Neuroferritinopathy: Pathophysiology, Presentation, Differential Diagnoses and Management

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Abstract

Background: Neuroferritinopathy (NF) is a rare autosomal dominant disease caused by mutations in the ferritin light chain 1 (FTL1) gene leading to abnormal excessive iron accumulation in the brain, predominantly in the basal ganglia.

Methods: A literature search was performed on PubMed, for English-language articles, utilizing the terms iron metabolism, neurodegeneration with brain iron accumulation, and NF. The relevant articles were reviewed with a focus on the pathophysiology, clinical presentation, differential diagnoses, and management of NF.

Results: There have been nine reported mutations worldwide in the FTL1 gene in 90 patients, the most common mutation being 460InsA. Chorea and dystonia are the most common presenting symptoms in NF. There are specific features, which appear to depend upon the genetic mutation. We discuss the occurrence of specific mutations in various regions along with their associated presenting phenomenology. We have compared and contrasted the commonly occurring syndromes in the differential diagnosis of NF to guide the clinician.

Discussion: NF must be considered in patients presenting clinically as a progressive movement disorder with variable phenotype and imaging evidence of iron deposition within the brain, decreased serum ferritin, and negative genetic testing for other more common movement disorders such as Huntington’s disease. In the absence of a disease-specific treatment, symptomatic drug therapy for specific movement disorders may be used, although with variable success.

Keywords: Neuroferritinopathy, FTL1 gene, chorea, dystonia, neurodegeneration with brain iron accumulation, Huntington’s disease, hereditary ferritinopathy

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Introduction

Neuroferritinopathy (NF) is an autosomal dominant, late-onset basal ganglia disorder resulting from mutations in the gene for ferritin light chain 1 (FTL1) on chromosome 19q13.1,2 The pathogenic mutations in the FTL1 gene cause pathological iron deposition and ferritin inclusions in various brain regions, respecting the pattern observed in normal aging.1 NF belongs to the group of disorders collectively known as neurodegeneration with brain iron accumulation (NBIA). The NBIAst present as a progressive extrapyramidal syndrome with abnormally increased iron deposition in the brain, particularly affecting the basal ganglia.3 Pantothenate kinase-associated neurodegeneration (PKAN) and PLA2G6-associated neurodegeneration are the two most common disorders in this group. NF is one of only two disorders in this expanding group of NBIAst caused by a mutation in genes directly involved in iron metabolism; the other being aceruloplasminemia.4 It is the only autosomal dominant NBIA disorder, and patients present late in adulthood with combinations of movement disorders.2 To date, 90 cases of NF have been identified with nine causative mutations. On the basis of recent advances in our knowledge about NF, we review the various aspects of NF, namely the pathophysiology, genetics, clinical manifestations, differential diagnosis, treatment options, and prognosis.

Pathophysiology

The brain requires iron for many of its essential activities including transport of oxygen, energy generation, development of oligodendrocytes,
myelin synthesis, production of neurotransmitters (dopamine, serotonin, and norepinephrine), and metabolism of nitric oxide. The brain contains about 30–40 mg of iron, which forms less than 1% of the total iron in our body. Iron content in the brain increases with age, but it is still unclear whether its accumulation in neurodegenerative disorders is a primary or a secondary phenomenon. The distribution of iron in the brain is not homogeneous. The basal ganglia (caudate, putamen, and globus pallidus) have the highest iron concentrations, while the cortex, brainstem, and cerebellum have relatively lower concentrations. Iron is mainly stored intracellularly in the ferritin complex; however, in the substantia nigra and locus ceruleus, neuromelanin is the major iron storage molecule.

