Part I

Neurodegenerative Diseases

CASE 1

Asim K. Bag, Lázaro Luís Faria do Amaral

Clinical Presentation

A 31-year-old woman presented with a three-year history of gradually worsening bradykinesia, rigidity, tremor, dystonia, dysphagia, and severe neurocognitive decline. Her symptoms were not levodopa-responsive. Her family states that she had severe developmental delay in early childhood, along with mental retardation. Although the mental retardation was static for an extended period, the family noted history of recent neurocognitive decline. Magnetic resonance imaging was performed (shown below) for further follow-up.

Imaging

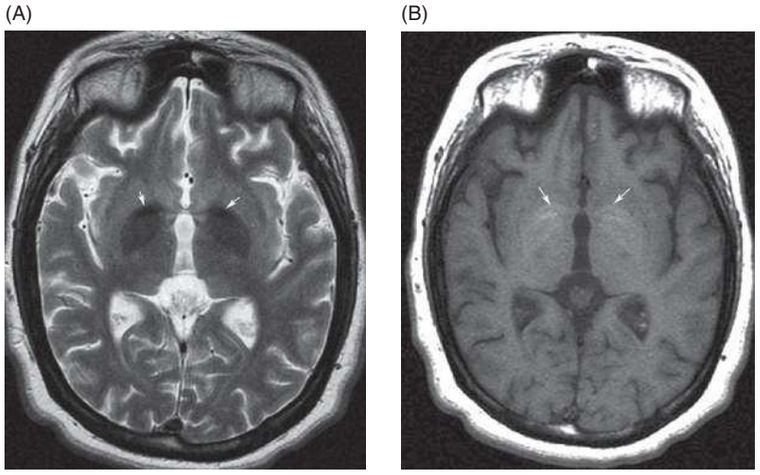

Fig. 1.1 (A) Axial T2WI and (B) T1WI through the level of the basal ganglia. Taken with permission from: Amaral LLF, Gaddikeri S, Chapman PR, Roy R, Gaddikeri RS, Marussi VH, Bag AK. Neurodegeneration with brain iron accumulation: clinicoradiological approach to diagnosis. *J Neuroimaging* 2015; 25(4): 539–51.

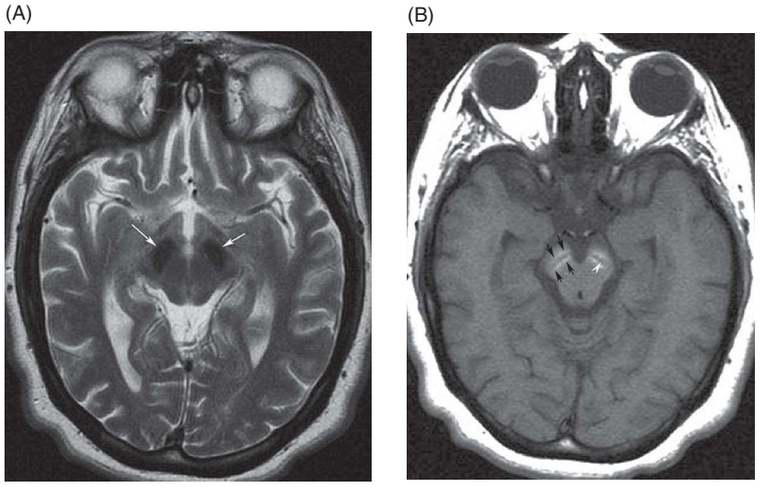

Fig. 1.2 (A) Axial T2WI and (B) T1WI through the level of the substantia nigra. Taken with permission from: Amaral LLF, Gaddikeri S, Chapman PR, Roy R, Gaddikeri RS, Marussi VH, Bag AK. Neurodegeneration with brain iron accumulation: clinicoradiological approach to diagnosis. *J Neuroimaging* 2015; 25(4): 539–51.

Beta-Propeller Protein-Associated Neurodegeneration (BPAN)

Primary Diagnosis

Beta-propeller protein-associated neurodegeneration (BPAN)

Differential Diagnoses

Pantothenate kinase-associated neurodegeneration (PKAN)
Phospholipase-associated neurodegeneration (PLAN)
Mitochondrial membrane protein-associated neurodegeneration (MPAN)
Early-onset Parkinson disease

Imaging Findings

Fig. 1.1: (A) Axial T2-weighted MR image through the level of basal ganglia demonstrated T2 hypointensity secondary to iron deposition involving bilateral globus pallidi (arrows) and mild diffuse brain atrophy as suggested by prominence of ventricles and sulci. (B) Axial T1-weighted MR image through the same level demonstrated subtle, increased T1 signal in the globus pallidi (arrows). Fig. 1.2: (A) Axial T2-weighted MR image demonstrated evidence of increased iron deposition involving bilateral substantia nigra (arrows). (B) Axial T1-weighted MR image through the level of substantia nigra demonstrated bilateral symmetric, high T1 signal involving the substantia nigra (black arrows), with a band of central T1 hypointensity (white arrowhead), virtually pathognomonic of BPAN.

