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Case Report

"Eye of tiger sign" mimic in an adolescent boy with mitochondrial membrane protein associated neurodegeneration (MPAN)

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Abstract

Neurodegeneration with brain iron accumulation (NBIA) refers to an inherited heterogeneous group of disorders pathologically characterized by focal brain iron deposition. Clinical phenotype, imaging findings and genotype are variable among the different types of this disorder. In this case report, we describe the imaging finding of an adolescent boy with mitochondrial membrane protein associated neurodegeneration (MPAN), a subentity of NBIA. Magnetic resonance imaging of brain revealed hypointensity of globi pallidi with medial medullary lamina appearing as a hyperintense streak in T2 weighted images. Mild cerebellar atrophy in T2 weighted images and blooming of substantia nigra and globi pallidi in susceptibility weighted images were also observed. Imaging findings in patients with MPAN mimics the eye of tiger appearance in patients with pantothenate kinase associated neurodegeneration. Classical phenotype and eye of tiger sign mimic in imaging of patients with NBIA should raise the suspect for MPAN. Genetic studies helps in the confirmation of diagnosis of this neurodegenerative disorder.

Keywords: Neurodegeneration; Brain iron accumulation; Eye of tiger sign

1. Introduction

Neurodegeneration with brain iron accumulation (NBIA) refers to a heterogeneous group of disorders with extrapyramidal symptoms, varying cognitive impairment and neuropathological hall mark of increased focal brain iron deposition with neuronal loss and gliosis [1,2]. "Eye of tiger sign" has been classically reported in patients with pantothenate kinase associated neurodegeneration (PKAN). In this report, we describe the imaging findings mimicking "eye of tiger sign" in an adolescent boy with classical clinical phenotype and genotype of MPAN.

2. Clinical report

Fourteen year old boy born second in birth order to a third degree consanguineously married Indian parents was brought with concerns of difficulty in walking from 9 years of age. There were no antenatal risk factors or

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adverse perinatal events. All milestones were attained age appropriately. Prior to onset of illness, he was attending school with an average scholastic performance. At 9 years of age, he was noticed to have insidious onset progressive difficulty in walking with frequent falls while walking. He developed slowness of gait and he could not run or climb stairs without support. He had progressive stiffness involving both lower limbs and also had a decline in academic performance. He had mood swings and inappropriate laughter. There was no history of vision, hearing disturbances or involuntary movements. He had 2 episodes of simple febrile seizures at 2 and 3 years of age. Twenty year old elder brother also has progressive deterioration of motor skills with slow cognitive decline noticed from the end of first decade. His ambulation was preserved and he was attending college with an average academic performance.

On examination, our index patient was moderately built and there was no hypogonadism or alopecia. Anthropometry and vitals were normal. Mini mental state examination score was 24. Bilateral optic atrophy and pseudobulbar palsy were present. Spasticity of both lower limbs with exaggerated deep tendon reflexes was observed. Bilateral foot drop, pes cavus, ankle contractures and loss of ankle reflexes were found. Other muscle stretch reflexes were exaggerated with bilateral extensor plantar responses. Hypomimia and bradykinesia were also noted. Scissoring gait was observed during gait examination. Sensory system examination was normal and there were no cerebellar signs.

Magnetic resonance imaging (MRI) brain revealed symmetric long TR hypo intensity of the globi pallidi and substantia nigra with suggestion of faint T2 hyper intensity of medial medullary lamina, a thin layer of white matter which separates the internal and external

