Clinical/Scientific Notes

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CORTICAL PENCIL LINING IN NEUROFERRITINOPATHY: A DIAGNOSTIC CLUE

Neurodegeneration with brain iron accumulation (NBIA) includes pantothenate kinase-associated neurodegeneration (PKAN, NBIA1), PLA2G6-associated neurodegeneration (PLAN, NBIA2), neuroferritinopathy, aceruloplasminemia, and MIN-associated neurodegeneration (MPAN).[1] Clinically, they can have similar presentation, with a combination of progressive extrapyramidal, cognitive, and bulbar features.[1] Since genetic testing is costly and not easily accessible, MRI clues, such as the eye of the tiger sign for PKAN,[2,3] are useful to guide the confirmatory genetic analyses. Herein, we describe a distinct imaging pattern of cortical iron deposition on susceptibility-weighted MRI (SWI) in genetically proven cases of neuroferritinopathy, which is not seen in genetically proven cases of PKAN or PLAN, the 2 most common forms of NBIA.

Case reports. ***Case 1.*** A 79-year-old woman with no significant family history had a 13-year history of slurred speech, which progressed to complete anarthria. She had swallowing problems and required a PEG tube. On examination, she had prominent craniocervical and arm dystonia, parkinsonism, and a shuffling gait. Ferritin was low (19 μg/L, normal range 30–400 μg/L).

MRI T2 fast spin echo images showed T2 hyperintensity with areas of apparent cavitation involving the globus pallidus, putamen, caudate, and cerebral peduncles bilaterally with hypointensity around their periphery. The SWI sequence showed a fine band of low signal following the contour of the cerebellar and cerebral cortex consistent with iron deposition in the cortex. This appeared as a thin line of loss of signal appearing as if traced with a black pencil. This lining was also seen in the periphery of the deep gray matter structures globus pallidus, putamen, caudate, red nuclei, substantia nigra, and dentate nuclei (figure, A.a) and around the areas of apparent cavitation. Genetic testing showed the presence of the common pathogenic mutation c.460dupA in the ferritin light chain (*FTL*) gene.

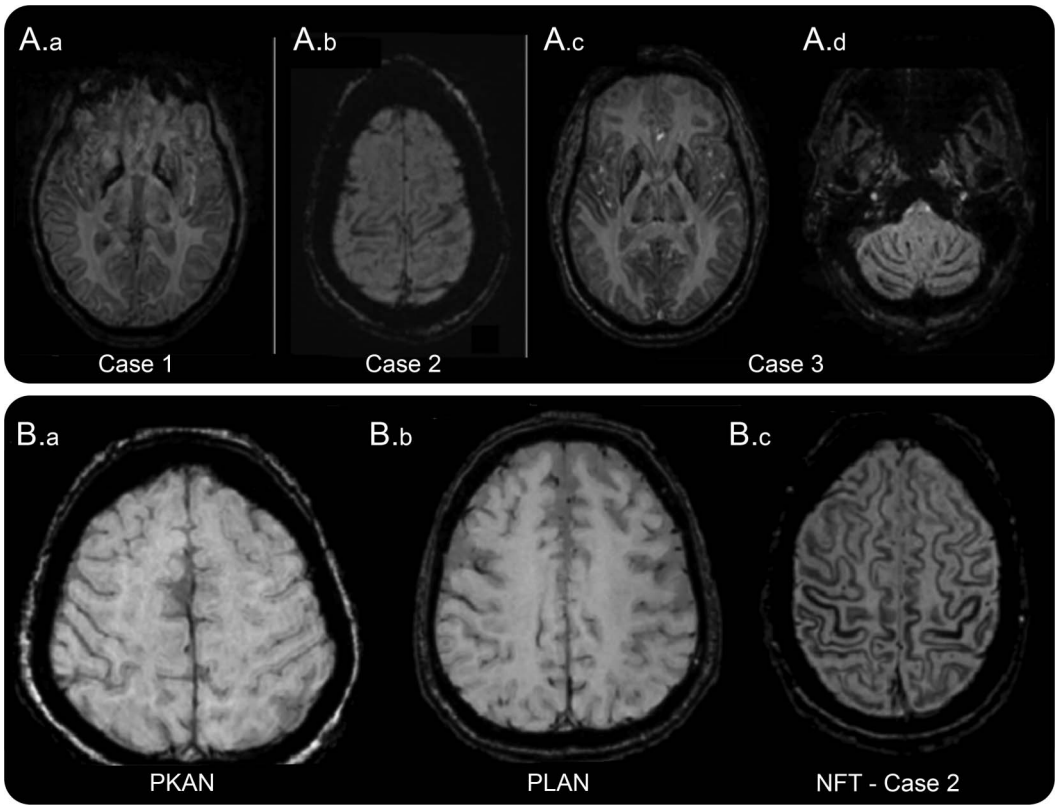
Case 2. A 37-year-old woman with no significant family history had an 18-month history of abnormal posturing of her left arm and difficulties with speech and swallowing. On examination, she had jaw closing dystonia and upper limb dystonia, with bradykinesia on finger tapping and dystonic gait. Serum ferritin was 15 μg/L (normal range for her age 13–150 μg/L). MRI showed irregular cavitation of the globus pallidus and medial putamen bilaterally. SWI showed a band of hypointensity at the periphery of the cavities and the noncavitated putamen and caudate along with *pencil lining*, most conspicuous in the motor strip in the cortex (figure, A.b). Genetic testing disclosed the pathogenic duplication c.460dupA in *FTL*.