Discussion

Global developmental delay, early childhood neurocognitive decline that remains static for years, juvenile or young-adult onset of worsening of neurocognitive changes, and the development of progressive, levodopa-resistant Parkinsonian features suggest the diagnosis of beta-propeller protein-associated neurodegeneration (BPAN). Virtually pathognomonic MRI findings in the substantia nigra (bilateral symmetric, high T1 signal involving substantia nigra with a band of central T1 hypointensity) confirm the diagnosis of BPAN.

Late-onset PKAN (see Part I: Case 4) may be considered in the differential diagnosis; however, typical eye-of-the-tiger sign in the globus pallidus is absent. Moreover, the T1 hyperintensity of the subthalamic nucleus (STN) is not characteristic of PKAN. PLAN (see Part I: Case 5) is a disease of early childhood, and is characterized by more severe symptoms, most notably cerebellar atrophy. Most patients with PLAN succumb to the disease by 10 years of age. The characteristic T2 hyperintensity of the medial medullary lamina, between the globus pallidus interna and externa, the characteristic imaging finding in MPAN (see Part I: Case 2) is not present in this patient. Although symptoms complex is suggestive of Parkinson disease, levodopa-nonresponsiveness and evidence of excessive deep nuclei iron accumulation are not features of early-onset Parkinson disease.

Recently defined, BPAN is the only X-linked subtype of neurodegeneration with brain iron accumulation (NBIA) due to a mutation in the *WDR45* gene at the Xp11.23 locus. In the past, this entity was named *static encephalopathy* (of childhood) *with neurodegeneration in adulthood* (SENDA). After the underlying genetic defect was identified, this NBIA subtype was renamed or reclassified as BPAN, similar to the other subtypes of NBIA.

In BPAN, patients present with global developmental delay, including delayed language and motor skills. Unlike other subtypes of early manifested NBIA, the clinical presentation of delayed development remains relatively static until adolescence/young adulthood. Abnormal movement or neurocognitive decline is absent in childhood. As the patient approaches adolescence and early adulthood, progressive neurodegeneration symptoms including dystonia, Parkinsonian syndromes, and neurocognitive decline start to appear. Although the benefit is only short lasting, Parkinsonian symptoms may improve with initiation of levodopa therapy. This characteristic pattern of disease progression, from childhood to young adulthood, was the basis for the previous name, *SENDA*.

As in other subtypes of NBIA, iron deposition is the key imaging abnormality. The earliest and most concentrated iron accumulation occurs in the substantia nigra. Although iron deposition does occur in the globus pallidus, it usually follows iron deposition in the substantia nigra and is less severe, unlike the other NBIA subtypes. Evidence of iron deposition can only be seen in the STN on iron-sensitive sequences, as disease progression occurs when there may not be any apparent iron deposition in the globus pallidus. Paired bands of linear T1 hyperintensity separated by a relatively T1 hypointense area is a distinguishing and virtually pathognomonic finding in patients with BPAN. The bright T1 signal may be due to formation of iron-melanin complexes from the release of neuromelanin in the dying pigmented neurons of the STN pars compacta.

Key Points

- BPAN should be clinically suspected when the onset of global developmental abnormalities is early in childhood and remains relatively stable until adolescence before it deteriorates and with the development of seizures and stereotypes.
- Bilateral symmetric, high T1 signal involving substantia nigra with a band of central T1 hypointensity is a virtually pathognomonic imaging sign of BPAN.
- If characteristic clinical and radiologic findings are present, the diagnosis can be confirmed by molecular genetic analysis.

Suggested Reading

Amaral LLF, Gaddikeri S, Chapman PR, et al. Neurodegeneration with brain iron accumulation: clinicoradiological approach to diagnosis. *J Neuroimaging* 2015; 25(4): 539–51.

Hayflick SJ, Kruer MC, Gregory A, et al. Beta-propeller protein-associated neurodegeneration: a new X-linked dominant disorder with brain iron accumulation. *Brain* 2013; 136(Pt 6): 1708–17.

Part I

Neurodegenerative Diseases

CASE 2

Aparna Singhal, Lázaro Luís Faria do Amaral, Asim K. Bag

Clinical Presentation

An 11-year-old boy presented with a history of relatively rapidly progressive cognitive decline and motor neuropathy. This was accompanied by gradual development of extrapyramidal signs, dystonia, visual abnormalities, and Parkinsonian features. On further questioning, his parents revealed that their other child also had similar symptoms. Extensive hematologic studies were negative. Ophthalmologic evaluation revealed optic atrophy but no features of pigmentary retinal degeneration.

