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Neuroferritinopathy: a new inborn error of iron metabolism

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Abstract

Neuroferritinopathy is an autosomal dominant progressive movement disorder which occurs due to mutations in the ferritin light chain gene (*FTL1*). It presents in mid-adult life and is the only autosomal dominant disease in a group of conditions termed neurodegeneration with brain iron accumulation (NBIA). We performed brain MRI scans on 12 asymptomatic descendants of known mutation carriers. All three harbouring the pathogenic c.460InsA mutation showed iron deposition; these findings show pathological iron accumulation begins in early childhood which is of major importance in understanding and developing treatment for NBIA.

Keywords

Neurodegeneration; Brain iron; Ferritin; Extrapyrarnidal; Metabolism; Movement disorder

Introduction

Neuroferritinopathy (MIM 606159, also called hereditary ferritinopathy and neurodegeneration with brain iron accumulation type 2, NBIA2) is an autosomal dominant, adult-onset progressive movement disorder that occurs due to mutations in the ferritin light

chain gene (*FTL1*). The original mutation, discovered in 2001, involves the insertion of adenine at position 460-461 which alters the carboxy-terminal residues of the gene product [1].

Seven pathogenic mutations in *FTL1* have since been described [1-7]. Six are frameshift mutations which alter the reading frame and are predicted to extend the ferritin light chain peptide at the site of the pore in the ferritin molecule. The remaining report, where attribution of phenotype to the genetic change is less certain, involves a missense mutation that disrupts the ferritin dodecahedron structure.

The mutations result in the accumulation of ferritin and iron within central neurons, in particular within the basal ganglia [1-4], leading to oxidative stress and ultimately resulting in neurodegeneration [2, 8].

Neuroferritinopathy is only one of a group of conditions characterised by iron accumulation within the brain termed NBIA [9]. At present, mutations in seven genes have been identified and associated with NBIA phenotypes [10], and these conditions provide a direct link between iron accumulation and neurodegeneration.

The well-recognised forms of genetic NBIA are conditions such as pantothenate kinase-associated neurodegeneration and PLA2G6-associated neurodegeneration which can be classified as inborn errors of metabolism, in which radiological features of iron deposition and clinical extrapyramidal features present in infancy and often rapidly progress throughout childhood [9, 11].

Uniquely, however, neuroferritinopathy is the only autosomal dominant NBIA syndrome, and in contrast to many of the other NBIA disorders, patients present late in adulthood with a variety of extrapyramidal movement disorders such as asymmetric focal onset chorea or focal dystonia [12].

Given the central role of iron deposition in the pathophysiology of neuroferritinopathy, any treatment aimed at preventing the onset of neurodegeneration should ideally be given before excess iron is detected. Before embarking on these studies, we used brain MRI to determine the earliest stage that iron accumulation could be detected by studying 12 young descendents of known c.460InsA *FTL1* mutation carriers.

Methods

Patients diagnosed with neuroferritinopathy under the care of JB or PFC were identified from case records. Subsequent assessment of family pedigrees of affected patients identified first-degree relatives of known carriers, and 12 participants were enrolled into the study.

Assenting participants then attended for a cranial MRI scan and blood sample for molecular genetic analysis of the *FTL1* mutation. Each participant was assigned a computer-generated random number to mark their blood sample and scan. Cranial MRI was performed using a Philips Intera 1.5 T scanner (Philips Medical Systems, Best, Netherlands) and included an axial T2* sequence to assess for hypointensities that might indicate abnormal iron

deposition. The MR images were assessed offsite by an experienced neuroradiologist who was blind to the molecular genetic results of the participants (AC, Brisbane, Australia).

The MRI scans were grouped by participants' age (6–16, 17–25, 26–36) to reduce the probability of inadvertent disclosure of genetic status. Subsequently, the results of the MRI images were correlated with the genetic testing results. Participants were blinded to the results of their MRI scans and genetic testing results throughout the study. The study was granted ethical approval by the Newcastle Research Ethics committee.

Results

In total, 12 subjects were enrolled aged 6–36. One subject could not tolerate the MRI examination and was excluded from the analysis. The 11 remaining subjects were stratified by age: 6–16 years (four subjects), 17–25 years (three subjects), 26–36 years (four subjects).

In eight subjects, cranial MRI showed no evidence of signal hypointensities suggestive of iron deposition; one child had an incidental finding of a choroid plexus cyst. These eight subjects tested negative for mutations in the *FTL1* gene.

Three subjects had signal hypointensities suggestive of iron deposition. Fortuitously, one fell in each of the age groupings. In each case, the signal abnormality was readily visible on T2* images. The distribution of signal abnormalities is indicated in Table 1 and visualised in Figs. 1, 2 and 3. The T2* hypointensity distribution was typical of neuroferritinopathy [13]. T1 abnormalities and T2* hyperintensities were not identified.