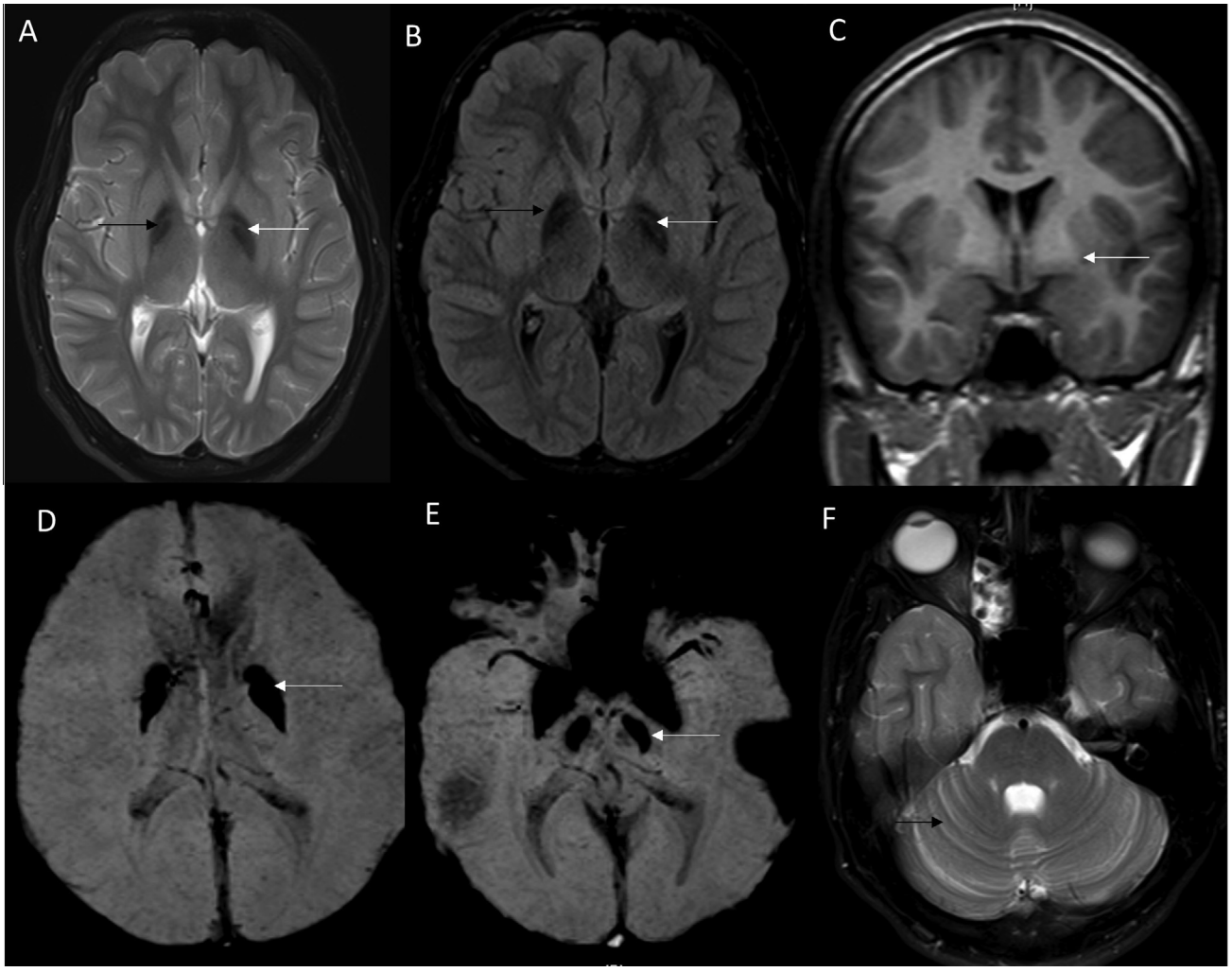

Fig. 1. MRI brain T2 axial and FLAIR (A and B) imaging of index case shows bilateral symmetric hypo intensity of globi pallidi (black arrows), faint hyper intensity is seen along the medial medullary lamina (white arrows). T1 coronal image (C) shows faint hyper intensity of globi pallidi. Susceptibility Weighted Imaging (SWI) shows hypointensity and blooming of globus pallidus and substantia nigra (white arrows in D and E, respectively). T2 axial image at cerebellar level (F) shows mild volume loss.