Case 3. A 54-year-old man with no significant family history presented with facial grimacing and dysphagia and dysarthria of 3-year duration. On examination, he had oromandibular dystonia with blepharospasm and gait ataxia. Ferritin 14 μg/L was low (normal range 30–400 μg/L). MRI demonstrated characteristic cavitation of the globus pallidus and medial putamen bilaterally. SWI showed low signal in the periphery of the deep gray nuclei themselves (figure, A.c), at the margins of the cavities and pencil lining of the cerebral and cerebellar cortex (figure, A.c and A.d). Genetic testing showed the c.460dupA mutation in *FTL*.

Review of neuroimaging of normal subjects, 3 patients with genetically proven PKAN (one of these is illustrated in the figure, B.a) and 2 with PLAN (one of these is illustrated in the figure, B.b) by an experienced neuroradiologist (M.E.A.), did not reveal any cortical iron deposition on SWI. We also reviewed the literature on imaging in NBIAs and there were no reports of cortical iron deposition in PKAN, MPAN, or PLAN cases.[3,4] However, cortical iron deposition was seen in 15 of 21 patients (71%) with neuroferritinopathy, and 4 patients (100%) with aceruloplasminemia, but no characteristic pattern was identified.[4] A case with genetically proven neuroferritinopathy[5] had an MRI with a similar pencil lining as our cases on SWI, but this pattern or cortical SWI changes were not noted.

Discussion. Neuroferritinopathy is caused by mutations in the *FTL* gene and deposits of "ferritin bodies" in the caudate nucleus, putamen, globus pallidus, cerebellar granule cells and Purkinje cells, and cortical gray matter.[1] This topography matches closely with the

Figure Magnetic resonance SWI in neuroferritinopathy highlighting the "pencil lining in cortex and the deep gray matter"



(A) Magnetic resonance susceptibility weighted images (SWIs) from patients with neuroferritinopathy. (A.a) Pencil lining of cortex and deep gray matter (case 1). (A.b) Pencil lining of motor strip in cortex (case 2). (A.c) Pencil lining of cortex and deep gray matter (putamen and globus pallidus) (case 3). (A.d) Pencil lining of cerebellum (case 3). (B) Magnetic resonance SWIs. (B.a) PKAN (pantothenate kinase-associated degeneration) showing absence of pencil lining for comparison. (B.b) PLAN (PLA2G6-associated neurodegeneration) showing absence of pencil lining for comparison. (B.c) Neuroferritinopathy (case 2) showing "cortical pencil lining."

regions with low magnetic susceptibility observed on MRI in our patients and in cases reported previously.[4,5] It is also possible that pencil lining reflects excessive iron deposition in areas of the brain that are physiologically rich in iron predominantly in the gray matter.[6,7]

We did not have any cases of aceruloplasminemia available for review. It is possible that this sign may also be seen in aceruloplasminemia, which is another condition reported to have cortical iron deposition on T2* and fast spin echo MRI.[4] However, aceruloplasminemia is a very rare disorder and, unlike the common NBIAs, there are certain specific features such as diabetes and anemia that can easily guide genetic testing.