All three were subsequently shown to harbour the c.460insA mutation (see Figs. 1, 2 and 3). The severity of T2* abnormalities appears to correlate with the increasing age of the subject (Table 1).

Discussion

This study shows that despite presenting clinically in mid-adult life, the iron deposition in neuroferritinopathy actually begins in early childhood, decades before symptomatic presentation. These findings have significant implications for the diagnosis of NBIA syndromes, in understanding disease pathogenesis and developing treatment modalities.

Hypointensity on T2* imaging can be used as a surrogate for brain iron deposition in the appropriate clinical context [13], and our knowledge of NBIA has been rapidly expanding since the identification of the first genetic mutations associated with NBIA1, originally termed Hallervorden–Spatz syndrome, and neuroferritinopathy, or NBIA2, both in 2001 [1, 14]. Neuroferritinopathy remains the only autosomal dominant NBIA syndrome [9], and this study shows that, whilst the condition presents clinically in mid-adult life, from a radiological perspective, it should now also be considered as an inborn error of metabolism and become accepted as an additional cause of iron deposition on MRI imaging in children [13].

Authors have previously speculated as to whether iron deposition is involved in the initiation of neurodegeneration or an epiphenomenon and downstream effect of abnormal cellular metabolism in NBIA disorders and neurodegenerative diseases [15]. The argument against causality may stem from the observation that some patients with known genetic mutations and phenotypic features of NBIA syndromes can have no iron deposition on neuroimaging [16, 17], in addition to excess iron which is often seen within the brain and basal ganglia in normal ageing [18, 19]. However, with all of the participants in our study showing no clinical features of neuroferritinopathy at the time of MRI imaging, our study supports a causal role of iron in initiating neurodegeneration in neuroferritinopathy and therefore potentially for other neurodegenerative diseases.

Perhaps the most important finding of this study is the potential implication for treatment regimes. Since the discovery of NBIA disorders, therapeutic targets that may be able to slow the progression of disease have remained limited. In our institute, we have attempted iron chelation in a handful of symptomatic patients with little benefit [12], though a recent case report of a patient with an idiopathic NBIA syndrome has suggested some ability to improve clinical and radiological features [20].

Whilst attempting to minimise iron accumulation remains a potential treatment paradigm, an alternative lies in tackling the oxidative stress which is caused by iron deposition [8]. The link between iron misregulation and oxidative damage is similar to current evidence regarding the pathogenesis of Friedreich's ataxia in which loss of frataxin impairs mitochondrial iron handling resulting in increased oxidative stress and cellular damage [21]. In the case of Friedreich's ataxia, clinical trials have shown benefit with antioxidant therapy such as idebenone [22, 23], with clinical benefits particularly apparent in children and younger patients. This demonstrates the importance of early treatment instigation in these patients [23] and, in conjunction with the findings of this study, supports the case for early intervention in patients with neuroferritinopathy.

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Fig. 1. Transaxial T2*-weighted gradient echo images at the level of the **a** midbrain, **b** basal ganglia, **c** thalami and **d** motor cortex. Gene-positive subject (subject A) from the 6–16-year-old group. Signal hypointensity is seen in the substantia nigra (**a**, **b**) and globus pallidus (**c**)

Fig. 2. Subject B (17–25-year-old group). T2* signal hypointensity in the substantia nigra (**a**, *arrow*), red nucleus (**a**, *arrowhead*), globus pallidus (**b**, **c**) and thalami (**c**, *arrow*). There is faint hypointensity involving the motor strip (**d**, *arrow*)

Fig. 3. Subject C (27–36-year-old group). Substantia nigra and red nucleus (**a**), globus pallidus and thalamus (**b**, **c**) and motor cortex (**d**) T2* signal hypointensity. The thalamic hypointensity in particular is more prominent than in subjects A and B

Table 1

Distribution of signal hypointensity in three subjects positive for the c.460insA mutation

Subject	Sequence	Location of signal hypointensity							
		Dentate	RN	SN	GP	Thal	Caud	Put	MCort
A (age group 6–16)	T2*	–	–	+	+	–	–	–	+
	T2	–	–	–	–	–	–	–	–
B (age group 17–25)	T2*	–	+	+	+	+	–	–	–
	T2	–	–	–	+/-	–	–	–	–
C (age group 26–36)	T2*	–	+	+	+	+	+	–	+
	T2	–	–	–	+	–	–	–	–

Dentate dentate nucleus, *RN* red nucleus, *SN* substantia nigra, *GP* globus pallidus, *Thal* thalamus, *Caud* caudate nucleus, *Put* putamen, *Mcort* motor cortex