Imaging

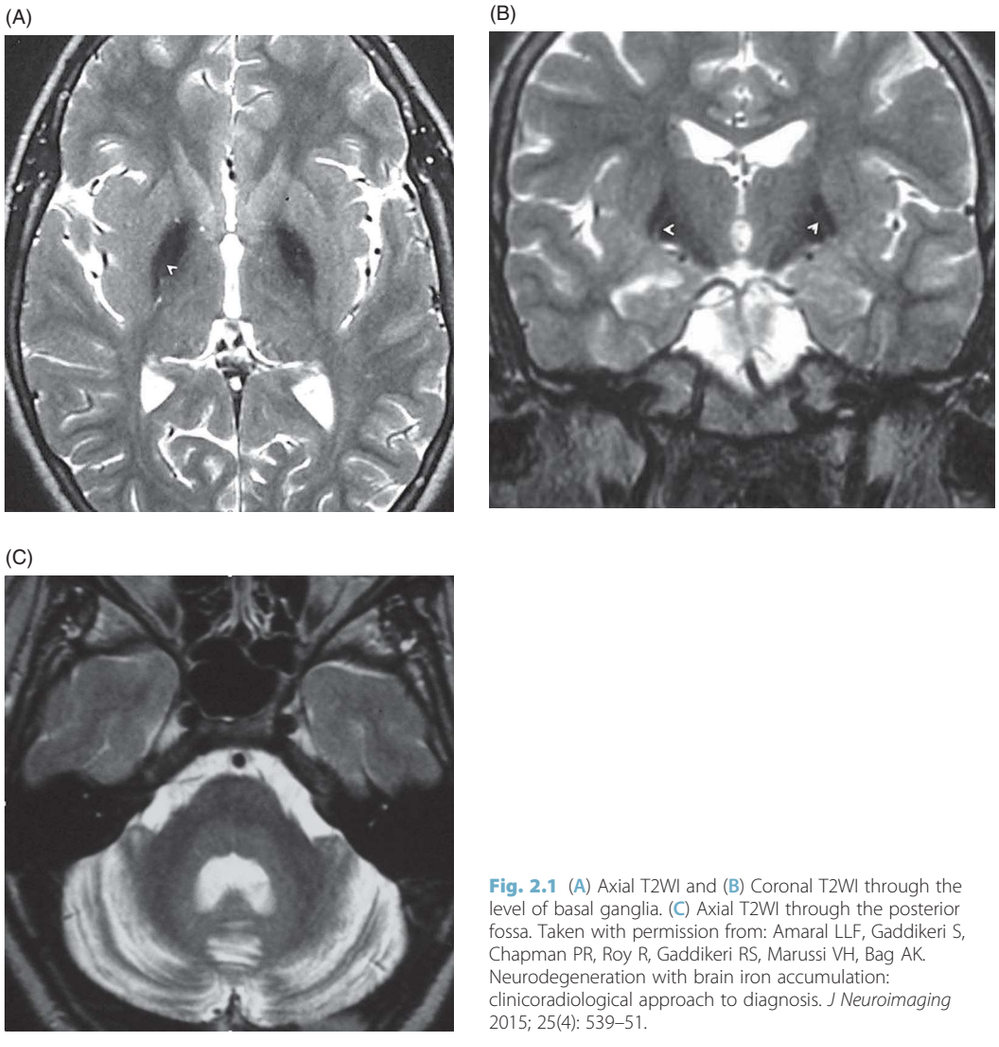

Fig. 2.1 (A) Axial T2WI and (B) Coronal T2WI through the level of basal ganglia. (C) Axial T2WI through the posterior fossa. Taken with permission from: Amaral LLF, Gaddikeri S, Chapman PR, Roy R, Gaddikeri RS, Marussi VH, Bag AK. Neurodegeneration with brain iron accumulation: clinicoradiological approach to diagnosis. *J Neuroimaging* 2015; 25(4): 539–51.

Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN)

Primary Diagnosis

Mitochondrial membrane protein-associated neurodegeneration (MPAN)

Differential Diagnoses

Pantothenate kinase-associated neurodegeneration (PKAN)
Phospholipase-associated neurodegeneration (PLAN)
Beta-propeller protein-associated neurodegeneration (BPAN)
Early-onset Parkinson disease

Imaging Findings

Fig. 2.1: (A) Axial T2WI through the level of basal ganglia demonstrated diffuse T2 hypointensity involving the bilateral globus pallidi, and diffuse brain atrophy. Subtle linear T2 hyperintensity (arrowhead) was seen in the medial medullary lamina between the globus pallidus interna and globus pallidus externa. (B) Coronal T2WI through the basal ganglia demonstrated T2 hypointensity involving the bilateral basal ganglia. T2 hyperintensity involving the medial medullary lamina (arrowheads) is more clearly visualized on both sides compared to the axial images. (C) Axial T2WI through the posterior fossa demonstrated significant atrophy of the cerebellar hemispheres as evinced by prominence of sulci.