To get into the brain, iron needs to cross the blood-brain barrier and blood-cerebrospinal fluid (CSF) barrier. Iron is transported by transferrin (Tf), which binds to transferrin receptors (TfR) on the cell surface. Of the two TfRs (TfR1 and TfR2), TfR1 plays the primary role in iron transfer. The Tf–TfR system is mainly responsible for exporting iron from the vascular lumen into the vascular endothelial cells. Iron is exported out of the basolateral membrane through some unknown transporters, which may involve ferroportin. Extracellular iron then enters the astrocytes as low molecular weight complexes (e.g., citrate, adenosine triphosphate, ascorbate) or it may enter the neurons via the Tf–TfR pathways (Figure 1). Iron can be stored as ferritin in astrocytes and released through ferroportin and ceruloplasmin, the ferroxidase that oxidizes ferrous iron. Astrocytes are ideally positioned to take up iron from the circulation and disperse it among other central nervous system cells.

Ferritin, the major iron storage protein, has a spherical shell with an internal cavity that can store 4,500 iron atoms. It is composed of two subunit types, heavy (H) and light (L), which are encoded by genes on chromosomes 11 and 19, respectively. Both H and L chains are essential as the heteropolymers assimilate iron more effectively than homopolymers. In NF, the mutations produce a lengthening of the C terminus of the L chain that impairs its normal interaction with the heavy chain, thereby impairing the iron-binding capacity of ferritin. This results in accumulation of ferrous or free iron (Fe²⁺), which causes damage by producing free radicals, and a compensatory upregulation of ferritin production (Figure 1). Oxidative stress leads to neurodegeneration. Mitochondrial dysfunction may also contribute to the cellular dysfunction in NF probably by affecting neuronal intramitochondrial iron handling.

Curtis et al. were the first group to report NF cases in a large north England family from the Cumbria region who had dominantly inherited, adult-onset basal ganglia disease. They found a mutation of an adenine insertion at position 460–461 in exon 4 of the FTL1 gene, which caused a frameshift and led to alterations at the C terminus of the gene product. The number of reported cases and mutations in NF are gradually increasing, thus underlining the fact that NF is neither purely confined to the population of north England nor confined to a common founder, as was once thought (Table 1). Most FTL1 mutations are located on exon 4, commonly resulting in a

Figure 1. Cellular Iron Metabolism in the Central Nervous System and Abnormalities in Neuroferritinopathy. Adapted from Dringen et al., Schneider et al., and Levi and Finazzi. Ferritin (TF) bound ferric iron (Fe³⁺) enters the cell (astrocyte) through adenosine triphosphate (ATP)-dependent transferrin receptor (TfR)-mediated endocytosis, and ferrous iron (Fe²⁺) via a divalent metal transporter 1 (DMT1). STEAP 3, a ferrireductase, converts Fe³⁺ to Fe²⁺. Excess iron is stored in ferritin as Fe³⁺. Fe²⁺ is exported out via ferroportin (FP), where it is oxidized by ceruloplasmin (CP) to Fe³⁺ and is available for other central nervous system cells, i.e., neurons and oligodendrocytes. The solid arrows show the normal iron metabolic pathways and the dotted arrows depict the pathogenic mechanisms in neuroferritinopathy (NF). The FTL1 gene mutation reduces the effectiveness of iron incorporation in ferritin and causes faster ferritin degradation. In turn, the increase in cytosolic iron induces upregulation of the abnormal ferritin. This stimulates production of reactive oxygen species (ROS) and oxidative damage leading to proteasome impairment and cell death. H, Heavy Subunit; L, Light Subunit.
Table 1. Summary of the Genetics, and Clinical and Radiological Features of All Reported Neuroferritinopathy Cases

