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Low prevalence of *PANK2* mutations in Brazilian patients with early onset generalised dystonia and basal ganglia abnormalities on MRI

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Neurodegeneration with brain iron accumulation (NBIA) is a heterogeneous group of degenerative diseases presenting with movement disorders. Causative mutations have been identified, first in *PANK2*, encoding pantothenate kinase 2, and later in *PLA2G6*, a calcium independent phospholipase A2 enzyme.¹² NBIA types 1 and 2 are the denominations used to label these two entities. The clinical picture includes pyramidal syndrome, movement disorders, cerebellar dysfunction, ophthalmoparesis and ocular disturbance. A neuroradiological hallmark of NBIA type 1 is the “eye-of-the-tiger” sign, characterised by bilateral areas of hyperintensity surrounded by a ring of hypointensity in the medial *globus pallidus* on T2-weighted MRI. Radiological findings in NBIA type 2 comprise cortical atrophy in the cerebellum, increased iron deposition in *globus pallidi* and *substantia nigra* seen as reduced signal on T2 FLAIR and T2* gradient and diffusion weighted MRI sequences, reduced volume of the optic chiasm and optic nerves and cerebral white matter changes. In this paper, we report clinical, neurological and molecular findings of Brazilian patients with clinical diagnosis of NBIA type 1.

METHODS

We identified consecutive patients during the years of 2005 and 2006 in the UFMG Movement Disorders Clinic with early onset generalised dystonia and basal ganglia abnormalities on neuroimaging studies compatible with the diagnosis of NBIA. We performed a detailed family history assessment and neurological exam and rated dystonia with the Burke–Fahn–Marsden Scale. DNA was extracted from peripheral lymphocytes according to routine procedures. Amplification of the coding exons of *PANK2* by polymerase chain reaction was performed as previously described, followed by sequencing.¹

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Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Ethics Committee of the Federal University of Minas Gerais.

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The study was approved by the local ethics committee and recruited patients provided signed informed consent.

RESULTS

We examined 576 patients, of whom 195 had a diagnosis of dystonia. From the dystonia group, 14% had early onset (age at onset=14.8 (7.7) years) and 6 (3% of all dystonia patients) displayed imaging changes in the basal ganglia consistent with those seen in NBIA type 1: five had the typical “eye-of-the-tiger” sign and one had a reduction in T2 signal in the globus pallidi and substantia nigra (Table 1). Blood count, liver and kidney function, lipid profile, alpha-fetoprotein, serum B12, folate, copper, ceruloplasmin, ferritin, serum immunoglobulin, creatinine phosphokinase, serum lactate and ammonia were normal in all patients submitted to this study. The age at onset of NBIA was 15.8(10.5) years. Sequence analysis revealed that three brothers had a homozygous mutation (N294I) of the *PANK2* gene. These patients, born of a consanguineous marriage, had onset of their illness at the age of 16, 26 and 30 years, presenting with focal dystonia (writer’s cramp), paroxysmal dystonia, epilepsy, Parkinsonism (hypophonia, bradykinesia, postural instability, festination and gait freezing), dysarthria, pyramidal signs and the “eye-of-the-tiger sign” on MRI. The illness of all patients has displayed a slow progression. The Burke–Fahn–Marsden Scale scores of the patients were, respectively, 7, 14 and 10 and did not change over time. There was no response to therapeutic agents such as levodopa and biperiden. Sequence analysis of the *PANK2* gene of the other three patients, two with the typical “eye-of-the-tiger” sign, did not reveal mutations in *PANK2*.

CONCLUSION

In a large consecutive series of patients with dystonia, we identified 3% of patients with clinical and radiological features of NBIA. This rather high frequency of a rare illness is most likely accounted for the selection bias often seen in tertiary health units. Previous studies identified *PANK2* mutations in the majority of typical and one third of atypical cases of NBIA.³ In those series, there were no mutations of this gene in patients without the “eye-of-the-tiger” sign. In line with this finding, we identified the N294I mutation in three patients with typical “eye-of-the-tiger” sign on MRI. In contrast, we could not find any mutations in two patients with the typical sign. Several authors have found a tight correlation between the presence of “the eye-of-the-tiger” sign and *PANK2* gene mutations, suggesting that this neuroradiology finding is a pathognomonic feature of NBIA type 1.³ However, other authors have reported patients with “eye-of-the-tiger sign” without *PANK2* mutations.⁴ Conversely, N294I mutation in *PANK2* has already been described in patients with atypical disease, that is, late onset, pure Parkinsonism and slow progression.³ Moreover, there are reports of patients carrying *PANK2* mutation who initially presented with the “eye-of-the-tiger” sign, which disappeared later during the course of the disease.⁵ Despite the small number of subjects in our study, our findings support that notion that *PANK2* mutations are not invariably associated with the “eye-of-the-tiger sign”.

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Table 1

Clinical description of the patients

Patient	Gender	Age at onset	Familial history	Consanguinity	First symptom	Features	Image	PANK2 mutations
200656	M	2	Negative	Negative	Gait disturbance (equinovarus foot)	Anarthria, generalised dystonia, opisthotonus, Babinski sign	Reduction in T2 signal in the globus pallidi and substantia nigra	Negative
200666	F	12	Negative	Negative	Gait disturbance and dysarthria	Ataxia, cognitive impairment, generalised dystonia, orofacial dyskinesia, anarthria and dysphagia	Eye-of-the-tiger sign	Negative
200635	F	9	Negative	Negative	Gait disturbance and dysarthria	Spasticity, aquileu clonus, Babinski sign, rigidity, generalised dystonia	Eye-of-the-tiger sign	Negative
200642 *	M	30	Positive, sister and brother	Positive	Writer cramp	Hyperreflexia, slight isometric and intentional tremor, dysarthria, hypophonia, postural instability and bradykinesia	Eye-of-the-tiger sign	N294I
200641 *	F	16	Positive, two brothers	Positive	Dysarthria and Gait disturbance	Epilepsy, rigidity, bradykinesia, postural tremor, enhanced reflexes, dissinergy, postural instability, paroxysmal dystonia, freezing and gait festination	Eye-of-the-tiger sign	N294I
200643 *	M	26	Positive, sister and brother	Positive	Isometric and postural tremor in superior limbs	Retropulsion, dysarthria, mask face, bradykinesia, clonus, Babinski sign.	Eye-of-the-tiger sign	N294I

* Siblings.