Discussion

Genetic analysis demonstrated a mutation of the *C19orf12* gene, confirming the diagnosis of mitochondrial membrane protein-associated neurodegeneration (MPAN). The early onset of gradually worsening neurologic symptoms is suggestive of a familial neurodegenerative disorder; this is confirmed by the presence of brain atrophy on imaging. Increased T2 hypointensity on the globus pallidus is suggestive of inappropriate iron accumulation and raises the concern for neurodegeneration associated with brain iron accumulation (NBIA). Linear increased T2 signal in the medial medullary lamina is suggestive of MPAN, a subtype of NBIA. BPAN (see Part I: Case 1) is excluded because of the absence of typical T1 hyperintensity in the basal ganglia and in the substantia nigra. Patients with PLAN (see Part I: Case 5) typically present very early in life, usually before 10 years of age.

Inappropriate brain iron deposition is a non-specific finding and can be seen as a manifestation of a neurodegenerative disease or normal aging. Presentation in early childhood excludes many neurodegenerative diseases such as Parkinson disease, Parkinson-plus syndromes, and Alzheimer disease. Neuroferritinopathy (see Part I: Case 3) and aceruloplasminemia (see Part I: Case 6), NBIA subtypes that typically manifest in older age groups, were also excluded, as there were no typical imaging findings and the other blood work did not demonstrate low ferritin or ceruloplasmin, respectively. The clinical presentation of this patient overlaps with symptoms of PKAN (see Part I: Case 4). The *eye-of-the-tiger* sign, the characteristic imaging manifestation of PKAN, was not present on imaging. No features suggestive of pigmentary retinal degeneration, a frequent manifestation of PKAN, were noted.

A recently described phenotype, MPAN may account for approximately 5% of all NBIA subtypes. In *Online Mendelian Inheritance in Man*® (OMIM®, http://www.omim.org), MPAN is classified as NBIA type 4 (OMIM #614298). It is an autosomal recessive disorder caused by mutation in the *C19orf12* gene, the product of which is a mitochondrial membrane protein. This mutation causes mitochondrial dysfunction and altered lipid metabolism. As of 2013, 67 cases have been reported. The mean age of presentation is 11 years, with a range of 4–30 years. Progression of cognitive decline to dementia is almost a universal finding of MPAN. Motor neuropathy is another frequent manifestation that typically starts with upper motor signs followed by lower motor signs. Other clinical presentations include slowly progressive gait disorder from generalized dystonia and spastic paraparesis, cognitive decline, neuropsychiatric abnormalities, optic atrophy, and motor axonal neuropathy. In contrast to PKAN, MPAN is associated with optic atrophy, not pigmentary degeneration of retina. The onset of symptoms in MPAN is later in childhood with more gradual psychomotor regression, as compared to PKAN. However, cognitive decline progressing to severe dementia is more commonly associated with MPAN, as compared to PKAN.

Magnetic resonance imaging shows T2 hypointensity from iron accumulation in the globus pallidus and in the substantia nigra, in the vast majority of patients. T2 hyperintense streaking of the medial medullary lamina between the globus pallidus interna and externa is a characteristic finding, though not present in all cases. If present, this may discriminate MPAN from other NBIA subtypes. The *eye-of-the-tiger* sign is absent, distinguishing this NBIA subtype from the more common PKAN. The presence of nigral T2 hypointensity is similar to features seen in patients with another NBIA subtype, PLA2G6-associated neurodegeneration (PLAN), who may also show optic atrophy. However, PLAN patients show cerebellar atrophy, which is not always seen in MPAN (although it is seen on the given case). Magnetic resonance imaging of MPAN patients demonstrates additional T1 hyperintensity of the caudate nucleus and putamen, not seen in PLAN patients. On pathology, neuronal loss, iron deposits, axonal spheroids, Lewy bodies, and hyperphosphorylated tau-containing inclusions are seen.

Key Points

- MPAN should be suspected if presentation includes relatively rapidly progressing cognitive decline in older children with evidence of excessive iron deposition in the basal ganglia.
- Increased T2 signal in the medial medullary lamina between the globus pallidus interna and globus pallidus

externa is a more specific, but less sensitive imaging finding of MPAN.

- If characteristic clinical and radiologic findings are present, the diagnosis should be confirmed by molecular, genetic analysis.

Suggested Reading

Hartig M, Prokisch H, Meitinger T, Klopstock T. Mitochondrial membrane protein-associated neurodegeneration (MPAN). *Int Rev Neurobiol* 2013; 110: 73–84.