| FTL1 Mutation (In Order of Identification) | Place of Origin (Study) | Number of Cases (M:F) | Mean Onset Age (Years) | Movement Disorders | Co and Np | MRI Brain | Serum Ferritin |
|--------------------------------------------|-------------------------|-----------------------|------------------------|-------------------|----------|-----------|----------------|
| 460InsA                                    | UK                      | 41 (20:21), incl. 1 asymp. | 39.4                  | + + + + - - - + + + | • T2 decr. in DN, RN, SN, P, GP, Th, CN | Decr. | Incl. cases from other studies 1,15,23-25 |
|                                            | Ondo et al. 26          | USA                   | 2 (2:0)                | 48.5              | + + - + - + + - - + + | • T2 and flair lesions in the GP and cerebellum | Decr. |
|                                            | Australia (British ancestry) | 5 (5:0)          | 47                     | + + + + - + + + - | • T2 decr. & low normal (n=8) | Decr. (n=2) & low normal | Incl. cases from other studies 1,15,23-25 |
|                                            | Keogh et al. 28         | UK                    | 10 (5:5)               | 48.5              | + + + + - + + + + + | • BG cavitation, T2 decr. in Th 29, T1 incr. in CN and GP, cerebellar atrophy, lingual gyrus involvement 26 | Decr. |
|                                            | Batla et al. 30         | UK                    | 3 (1:2)                | 50.7              | + - + - + - + - + + - | • SWI showed pencil lining in cerebral and cerebellar cortex | Decr. |
|                                            | Vidal et al. 13         | France                | 11 (7:4)               | 36.8              | + + + + + - - - - + + | • T2 decr. and T1 incr. in BG | Decr. (n=2) |
|                                            | Maciel et al. 17        | Portugal              | 3 (2:1); incl. 2 asymp. | 13                 | - - + - - + - + - + + | • T2 incr. in GP, cerebellar atrophy | Decr. |
| FTL1 Mutation (In Order of Identification) | Place of Origin (Study) | Number of Cases (M:F) | Mean Onset Age (Years) | Movement Disorders | Co and Np | MRI Brain | Serum Ferritin |
|------------------------------------------|-------------------------|-----------------------|------------------------|------------------|-----------|-----------|----------------|
| 646InsC USA (French Canadian and Dutch ancestry; Mancuso et al. [16]) | 646InsC USA (French Canadian and Dutch ancestry; Mancuso et al. [16]) | 2 (1:1) | 56 | + + - - + + + + | - - - - - - | Cerebellar atrophy; T2 incr. in P, GP, CN and SN | Low–normal range |
| 469_484dup16nt Japan (Ohta et al. [32]) | 469_484dup16nt Japan (Ohta et al. [32]) | 2 (1:1) | Teenage | - - + + - - - + | + + + + + + | Cystic changes in GP and striatum; T2 incr. in Th, DN, and SN | Decr. |
| Italy (Storti et al. [14]) | Italy (Storti et al. [14]) | 1 (1:0) | Late 20s | + - + + + - - + | - - - - - - | Cavitation of bilateral LN; Cortical atrophy | Decr. |
| 458dupA France (Devos et al. [20]) | 458dupA France (Devos et al. [20]) | 1 (0:1) + 3 prev. reported (3:0)[2] | 24–44 | + - + - + - + + | + + + + + + | Cystic cavitation in BG; Iron deposition in DN, GP, and P | Decr. |
| 641_642dup Japan (Kubota et al. [19]) | 641_642dup Japan (Kubota et al. [19]) | 7 (7:0) | 51.8 | + + - + - - + + | + + + + + + | T2 incr. with surrounding decr. in GP and P | Low–normal range |
| 468dupT France (Moutton et al. [21]) | 468dupT France (Moutton et al. [21]) | 1 (1:0) | 27 | + + - - - - - + | - - - - - - | BG cavitations; Asymmetrical changes | Decr. |
| 468_483dup16nt Japan (Nishida et al. [22]) | 468_483dup16nt Japan (Nishida et al. [22]) | 1 (0:1) | 42 | + - - - + - + + | + + + + + + | T2 incr. with surrounding decr. in bilateral posterior GP and P; Mild cerebral and cerebellar atrophy | Normal serum ferritin; decr. CSF ferritin |