We conclude that *pencil lining*, reflecting pathologic iron deposition in the periphery of the cortex and other gray matter structures, is a useful radiologic sign of neuroferritinopathy. Screening for *FTL1* mutations should be considered first in an appropriate clinical setting, and also the presence of this sign.

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CLINICAL HETEROGENEITY OF PRIMARY FAMILIAL BRAIN CALCIFICATION DUE TO A NOVEL MUTATION IN *PDGFB*

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Primary familial basal ganglia calcification (PFBC) (previously known as idiopathic basal ganglia calcification or Fahr disease) is an autosomal dominant neurodegenerative disorder characterized by bilateral cerebral calcification primarily affecting the basal ganglia. Recently, mutations in *SLC20A2*,[1] *PDGFRB*,[2] and *PDGFB*[3,4] have been identified as causing PFBC. However, other than the original study,[3] there has been a paucity of descriptions of families with PFBC.[5]

Herein, we describe 4 cases of PFBC within a family due to a novel mutation in exon 4 of the *PDGFB* gene (c.C3657T:p.P122L) highlighting significant phenotypic heterogeneity.

Cases. ***Patient III.2.*** A 31-year-old woman presented with acute psychosis. She was diagnosed in childhood with mild learning difficulties, but reached normal motor milestones. Over the next 6 years, she had recurrent episodes of psychosis and depression requiring admission. At age 36, a CT scan of her head revealed basal ganglia calcification precipitating neurologic referral (figure, A.b).

Examination revealed jerky ocular pursuit, generalized chorea, and midline ataxia. Investigations revealed a normal full blood count, biochemistry, and autoantibodies. An EEG showed no encephalopathic features.

There was no family history of any neurologic disorder; however, the examining neurologist noted that the patient's mother, accompanying her to clinic, was ataxic (patient II.4).

Patient II.4. A retired shop worker was referred aged 60 years (figure). Both parents died in their 70s with no neurologic symptoms before death. She had 3 siblings, none of whom she remained in contact with.

She had episodic psychosis and depression for more than 20 years, and a 2-year history of falls and unsteady gait. Medical history included hypertension and heavy smoking. Examination revealed a severe midline ataxia with jerky ocular pursuit. There were no cognitive abnormalities or extrapyramidal features.

Serum biochemistry (including calcium and phosphate) was normal. A muscle biopsy showed normal histology, normal mitochondrial biochemical studies, and no mitochondrial DNA deletions. An EEG revealed transient sharp waves in the temporal regions. MRI showed calcium deposition in the globus pallidus and dentate (figure, A.d).

Over the next 5 years, her ataxia progressed but cognition remained normal (Mini-Mental State Examination score 28/30 at age 66).

Patient III.5. A woman aged 40 years was referred with a 2-year history of gait disturbance. She had no psychiatric history, cognitive symptoms, or evidence of abnormal movements. Examination revealed normal cognition, but a midline ataxia. A CT brain scan showed bilateral calcification of the globus pallidus (figure, A.c). Three years later, she developed a complex motor tic, and dystonic posturing of both feet. Formal neuropsychometry remained normal.

Patient IV.4. A 20-year-old woman was referred with a gait disturbance. She had no other medical or psychiatric history. Neurologic examination was normal. Brain MRI revealed small frontal noncalcified white matter changes not in keeping with PFBC, and no evidence of calcium in the basal ganglia even with susceptibility-weighted imaging (figure, A.a).

Supplemental data at Neurology.org