Hogarth P, Gregory A, Kruer MC, et al. New NBIA subtype: genetic, clinical, pathologic, and radiographic features of MPAN. *Neurology* 2013; 80(3): 268–75.

Kniffin CL. *Neurodegeneration with Brain Iron Accumulation 4; NBIA 4*. Baltimore, MD: Johns Hopkins University; 2011 [updated 11/12/2013; cited 2014]. Available from: http://omim.org/entry/614298.

Schulte EC, Claussen MC, Jochim A, et al. Mitochondrial membrane protein associated neurodegeneration: a novel variant of neurodegeneration with brain iron accumulation. *Mov Disord* 2013; 28(2): 224–7.

Part I

Neurodegenerative Diseases

CASE 3

Asim K. Bag, Victor Hugo Rocha Marussi, Lázaro Luís Faria do Amaral

Clinical Presentation

A 35-year-old man presented with dysarthria and gradually worsening gait and ataxia. His medical history included long history of hand tremor. Neurologic examination revealed cerebellar symptoms including dysmetria, hypotonia, micrographia, and mild cognitive impairment. Routine hematologic examinations including serum chemistries and hematologic profile were normal. Further testing demonstrated low serum ferritin levels. Cerebrospinal fluid examinations were within normal range. Magnetic resonance of the brain was performed and is shown below.

Imaging

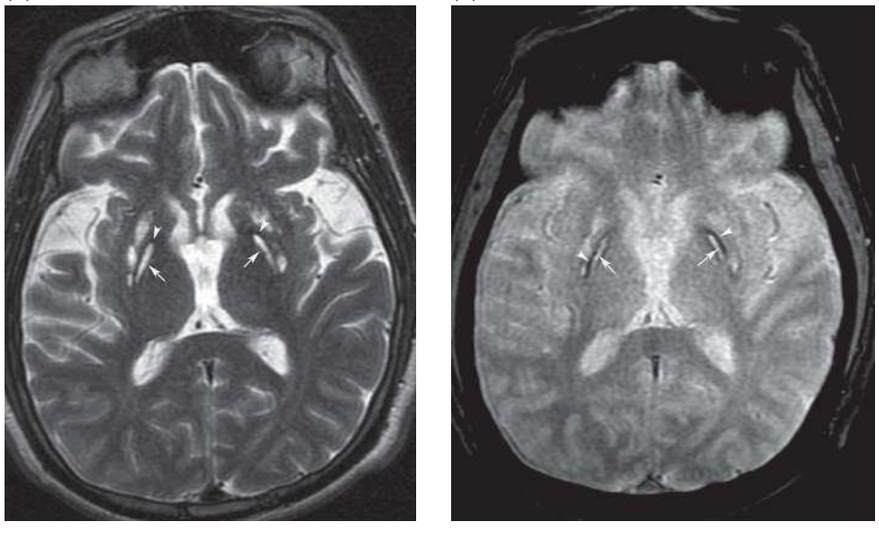

Fig. 3.1 (A) Axial T2WI through the basal ganglia. (B) Axial GRE image through the same level. Taken with permission from: Amaral LLF, Gaddikeri S, Chapman PR, Roy R, Gaddikeri RS, Marussi VH, Bag AK. Neurodegeneration with brain iron accumulation: clinicoradiological approach to diagnosis. *J Neuroimaging* 2015; 25(4): 539–51.