Abbreviations: A, Adenine Base; Asymp., Asymptomatic; At, Ataxia; BG, Basal Ganglia; C, Cytosine Base; Ch, Chorea; CN, Caudate Nucleus; Co, Cognitive Impairment; CSF, Cerebrospinal Fluid; D, Dystonia; Decr., Decreased; DN, Dentate Nucleus; Dup, Duplication; GP, Globus Pallidus; Ind., Including; Incr., Increased; Ins, Insertion; LN, Lenticular Nuclei; Np, Neuropsychiatric Manifestations; O, Orofacial Dyskinesia; P, Putamen; Pk, Parkinsonism; Prev., Previously; RN, Red Nucleus; SN, Substantia Nigra; SWI, Susceptibility-weighted Imaging; T, Thymine Base; Th, Thalamus; Tr, Tremor; T/S, Tics/Stereotypy.
frameshift, suggesting that this part of the gene is particularly vulnerable to mutation.11

Clinical features

NF usually presents in the second to fifth decade of life with the mean age of onset being around 40 years.1,2,13,15,19 Those with mutations other than 460InsA appear to have an earlier age of onset (Table 1). The gender of the patients does not affect the age of disease onset or clinical phenotype. Although no predilection was seen for any gender in the largest series,2 some series report male predominance.19,27,31 It was suggested that females might be less vulnerable to abnormal iron deposition owing to menstruation,19 which may explain an asymmetric 40-year-old female carrier in one of the reports.17 The disorder is thought to be fully penetrant by the age of 60.2,33 Clinical presentation does not differ with the age of onset. A strong family history is reported in most of the series.1,2,13. The disease progresses gradually, first involving basal ganglionic and/or cerebellar functions, and spreads to involve cortical functions in the late stages.1,2,13 The clinical manifestations vary among NF patients, which may be related to the variability in length of the mutant polypeptide and the resulting dominant negative effect of the modified last alpha-helix domain.14 However, there is no known correlation between the length of the mutant polypeptide and the age of onset. Environmental factors like dietary iron intake and other genes influencing iron metabolism may affect the clinical picture.21

Motor symptoms

NF may present with varied movement disorders. Three of the 90 cases reported to date were asymptomatic,2,17 and clinical data were not available for four additional reported NF patients.13,31 On analyzing all the symptomatic reported cases of NF (n=83; Figure 2), we found chorea (39.7%; n=33) and dystonia (38.5%; n=32) to be the commonest presenting features; however, these were not specific for any particular FITL mutation or a geographical region. Parkinsonism (6%; n=5) and tics (1.2%; n=1) as initial presentation were seen in only those patients with 460InsA mutations. Tremor (7.2%; n=6) at the disease onset was seen in patients of French ancestry with 498InsTC, and in Japanese patients with 469_484dup16nt. The 469_484dup16nt mutation is also seen in Italy, presenting with similar clinical features. Cerebellar ataxia (4.8%; n=4) as the presenting movement disorder was common in patients of French ancestry with 490InsTC mutations. Those with 460InsA mutations are unlikely to present with tremor and cerebellar ataxia.

The abnormal movements may remain asymmetric throughout the disease course in almost two-thirds of patients.5 Irrespective of the initial presentation, most patients develop dystonia (83%), predominantly in the lower limbs, and/or chorea (70%).2 Cerebellar symptoms such as dysmetria, ataxia, and palatal tremor are reported in patients with NF and may appear at any stage of the disease.2,13,14,16,17,20,22,23,26,31 Although unsteady gait and repeated falls may appear early in NF,14,27 the majority of patients remain mobile even after 20 years of disease onset.5 Patients with dystonic presentation have the most severe physical disability.2 Dysarthria and dysphagia have been reported in many patients.2,16,19,20,22,26,27,30,34 Oromandibular dyskinesia (65%), impairment of voice and speech (dysarthrophonia) with action-specific facial dystonia (63%) are commonly seen,2,13,20,22,24 and felt by one group to be specific to NF.32 Facial tics may be seen.32 Although changes in handwriting are expected to occur in most of the patients, micrographia has been specifically reported.16 Rarely, patients may present with ballistic movements,2 alien limb phenomenon,2 blepharospasm,2,24,30 or writer’s cramp.2

Pyramidal signs including spasticity,1 brisk deep tendon reflexes,32 and Babinski signs15,16,22 have been reported in patients with NF. Hypotonia may be seen.19,22,32 Although extracranial movements are usually well preserved, some patients may develop saccadic pursuit,1,16,23 slow saccades,16,22,23 and apraxia of eyelid opening.16,23 Limitation of vertical eye movements30 and horizontal oculomotor dysmetria21 are reported.