segments of the globus pallidus as shown in Fig. 1A, B and corresponding T1 imaging (Fig. 1C) showed minimal hyper intensity of globi pallidi. Mild cerebellar atrophy was also noted as shown in Fig. 1F. Susceptibility weighted images (Fig. 1D and E) showed marked symmetric blooming of the globi pallidi and substantia nigra suggesting increased mineral deposition. His elder sibling also had similar MRI brain findings (Fig. 2A and B). Comparison of classical "eye of tiger sign" and "eye of tiger sign" mimic is shown in Fig. 3A and B.

Nerve conduction studies had shown asymmetric axonal neuropathy and somatosensory evoked potential of tibial nerve was suggestive of bilateral dorsal cord dysfunction. Blood heavy metal screening was normal. Serum ceruloplasmin and ferritin were normal. Screening for inborn error of metabolism including blood lactate, ammonia, serum aminoacids and urine organic acids did not detect any abnormality. Clinical exome sequencing revealed a previously reported homozygous missense mutation in *C19orf12* gene [c.194G>T (ENST00000392278); p.G65V] [3]. Symptomatic treatment for spasticity with baclofen and physiotherapy were initiated in our patients.

3. Discussion

Estimated prevalence of NBIA is 1–3 per 1,000,000 [2]. Mitochondrial membrane protein associated neurodegeneration (MPAN) is a subentity of NBIA with autosomal recessive inheritance and diagnosis is established by biallelic pathogenic variants in *C19orf12*. *C19orf12* protein is localized in mitochondria and endoplasmic reticulum. Pathogenic mutations in this gene are postulated to cause dysfunction of lipid homeostasis in mitochondria. Affected patients usually have survival into adulthood. Clinical phenotype of MPAN is characterized by progressive spastic paraparesis, dystonia, cognitive deterioration and neuropsychiatric manifestations [4]. Other clinical features seen in MPAN are bulbar symptoms, optic atrophy, lower motor neuron involvement (LMN) and parkinsonism. In our index case, the adolescent boy had a classical clinical phenotype of MPAN with progressive spastic paraparesis, slow cognitive decline, extrapyramidal and distal LMN signs.

MRI brain is the fundamental investigation that aids in diagnosis and characterization of various subtypes of NBIA. Among the MRI brain images of various NBIA subtypes, iron accumulation in globus pallidus and substantia nigra were observed in MPAN, phospholipase associated neurodegeneration (PLAN), fatty acid hydroxylase associated neurodegeneration (FAHN), Coenzyme A synthetase protein associated neurodegeneration (COPAN), beta propeller protein associated neurodegeneration (BPAN), Kufor Rakeb syndrome (KRS) and Wood House Sakati disease [5]. White matter signal changes have been described in KRS, FAHN and BPAN [5,6]. Iron deposition in the caudate and putamen have been reported in KRS and neuroferritinopathy. In aceruloplasminaemia, increased iron deposition has been documented in liver, pancreas, cere-