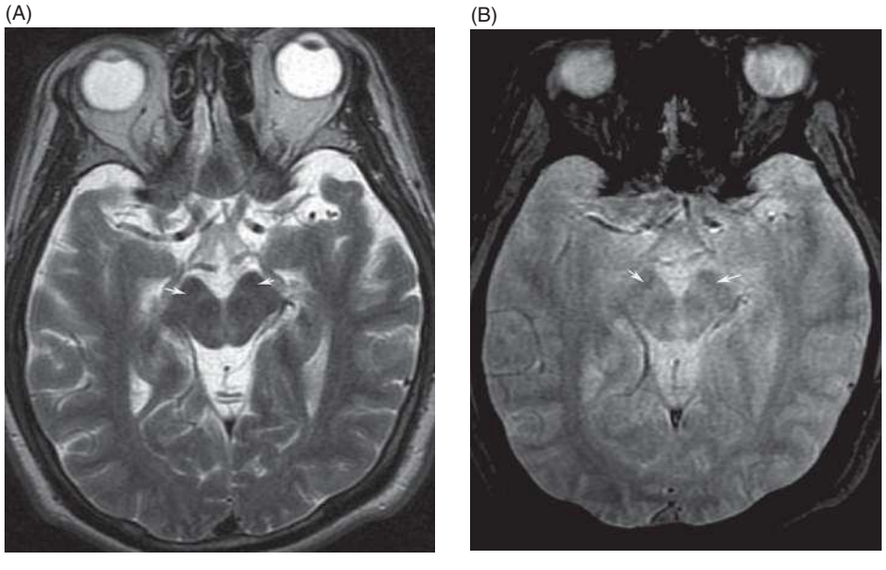

Fig. 3.2 (A) Axial T2WI. (B) GRE sequence through the substantia nigra. Taken with permission from: Amaral LLF, Gaddikeri S, Chapman PR, Roy R, Gaddikeri RS, Marussi VH, Bag AK. Neurodegeneration with brain iron accumulation: clinicoradiological approach to diagnosis. *J Neuroimaging* 2015; 25(4): 539–51.

Neuroferritinopathy

Primary Diagnosis

Neuroferritinopathy

Differential Diagnoses

Aceruloplasminemia
Pantothenate kinase-associated neurodegeneration (PKAN)
Wilson disease
Leigh syndrome
Enlarged perivascular space

Imaging Findings

Fig. 3.1: (A) Axial T2WI through the basal ganglia demonstrated bilateral, almost symmetric, cystic degeneration of the globus pallidus (arrows) and putamen. A subtle T2 hypointense rim was noted at the anterior aspect of the globus pallidus (arrowheads). Also significant brain atrophy was noted as evidence by bilateral enlargement of sylvian fissures. (B) Axial gradient echo image through the same level demonstrated more obvious peripheral hypointensity on the lateral aspect (arrowheads) of the globus pallidus (arrows) due to abnormal iron deposition. Fig. 3.2: (A) Axial T2WI and (B) GRE sequence through the substantia nigra demonstrated no evidence of abnormal iron deposition in the substantia nigra (arrows).

Discussion

In an adult patient, the presence of cystic degeneration of the bilateral basal ganglia with evidence of abnormal iron deposition accompanied by progressively worsening of abnormal movement, cognitive disorders, and low serum ferritin are diagnostic of neuroferritinopathy.

Aceruloplasminemia (ACP) (see Part I: Case 6) is a subtype of neurodegeneration with brain iron accumulation (NBIA) presenting in the adult population. In ACP, there is more prominent signal abnormality involving the deep gray matter nuclei without any evidence of cystic degeneration. Patients with ACP develop diabetes mellitus and retinal degeneration. Additionally, ACP is characterized by low serum ceruloplasmin and high serum ferritin level. PKAN (see Part I: Case 4), usually a disease of childhood, can also present in early adulthood. Presentation of PKAN in the fourth decade, as in this patient, is extremely rare. In addition, intense, abnormal pallidal iron deposition, with a central area of rarefaction evidenced by a T2 hyperintensity (*eye-of-the-tiger sign*), is the typical imaging presentation of PKAN, not complete cystic pallidal degeneration as seen in neuroferritinopathy (NFT).

The presence of abnormal T2 hyperintensity in the basal ganglia can also be seen in Leigh syndrome, but Leigh syndrome typically manifests in the first two years of life with ophthalmoplegia, cranial nerve palsy, and respiratory failure. In addition, there is high brain and CSF lactate levels on MR spectroscopy. Although bilateral basal ganglia T2 hyperintensity can be present in Wilson disease, Kayser-Fleischer ring in bilateral iris and hepatic failure are additional clinical findings that were absent in our patient. Though enlarged perivascular space can have a large cyst-like appearance, on occasion, similar to NFT, it is not associated with peripheral T2/GRE hypointensity due to excessive iron accumulation.

Neuroferritinopathy is one of the many subtypes of NBIA that is transmitted as an autosomal dominant trait and is due to mutation of the ferritin light chain gene on chromosome 19q. Mutated ferritin light chains lose their capacity for iron storage and metabolism, thus free iron is released within affected cells. This free iron can induce oxidative stress and subsequent neuronal degeneration, particularly in basal ganglia. This also explains characteristic low serum ferritin level. Unlike many other NBIA subtypes, NFT presents later in life, usually after 30 years of age. Extrapyramidal symptoms such as choreoathetosis, dystonia, and Parkinsonian symptoms usually predominate. Palatal myoclonus and orolingual dyskinesias ataxia can also be presenting symptoms. Neurocognitive decline is usually a late finding.

Neuroferritinopathy has distinctive imaging findings including bilateral, almost symmetric, cystic degeneration involving the bilateral globus pallidus, substantia nigra, and deep cerebellar nuclei. Areas of cystic degeneration are lined by hypointense rim due to excess iron deposition. Mild to moderate brain atrophy is frequently associated with cystic degeneration.