Cognitive decline and psychiatric symptoms

The onset of cognitive impairment may vary from the first decade to more than three decades after the onset of motor symptoms.2,13,15,19,21,25,32,34 One study reported neurocognitive features presenting within 5 years of onset of the motor manifestations.34 Mild deficits in verbal fluency may be seen early.7 Features suggestive of frontal and subcortical cognitive impairment like disinhibition, reduced verbal fluency, executive dysfunction (working memory), and attention difficulties predominate.2,13,15,21,25 Rarely, patients may present with psychiatric symptoms (2.4%; n=2) (Figure 2). Japanese patients presented more commonly with psychiatric symptoms and cognitive decline. Anxiety,13 paranoid delusions,35 acute psychosis,17 or depression16,19,20 have been reported to occur anytime in the course of NF.

Other features

Sleep disturbances, including insomnia,13 sleep apnea,35 and central sleep apnea with restrictive respiratory insufficiency causing excessive
daytime sleepiness, have been reported. Other features may include areflexia and a positive Romberg test; features of dyautonomia such as othostatic hypotension, constipation, urinary incontinence and impotence; fatigue and pseudobulbar effect. Chronic headache may also be a presenting symptom. Sensory abnormalities in the large fiber sensations (vibration and proprioception) and positive frontal release signs have been reported.

**Differential diagnoses**

The varied clinical presentations of NF make for a long list of differential diagnoses. Common differential diagnoses are listed in Table 2. Others may include Niemann–Pick type C (NPC) and mitochondrial disease. Marked supranuclear gaze impairment favors a diagnosis of NPC. Although there are overlaps in the clinical, radiological, and muscle biopsy findings between NF and mitochondrial disorders, positive genetic testing for FT1 mutation confirms the diagnosis of NF. Additional brain immunochemistry abnormalities indicate a secondary defect of the respiratory chain in NF. Early in the course of NF, patients may present with features of writer’s cramp, blepharospasm, or restless leg syndrome. A family history of NF, decreased serum ferritin, and magnetic resonance imaging (MRI) brain suggestive of abnormal iron storage in the basal ganglia may point to the diagnosis of NF in such patients.

**Laboratory investigations**

Complete blood count, renal function tests, copper studies (serum ceruloplasmin and copper, and 24-hour urinary copper), and serum creatine kinase are typically normal in NF. Liver function tests may be abnormal. Serum ferritin levels may be decreased or in the normal range. Although decreased serum ferritin was not uniformly seen in all the cases, a low serum ferritin in the setting of an unknown movement disorder with autosomal dominant family history suggests the diagnosis of NF. In the largest series of patients, the serum ferritin was decreased in 82% of males and all postmenopausal females, but only in 23% of premenopausal females. This may be explained because of the loss of iron owing to menstruation in premenopausal females. Decreased CSF ferritin was reported by Nishida et al. Nerve conduction studies are normal.