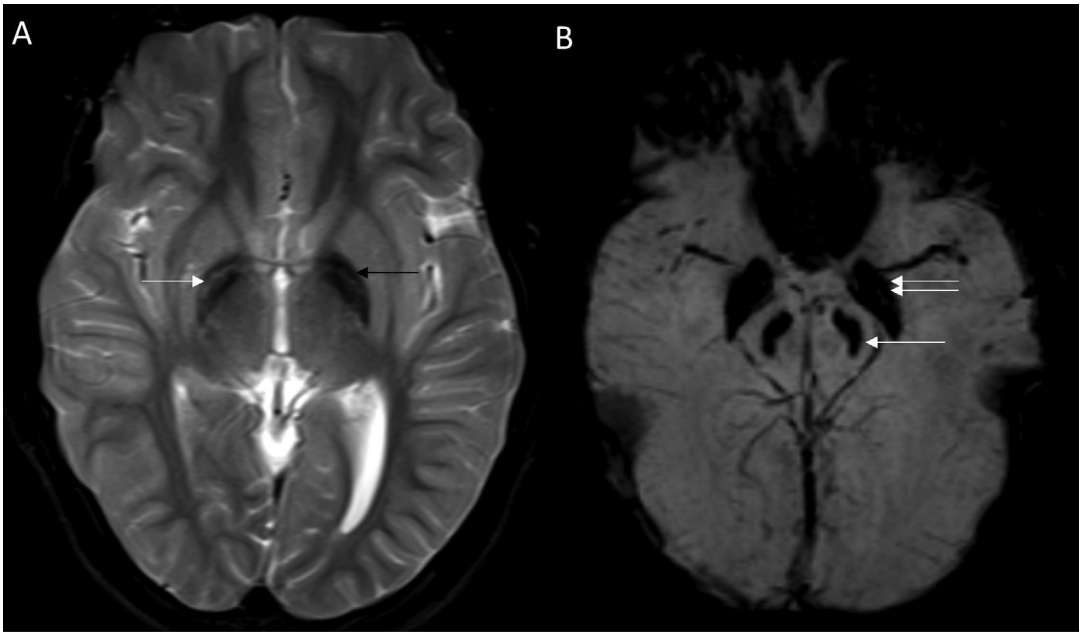

Fig. 2. MRI brain T2 axial (A) image of the elder sibling showing bilateral symmetric hypo intensity of the globi pallidi (black arrow) with faint hyper intensity of medial medullary lamina (white arrow). SWI image (B) showing hypo intensity and blooming of globus pallidus (double arrows) and substantia nigra (white arrow).

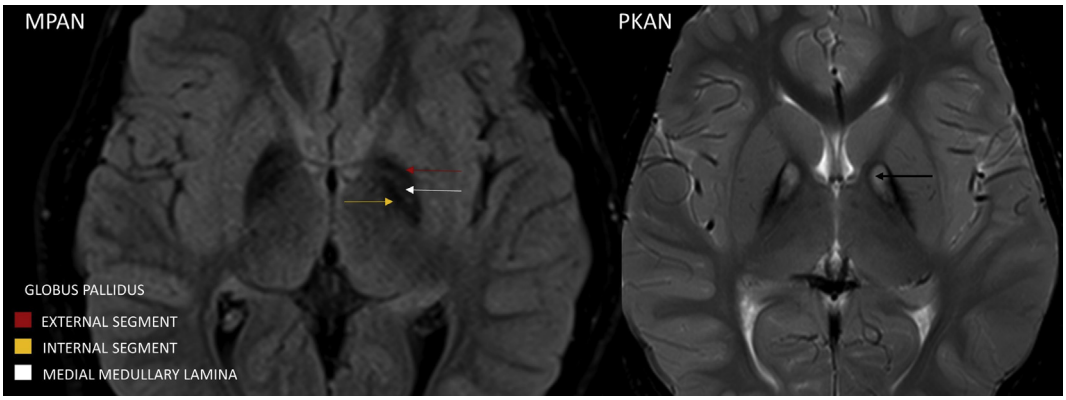

Fig. 3. Axial FLAIR imaging (A) shows hypo intensity of the internal and external segments of globus pallidus with faint hyper intensity of the medial medullary lamina separating them. The typical appearance of PKAN on T2 axial image (B) shows bilateral symmetric globus pallidus hypointensity. The central hyperintensity (black arrow) in comparison to MPAN is more rounded and hyperintense and does not confine to the medial medullary lamina.