Key Points

- Neuroferritinopathy should be suspected in adult patients with early-onset Parkinsonian syndrome and cystic pallidal degeneration surrounded by hypointense rim on GRE and/or T2WI.
- Low serum ferritin level is characteristic.
- If characteristic clinical and radiologic findings are present, the diagnosis is almost certain and should be confirmed by genetic analysis.

Suggested Reading

Amaral LLF, Gaddikeri S, Chapman PR, et al. Neurodegeneration with brain iron accumulation: clinicoradiological approach to diagnosis. *J Neuroimaging* 2015; 25(4): 539–51.

Fatima Z, Ishigame K, Araki T. Case 193: Neuroferritinopathy–a brain iron accumulation and neurodegenerative disorder. *Radiology* 2013; 267(2): 650–5.

Part I

Neurodegenerative Diseases

CASE 4

Aparna Singhal, Lázaro Luís Faria do Amaral, Asim K. Bag

Clinical Presentation

A five-year-old boy presented with history of gradual development of postural and gait abnormalities, pyramidal and extrapyramidal symptoms, oromandibular dystonia, and neurocognitive decline. On neurologic evaluation, profound oromandibular dystonia was noted. Ophthalmologic evaluation revealed night blindness and visual field constriction, but no feature of optic atrophy. Hematologic studies did not reveal any significant abnormality. An MRI was performed with a 1.5T magnet.

Imaging

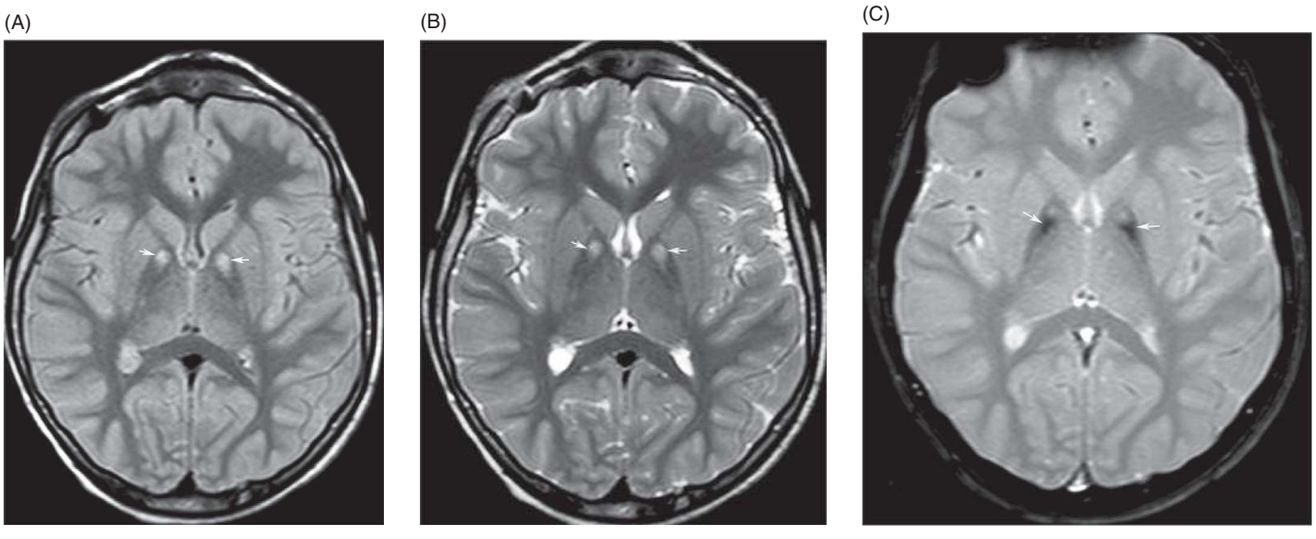

Fig. 4.1 (A) Axial FLAIR and (B) T2WI and (C) GRE images through the globus pallidi. Taken with permission from: Amaral LLF, Gaddikeri S, Chapman PR, Roy R, Gaddikeri RS, Marussi VH, Bag AK. Neurodegeneration with brain iron accumulation: clinicoradiological approach to diagnosis. *J Neuroimaging* 2015; 25(4): 539–51.

Pantothenate Kinase-Associated Neurodegeneration (PKAN)

Primary Diagnosis

Pantothenate kinase-associated neurodegeneration (PKAN)

Differential Diagnoses

Other neurodegeneration with brain iron accumulation (NBIA) subtypes
Carbon monoxide poisoning
Metabolic abnormality

Imaging Findings

Fig. 4.1: (A) Axial FLAIR MR image demonstrated increased T2 signal in the center of the globus pallidi (arrows). (B) Axial T2WI through the same level demonstrated increased T2 signal in the center of the globus pallidi (arrows). (C) Axial GRE image through the same level demonstrated hypointensity, secondary to iron deposition, in the posterior and lateral aspect of globus pallidi (arrows). Please note there is also no associated brain atrophy or abnormal T2 signal in the white matter.