**Neuroimaging**

Key features on brain imaging support the diagnostic consideration of NF. Features of iron deposition precede evidence of atrophy and necrosis on brain MRI. Brain MRI may show basal ganglia cavitation or cystic changes (predominantly in the globus pallidus and putamen), hyperintensity with surrounding hypointensity on T2-weighted imaging involving the putamen, pallidum, thalamus, substantia nigra, and the dentate nucleus, cortical atrophy, pontine atrophy, and cerebellar atrophy. T2-weighted images showing a hypointense rim with hyperintense center in the globus pallidus (“eye of the tiger sign”), considered pathognomonic of PKN, is reported in NF. This MRI signature may also be seen in cortico-basal ganglionic degeneration, multiple system atrophy, progressive supranuclear palsy, and pure akinesia with gait freezing. While thalamic iron stores correlate with the severity of dystonia, voxel-based analysis showed correlation between caudate iron stores and globus pallidus cavitation to the severity in NF patients. Iron deposition in the cortex, on susceptibility-weighted imaging sequence on MRI, produces a hypointense fine signal band along the cortical contours and is termed “pencil-lining.” Patients older than 50 years of age or those with disease duration of more than 10 years develop more severe basal ganglia cavitation. Rarely, the brain MRI may be normal in the initial stage of the disease. Asymptomatic persons with positive gene mutation may have abnormal brain MRI. MRI brain findings in some patients with NF may remain asymmetric.

**Genetic testing**

Genetic testing for the FT1 gene mutation on chromosome 19q13.3 is confirmatory. Rarely, the individual may be asymptomatic despite a confirmed mutation. Of the nine causative FT1 mutations reported to date, 460insA is the most common in patients of British descent and 490insTC is common in patients with French ancestry. The 460insA mutation has not been found in Japanese patients.

**Neuropathology**

Mild cerebral and cerebellar atrophy with basal ganglia cavitation and numerous iron-positive inclusions especially in the globus pallidus and putamen are seen on neuro-pathological examination. Intrauclear and intracytoplasmic ferritin deposition in astrocytes and oligodendroglia are seen in the caudate nucleus, putamen, globus pallidus, and in gray and white matter regions. Ferritin deposits are also seen in cerebellar granule cells and Purkinje cells. The ferritin deposits may be seen in the parenchymal cells of other organs like skin fibroblasts, renal tubule cells, and endothelial cells of muscle capillaries. Intraneural iron and ferritin inclusions are also found in hepatocytes. This points to the fact that the pathology of NF is not limited to the brain tissue only and some authors suggested that “hereditary ferritinopathy” is a better term than the more restrictive “neuroferritinopathy.” Muscle biopsy in a few NF patients showed evidence of mitochondrial respiratory chain defects. Chinnery et al. found a higher percentage of cytochrome c oxidase negative fibers than expected for age in two out of nine NF patients who underwent muscle biopsy. Respiratory chain complex assays reported in eight patients found isolated or combined defects in seven of them. While isolated defects in complex I and complex III were seen in three and one patient respectively, three other patients had a combined defect involving multiple respiratory chain complexes. A generalized deficiency was reported in a sample of post-mortem cerebellar tissue. These respiratory chain defects suggest mitochondrial dysfunction in NF.
| Inheritance Pattern | Disease Similarities | Clinical | Pathology and Biochem. | Clinical | Pathology and Biochem. |
|---------------------|---------------------|-----------|------------------------|-----------|------------------------|
| Autosomal recessive | PKAN<sup>3,36</sup> | Ataxia, Dystonia, Tremor, Cognitive decline | T2 decr. in GP | Iron and ferritin deposition in BG | Onset before 6 years in 90% | Classic “eye of the tiger” sign, central T2 incr. and surrounding decr. in GP |
| Aceruloplasminemia<sup>3,36</sup> | Dystonia, Dysarthria, Ataxia, Cognitive decline | T2 decr. in GP | Iron deposition in brain (BG, DN, Th, cerebral, and cerebellar cortices) | Diabetes, Anemia, Early cognitive decline, Ataxia more common, Retinal involvement | T2 decr. in DN, SN, CN, P, Th, and cerebral cortex | No cavitation, No cavitation, Iron deposition in retina, pancreas, and liver in all patients, Incr. serum ferritin |
| Wilson’s disease<sup>37,38</sup> | Dystonia, Chorea, Parkinsonism, Ataxia | Cortical, cerebellar and BG atrophy | Iron deposition in BG | Young onset, Early psychiatric and hepatic features, Corneal K-F rings | T2 incr. in P, GP, CN, and Th, “Face of giant Panda” sign in mid-brain (T2 incr. around RN) | Copper deposition in BG, Decr. serum ceruloplasmin and increased 24-hour urinary copper |
| Chorea-acanthocytosis<sup>39</sup> | Chorea, Orofacial dyskinesia, Dystonia, Tics, Parkinsonism | BG atrophy | Neuronal loss and gliosis in the striatum, GP and SN | AR, Young adult onset, Seizures, Tics more common, Self-mutilation, Oculomotor abnormalities, Myopathy, Neuropathy | Caudate atrophy (predilection for the head of CN) | Acanthocytes in peripheral blood smear, Elevated CK |
### Table 2. Continued

