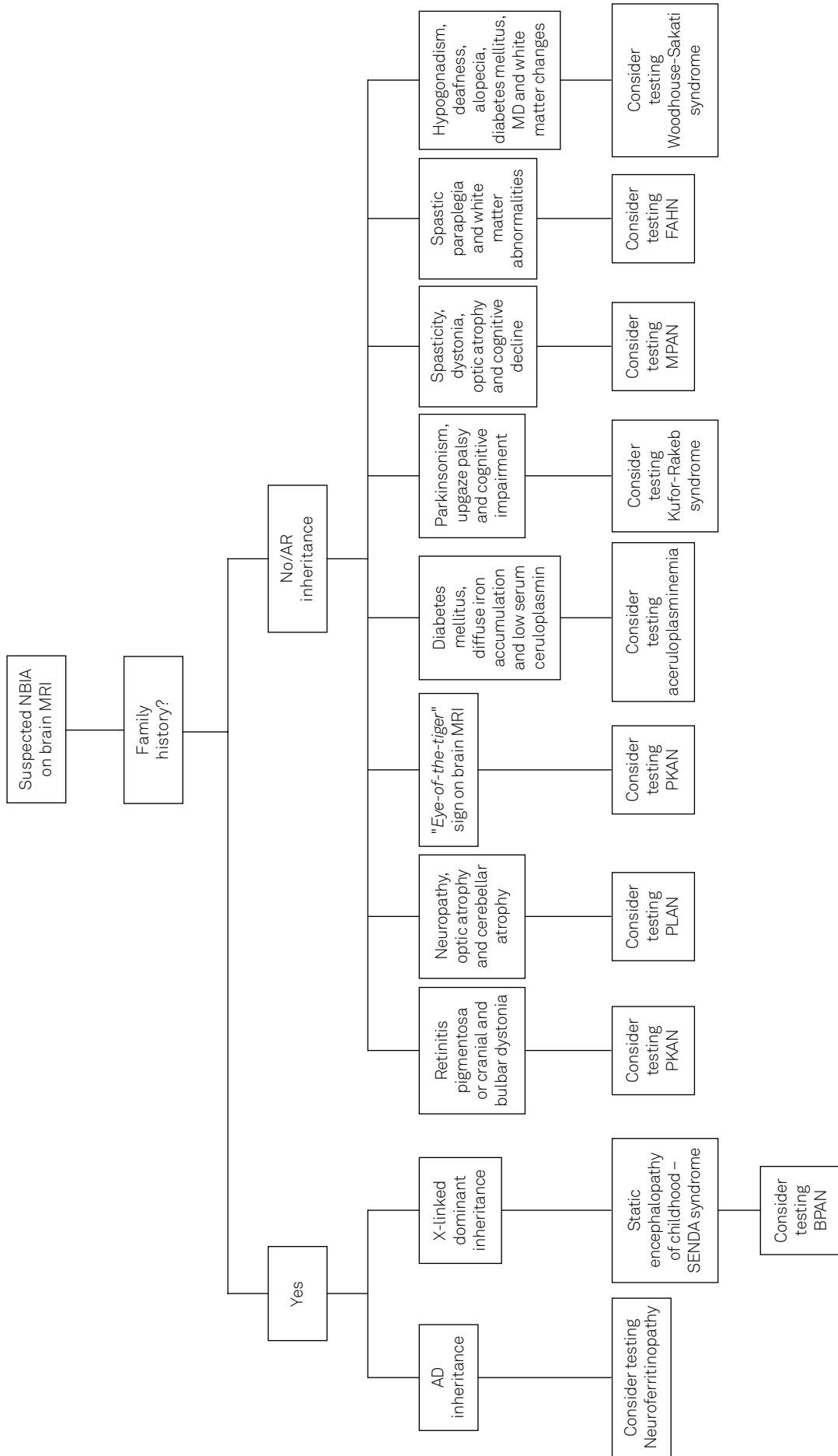
Woodhouse-Sakati syndrome and SCPx deficiency

Woodhouse-Sakati syndrome is a rare autosomal recessive disorder caused by a mutation in the *C2orf37* gene, manifesting with hypogonadism, deafness, alopecia, diabetes mellitus and progressive dystonia, chorea, dysarthria and cognitive impairment. Brain MRI discloses iron accumulation in the substantia nigra and globus pallidus, and white matter lesions. However, some patients may have only subtle white matter abnormalities^{57,58}.

Finally, sterol carrier protein x (SCPx) deficiency has been associated with NBIA in a patient with adult-onset spinocerebellar ataxia, slow ocular saccades, and deafness. 3T MRI brain revealed abnormal T2 signal and susceptibility-weighted sequences suggested increased mineral deposition in the basal ganglia. Potentially pathogenic mutations were identified in SCP2. SCPx is a peroxisomal enzyme with thiolase activity required for the breakdown of branched chain fatty acids and the pathogenic effects are likely to be mediated by the accumulation of branch chain fatty acids, as in other peroxisomal disorders. Patients with SCP2 mutation may have abnormal fatty-acid acyl-CoA metabolism, which has emerged as a common disease mechanism in NBIA. This suggests that the brain iron accumulation is secondary to an underlying metabolic defect, questioning the role of iron chelation as a treatment in all forms of NBIA⁵⁹.

Diagnostic approach to neurodegeneration with brain iron accumulation

To diagnose the NBIA subtype is a challenge. Careful attention to clinical phenotype and neuroimaging features is crucial. Family history in order to determine inheritance is relevant since mendelian inheritance forms may direct investigation to neuroferritinopathy. Neuroimaging features may disclose key findings for different NBIA subtypes (Table 2). Altogether, clinical features including non-neurological manifestation, associated movement disorders, age at onset, family history and detailed neuroimaging characteristics should guide to the genetic testing investigation (Figure 6).



NBIA: neurodegeneration with brain iron accumulation; MRI: magnetic resonance imaging; AD: autosomal dominant; AR: autosomal recessive; MD: movement disorders; BPAN: beta-propeller protein-associated neurodegeneration; PKAN: pantothenase kinase-associated neurodegeneration; PLAN: phospholipase A2 associated neurodegeneration; MPAN: mitochondrial membrane protein-associated neurodegeneration; FAHN: fatty acid hydroxylase-associated neurodegeneration.

Figure 6. A guidance with clinical and neuroimaging tips to better require specific genetic testing in NBIA patients.

Table 2. Key imaging findings for different NBIA subtypes.

| NBIA subtype | Neuroimaging features |
|---------------------------|---|
| PKAN | “Eye-of-the-tiger” sign due to bilateral symmetrical rarefaction of central globus pallidi |
| PLAN | Iron accumulation in globus pallidi and substantia nigra; cerebellar atrophy |
| Neuroferritinopathy | Cystic degeneration of globus pallidi, putamen, caudate, substantia nigra and cerebellar nuclei |
| Aceruloplasminemia | Widespread brain iron deposition |
| BPAN | High T1 signal involving substantia nigra; hypointense signal in the substantia nigra |
| Kufor-Rakeb syndrome | Decreased dopamine transporter binding |
| MPAN | T2 hyperintensity in medial medullary lamina between globus pallidus interna and externa |
| FAHN | Iron accumulation in globus pallidi, white matter abnormalities, corpus callosum atrophy |
| CoPAN | Bilateral “eye-of-the-tiger” sign; CT scan shows bilateral basal-ganglia calcification |
| Woodhouse-Sakati syndrome | Iron accumulation in globus pallidi and white matter abnormalities |

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