Discussion

The clinical presentation is classic for typical PKAN. The disease manifests in children between three and five years of age, with gradually progressing gait abnormalities and pyramidal-extrapyramidal symptoms. Presence of profound oromandibular dystonia, night blindness, and visual field constriction further support the diagnosis of PKAN. Evidence of excessive iron accumulation in the globus pallidi with central area of rarefaction, absence of white matter disease, and presence of brain or cerebellar atrophy confirms the diagnosis of PKAN.

The *eye-of-the-tiger* sign, demonstrated in this case, is characteristic, but not pathognomonic for PKAN. This sign can be seen in neuroferritinopathy (see Part I: Case 3), corticobasal degeneration (see Part I: Case 10), and multiple system atrophy (see Part I: Case 8). It can also be an imaging manifestation of normal aging. All of these diseases typically affect older patients, not children. Although there may be overlap of clinical symptoms between other NBIA subtypes such as mitochondrial membrane protein-associated neurodegeneration (MPAN) and phospholipase-associated neurodegeneration (PLAN), characteristic *eye-of the-tiger* sign is typically absent in these subtypes. Carbon monoxide poisoning can present as T2 hyperintensities in the globus pallidus, without surrounding T2 hypointensity related to excessive iron accumulation. In addition, other brain structures are often involved in carbon monoxide poisoning, such as the putamen, thalamus, and peripheral cortex.

PKAN is an autosomal recessive disorder due to mutations in the *PANK2* (pantothenate kinase 2) gene located on chromosome 20p13, with an estimated prevalence of 1:1,000,000, accounting for approximately half of all NBIA cases. In *Online Mendelian Inheritance in Man*® (OMIM®, http://www.omim.org) PKAN is described as NBIA type 1 (OMIM #234200). There are two types: typical and atypical. In the typical variant, onset occurs before six years of age in almost 90% of patients, typically with gait difficulty as the presenting symptom. There are pyramidal features (spasticity, hyperreflexia, and extensor plantar toe response) and extrapyramidal features (prominent dystonia) often with typical predominant orolingual-mandibular involvement. Other extrapyramidal features such as Parkinsonism, chorea, and neuropsychiatric features including attention deficit hyperactivity disorder, cognitive decline, and behavioral changes may be seen. Oculomotor abnormalities are common, seen partly because of midbrain degeneration. Around 70% of patients have electroretinographic evidence of retinopathy. Unlike PLAN and MPAN, optic atrophy is typically absent in PKAN. Typical PKAN has a rapidly progressive course with affected children usually becoming wheelchair-bound within a few years of disease onset.

Unlike typical PKAN, atypical PKAN is classically an adult-onset disease with age of onset between 20 and 30 years of age. Patients with atypical PKAN demonstrate less severe motor involvement as compared to the typical form and have frequently been reported to present with speech difficulties and atypical phenotypical features such as focal dystonia, less prominent extrapyramidal features, retinopathy, predominant cognitive decline, and psychiatric features.

On MRI, there is typical iron accumulation in the anteromedial part of the globus pallidus with extension into the genu of the internal capsule that is manifested as prominent T2 hypointensity. The presence of a central hyperintensity on the T2WI sequence within the surrounding area of hypointensity is called the *eye-of-the-tiger* sign and is characteristic of PKAN. It has been suggested that the hyperintense central pallidum indicates a primary tissue insult leading to neuronal loss, gliosis, and cavitation of the neuropil. The surrounding hypointense region indicates high iron deposition. It is unclear if the iron deposition plays a primary or secondary effect in PKAN. Iron deposition in the subthalamic nucleus and substantia nigra, in addition to globus pallidi has also been described. If present very early in life, bilateral hyperechogenicity in the substantia nigra and lenticular nucleus can be seen on transcranial sonography. Pathologically, iron accumulation is seen as rust-brown pigmentation in the globus pallidus grossly and microscopically; iron is mostly in the ferric form, in a perivascular distribution in the microglia and macrophages.

The exact pathophysiology of PKAN is poorly understood. The *PANK2*-encoded enzyme is key in coenzyme A synthesis, which is essential for fatty acid synthesis. Dysfunction of PANK2, thus, likely causes alteration in lipid metabolism. PANK2 is mainly targeted to mitochondria; its mutation may therefore also cause dysfunction of cellular energy metabolism. Null mutations of the *PANK2* gene result in complete absence of the enzyme and are more commonly seen in early-onset typical PKAN with rapidly progressive disease; whereas missense mutations result in partial loss of enzymatic function and are more commonly seen in late-onset, atypical PKAN with more slowly progressive disease. No drugs are currently available that can halt neurodegenerative progression in