| Inheritance Pattern | Disease | Similarities | Differences |
|---------------------|---------|--------------|-------------|
|                     |         | Clinical     | Radiology   | Pathology and Biochem. | Clinical | Radiology | Pathology and Biochem. |
| Autosomal dominant  | HD<sup>1,40</sup> | • Chorea | • Mild cortical atrophy | • Genetic anticipation<sup>1</sup> | • Caudate atrophy (tail and body of CN) | • Atrophy mainly in BG |
|                     |         | • Tics | | • Early personality changes and cognitive impairment | | |
|                     |         | • Ataxia | | • Tics common | | |
|                     |         | • Parkinsonism (Westphal variant) | | | | |
| DRPLA<sup>10</sup> | • Chorea | • Cerebellar atrophy | | • Genetic anticipation<sup>1</sup> | | |
|                     | | | | • Epilepsy and myoclonus | | |
|                     | | | | • Pontine tegmental atrophy | | |
| SCA<sup>10,41</sup> | • Ataxia | • Cerebellar atrophy | | • Genetic anticipation| | |
|                     | | | | • Marked cerebellar atrophy | | |
|                     | • Pyramidal signs | | | • Marked ataxia | | |
|                     | • Chorea (SCA 17) | | | • Nystagmus | | |
| Sporadic/ mixed (AR and AD) | Isolated or combined dystonia syndromes<sup>42</sup> | • Focal or generalized dystonia | • None specific | • Childhood onset | • None specific | • None specific |
| | | • Parkinsonism | | • Myoclonus | | |
| | Parkinsonism (IPD, parkin mutation)<sup>4,43</sup> | • Parkinsonism | • None specific | • DRD is levodopa responsive | | |
| | | | | • Iron deposition may be seen in SN | | |
| | | | | • Levodopa responsive | | |

Abbreviations: AD, Autosomal Dominant; AR, Autosomal Recessive; BG, Basal Ganglia; Biochem., Biochemical Parameters; CK, Creatine Kinase; CN, Caudate Nucleus; Decr., Decreased; DN, Dentate Nucleus; DRD, Dopa-responsive Dystonia; DRPLA, Dentato-Rubral-Pallido-Luysian Atrophy; GP, Globus Pallidus; HD, Huntington’s Disease; Incr., Increased; IPD, Idiopathic Parkinson Disease; K-F rings, Kayser–Fleischer Rings; P, Putamen; PD, Parkinson Disease; PKAN, Pantothenate Kinase-associated Neurodegeneration; RN, Red Nucleus; SCA, Spinocerebellar Ataxia; SN, Substantia Nigra; Th, Thalamus.

