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Indian-subcontinent NBIA: unusual phenotypes, novel PANK2 mutations, and undetermined genetic forms.

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Abstract

Neurodegeneration with brain iron accumulation (NBIA) is etiologically, clinically, and by imaging a heterogeneous group including NBIA types 1 [pantothenate kinase-associated neurodegeneration (PKAN)] and 2 (PLA2G6-associated neurodegeneration), neuroferritinopathy, and aceruloplasminaemia. Data on genetically defined Indian-subcontinent NBIA cases are limited. We report 6 patients from the Indian-subcontinent with a movement disorder and MRI basal ganglia iron deposition, compatible with diagnosis of an NBIA syndrome. All patients were screened for abnormalities in serum ceruloplasmin and ferritin levels and mutations in NBIA-associated genes [pantothenate kinase 2 (PANK2), PLA2G6 and ferritin light chain (exon 4)]. We present clinical, imaging and genetic data correlating phenotype-genotype relations. Four patients carried PANK2 mutations, two of these were novel. The clinical phenotype was mainly dystonic with generalized dystonia and marked orobulbar features in the 4 adolescent-onset cases. One of the four had a late-onset (age 37) unilateral jerky postural tremor. His mutation, c.1379C>T, appears associated with a milder phenotype. Interestingly, he developed the eye-of-the-tiger sign only 10 years after onset. Two of the six presented with adult-onset levodopa (L-dopa)-responsive asymmetric re-emergent rest tremor, developing L-dopa-induced dyskinesias, and good benefit to deep brain stimulation (in one), thus resembling Parkinson's disease (PD). Both had an eye-of-the-tiger sign on MRI but were negative for known NBIA-associated genes, suggesting the existence of further genetic or sporadic forms of NBIA syndromes. In conclusion, genetically determined NBIA cases from the Indian subcontinent suggest presence of unusual phenotypes of PANK2 and novel mutations. The phenotype of NBIA of unknown cause includes a PD-like presentation.

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