bral, cerebellar cortices, basal ganglia, thalamus and dentate nuclei [5]. Cerebellar atrophy has been described in patients with PLAN, MPAN, BPAN, Kufor Rakeb syndrome and aceruloplasminaemia [5–7]. Brainstem atrophy may be seen in KRS and FAHN [7]. Deposition of iron in the globus pallidus with classical "eye of tiger sign" has been described in patients with PKAN. Mimickers for "eye of tiger sign" in MRI brain are neuroferritinopathy, survivors of carbon monoxide poisoning, multiple system atrophy, Machado Joseph disease and Parkinson plus syndromes [8–11]. MRI brain in our patient had shown hyperintense streaking of the globus pallidus in the region of the medial medullary lamina and surrounding hypointensity suggesting the "eye of tiger sign" mimic. This MRI finding has been described in a series of patients with MPAN [1]. In patients with PKAN, hypointensity in globus pallidus occurs due to iron deposition and central hyperintensity occurs due to gliosis. In patients with MPAN, hypointensity in globus pallidus results from iron deposition and the medial medullary lamina stands out as a separate hyperintense streak. The "eye of tiger sign" seen in PKAN is typically larger, more hyper intense and does not confine to the medial medullary lamina, thus differentiating the PKAN patients from patients with MPAN.

Current standard of therapy for MPAN includes symptomatic treatment of spasticity, dystonia, parkinsonism, psychiatric symptoms and addressing the feeding difficulties with gastrostomy. Role of chelation therapy in treatment of MPAN is not yet established.

4. Conclusion

Classical phenotype and "eye of tiger sign" mimic in imaging of patients with NBIA should raise the suspect for MPAN. Genetic studies helps in the confirmation of diagnosis of this neurodegenerative disorder. Further research is essential to unravel the exact pathophysiology and solve the conundrum in the management of MPAN.

References

[1] Hogarth P. Neurodegeneration with brain iron accumulation: diagnosis and management. J Mov Disord 2015;8:1–13.
[2] Kalman B, Lautenschlaeger R, Kohlmayer F, Büchner B, Kmiec T, Klopstock T, et al. An international registry for neurodegeneration with brain iron accumulation. Orphanet J Rare Dis 2012;7:66.
[3] Hogarth P, Gregory A, Kruer MC, Sanford L, Wagoner W, Natowicz MR, et al. New NBIA subtype: genetic, clinical, pathologic, and radiographic features of MPAN. Neurology 2013;80:268–75.
[4] Gregory A, Hartig M, Prokisch H, Kmiec T, Hogarth P, Hayflick SJ. Mitochondrial membrane protein-associated neurodegeneration. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, et al., editors. Source Gene Reviews® [Internet]. Seattle (WA): University of Washington; 2014 Initial Posting: Feb 27, 2014.
[5] Levi S, Finazzi D. Neurodegeneration with brain iron accumulation: update on pathogenic mechanisms. Front Pharmacol 2014;5:99.
[6] Schneider SA, Dusek P, Hardy J, Westenberger A, Jankovic J, Bhatia KP. Genetics and pathophysiology of neurodegeneration with brain iron accumulation (NBIA). Curr Neuropharmacol 2013;11:59–79.
[7] Kruer MC, Boddaert N. Neurodegeneration with brain iron accumulation: a diagnostic algorithm. Semin Pediatr Neurol 2012;19:67–74.
[8] Strecker K, Hesse S, Wegner F, Sabri O, Schwarz J, Schneider JP. Eye of the tiger sign in multiple system atrophy. Eur J Neurol 2007;14:e1–2.
[9] Chang CL, Lin CM. Eye-of-the-tiger sign is not pathognomonic of pantothenate kinase-associated neurodegeneration in adult cases. Brain Behav 2011;1:55–6.
[10] Guillerman RP. The eye-of-the-tiger sign. Radiology 2000;217:895–6.
[11] Shirai W, Itoa S, Hattori T. Linear T2 hyperintensity along the medial margin of the globus pallidus in patients with Machado–Joseph disease and Parkinson disease, and in healthy subjects. AJNR 2007;28:1993–5.