<sup>1</sup>In successive generations, there may be an increase in the number of trimucleotide repeats in the affected gene leading to earlier age of onset.
Management

At present, there are no established guidelines or specific management recommendations for patients with NF. An individualized symptomatic approach to treatment is recommended. A number of drugs have been used for symptomatic management in NF with variable success. Dystonia either showed some improvement with anticholinergics such as trihexyphenidyl. While variable improvement in chorea, tics, and stereotypy were reported with sulpiride (D2 receptor blocker) and tetrabenazine (dopamine depleting agent) in some patients, the latter is associated with complications including sedation, parkinsonism, and depression.2,26,27,35 One report showed excellent response of facial tic/stereotypy and chorea with tetrabenazine.26 Parkinsonian symptoms of NF showed either no improvement or only some initial benefit with levodopa. Benzodiazepines (diazepam, clonazepam, and lorazepam) have been shown to improve dystonia in a few patients,2,25 but not in others.19,22 Antidepressants, like fluoxetine, were helpful in treating depression.16,19 Muscle relaxants, like baclofen, gave either partial or no benefit in treating dystonia. Various other drugs that have failed to improve the movement disorders include risperidone2, haloperidol13,19,27 tiapride,19 clonazepam,2 amitriptyline,2,16,35 apomorphine,2,35 amantadine,2 dopamine agonists,2,35 decanol,2,35 dantrolene,2 paroxetine,2,35 mitrazapine,2 gabapentin,2 sodium valproate,2,22,35 and carbamazepine.2,35 One author reported improvement in the finger dystonia of a patient with herbal medicine (Shakuyaku-kanzo-to).22 Physiotherapy in addition to drugs improved dystonia and gait in one patient.22 Speech amplification may help hypophonia.2

Moderate benefits have been reported with the use of botulinum toxin for dystonia affecting the neck, orofacial region (including blepharospasm), and extremities.2,16,21,35 Other symptomatic treatments include non-invasive positive pressure ventilation for sleep apnea and percutaneous endoscopic gastrostomy feeding for severe weight loss due to dysphagia.20,27 Dysphagia should be monitored and managed with swallowing assessment and dietary modification.2

A number of treatments have been used for modulating the brain iron stores in the hope of reversing the pathology, but none have been reported to be successful. A low-iron diet did not show benefit after 6 months of its institution.16 Iron chelation therapy with desferrioxamine (4,000 mg weekly subcutaneously for up to 14 months)2 and deferiprone (15 mg/kg/day for 6 months) have not been effective.2,14 No improvement was seen with monthly venesection.2,16,19 Although no benefit has been reported in the short term with iron-modulating therapies, the long-term response has yet to be studied.

Although NF progresses gradually but relentlessly in most of the patients,2,35 patients with a 458dupA mutation show a relatively rapid progression of parkinsonism, ataxia, and neuropsychiatric symptoms.20 Patients usually die of aspiration pneumonia.16,19 Other reported causes of death include community-acquired pneumonia,27 asphyxiation of food,19 and cardiomyopathy.20 It is not known whether this last cause was related to NF.

Conclusion

NF is a rare autosomal dominant disease with FTL1 mutation leading to abnormal excessive iron accumulation in the brain (predominantly in the basal ganglia) and other organ systems. In people of British descent, the most common mutation is 460InsA. Nine variant mutations in the FTL1 gene have been reported in various geographical regions. NF patients with mutations other than 460InsA appear to have an earlier age of onset. Although NF has heterogeneous clinical presentations, chorea and dystonia are the most common presenting symptoms; however, these are not specific to a mutation. There are however specific features that depend on the genetic mutation and hence on regional distribution as reviewed in this manuscript.

NF must be considered in patients presenting clinically as a relentlessly progressive movement disorder with variable phenotype and imaging evidence of iron deposition within the brain, decreased serum ferritin, and negative genetic testing for other more common movement disorders like Huntington’s disease. The FTL1 gene mutation should be suspected despite the lack of a positive family history, as new genetic mutations of this gene may occur in any population. Brain MRI is helpful, even during the pre-symptomatic period in relatives of affected patients, and unilateral or asymmetric lesions do not exclude the diagnosis. Although MRI features may overlap with other NBIA, basal ganglia cavitation and cortical “pencil-lining” on susceptibility-weighted imaging favors NF. Standard symptomatic drug treatment for specific movement disorders may be used with variable success. Chelation therapies have not been shown to be effective.
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