

Neurodegenerative Brain Iron Accumulation Disorder

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ABSTRACT

Introduction: We report two cases of Pentothenate Kinase-Associated Neurodegeneration (PKAN) which is a rare autosomal recessive neurodegenerative disorder with prevalence of 1 to 3 /1,000,000 having equal predisposition in both males and females characterized by rapidly progressive extrapyramidal symptoms, retinal degeneration and iron accumulation in basal ganglia. The MRI showing “eye of the tiger” sign is a characteristic diagnostic finding. This is one of the ten subtypes of Neurodegeneration With Brain Iron Accumulation (NBIA) disorder.

Case report: We are reporting two cases, one is a 10 year old named Jyoti and another is 9 yr old named Mamta who came with complaints of progressive dystonias, and diagnosed as rare neurodegenerative disorder PKAN.

Conclusion: We report these cases because of their rarity and how we can differentiate the NBIA subtypes by combining clinical and neuroimaging features. Treatment is only symptomatic, Deep brain stimulation therapy is a newer treatment modality with better outcomes.

Keyword: Brain Iron

INTRODUCTION

Neurodegeneration with Brain Iron Accumulation (NBIA) is a group of rare, genetic neurological disorders that are characterized by abnormal accumulation of iron in basal ganglia. Out of the ten forms, PKAN is one of the most common form of NBIA. Pentothenate kinase-associated neurodegeneration (PKAN) is a rare autosomal recessive progressive central nervous system degenerative disorder, with prevalence of 1 to 3 /1,000,000 with equal predisposition in both males and females¹, in which excessive iron is deposited in the neurons of globus pallidus and substantia nigra.² The disease is characterized by early childhood onset with progressive dystonia, rigidity, choreo-athetosis, dysarthria, mental changes and visual disturbances. Most of the patients have mutation in PANK2 gene which is localized on chromosome 20p12. PANK2 gene encodes pentothenate kinase enzyme which is required for phosphorylation of pantothenic acid in formation of coenzyme-A which results in underutilization of cysteine. Excess of cysteine chelates iron in globus pallidus which causes neuron degeneration, gliosis and spheroid formation (vacuolization). In T2W images of MRI the hypointensity in globus pallidus is due to iron deposition and central hyperintensity is secondary to gliosis and vacuolization which gives the characteristic “eye of the tiger” sign.² Two thirds of affected individuals demonstrate pigmentary retinopathy and bony spicules formation on fundoscopic examination.²

CASE REPORTS

Case 1: A 10 yr old girl named Jyoti, product of non-consanguineous marriage presented in emergency of Pediatric department of Government. Medical college Amritsar, Punjab, India with complaints of progressively increasing recurrent episodes of stiffness of upper and lower limbs with

jaw clenching, dysphagia, dysarthria, slowing of voluntary movements and progressive decline in school performance for past two years. Her perinatal history was uneventful. Toe walking was achieved at 3yrs of age with frequent falls. Now for the past 2 years progressively increasing spasms were interfering with her walking, daily activities and sleep. Her mother revealed some unexplained deaths in young children in both parents’ family. Her two elder siblings were in good health. On observation there was generalized hypertonia, with extension of all four limbs, fisting, scissoring of lower limbs and opisthotonus. She was conscious, cooperative but in great pain. On examination, upper and lower limbs showed grade-4 spasticity (modified Ashworth scale) and grade-3 power. Deep tendon reflexes showed hyperreflexia with bilateral extensor plantar response. Cranial nerves and sensory examination were normal.

Fundus examination showed bilateral bony spicules and signs of retinitis pigmentosa. On slit lamp examination, no Kayser-Fleischer(KF) ring was seen. Serum electrolytes, LFTs, serum iron, copper and ceruloplasmin levels were within normal limits. MRI examination was performed on 1.5 T scanner which showed hyperintensity in both globus pallidi on T2W and FLAIR images with peripheral hypointensity on T2W images, showing blooming on GRE T2W images (eye of the tiger sign) suggesting iron deposition (Figure-1).

Case 2: A 9 year girl named Mamta, product of non-consanguineous marriage presented in emergency of Pediatric department of Government. Medical college Amritsar, Punjab, India with complaints of frequent falls for past 5 yr with decline in school performance and now for the last 12 days of progressively increasing and recurrent episodes of stiffness of left upper limb.

Her perinatal history was not significant. There was history of delayed milestones, walking was achieved at 3yr of age with frequent falls which were associated with multiple trauma and affected her school performance. There was history of same disease in her elder sister who expired 5years back at 10 yr of age, after 1 year of diagnosis.

On observation there were tonic spasms of left upper limb with extension of neck to opposite side, without loss of consciousness, 6-7 times/day. She was conscious, cooperative and felt pain during spasms, could walk with assistance.

On examination, left upper limb and both lower limbs had

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How to cite this article: Gupta Anju Darshan Kumar, Simran K. Gill¹, Arvinder Singh, Karnail Singh. Neurodegenerative brain iron accumulation disorder. International Journal of Contemporary Medical Research 2017;4(2):418-420.

grade2 spasticity with normal power in all four limbs. Deep tendon reflexes in left upper limb and lower limb were exaggerated with bilateral extensor plantar reflexes. Cranial nerves and sensory examination were normal. On Fundus examination mild changes of retinitis pigmentosa were present. All lab investigations were normal. MRI findings showed evidence of hypointensity in globus pallidi bilateral on T2W images and central hyperintensity, blooming on GRE T2W images, displaying “eye of the tiger sign” (figure-2). Rest of brain anatomy was normal.

MRI reports of both the cases: Arrows shows “eye of the tiger” sign: central region of hyperintensity surrounded by a rim of hypointensity on T2W images of globus pallidus.

Both patients were managed symptomatically with anticholinergics, muscle relaxants (baclofen and benzodiazepines). Parents were also counselled regarding the course and nature of disease. Due to poor resources genetic study of both patients was not possible.

DISCUSSION

Neurodegeneration with Brain Iron Accumulation (NBIA) disorder was first described by Julius Hallervorden and Hugo Spatz in 1922 and so was formerly called Hallervorden and Spatz disease. Now there are 10 disorders are under the NBIA umbrella and PKAN is one of them. It is an autosomal recessive disorder characterized by progressive dystonia and basal ganglia iron deposition with onset usually occurs in first decade of life and after diagnosis, average survival is of 12 years.⁴ Hayflick et. al classified it into 2 different groups⁵:

Classical form: it is characterized by early onset, rapid progression and presence of the typical “eye of the tiger” sign on MRI.

Atypical form: it is characterized by late onset and slow progression. The “eye of the tiger” sign may or may not be present.

Currently ten disorders have been identified as subtypes of NBIA. There is phenotypic heterogeneity among NBIA disorders, making the diagnosis of these rare disorders really challenging. The following flow chart demonstrate that combining clinical and neuroimaging features, the physician may confirm NBIA disorders and correctly characterize the subtypes of NBIA (flowchart-1).⁶

The presence of pigmentary retinopathy is strongly suggestive of PKAN and is not seen in other forms of NBIA. Optic atrophy can be seen in Phospholipase Associated Neurodegeneration (PLAN), Fatty Acid Hydroxylase Associated Neurodegeneration (FAHN) and Mitochondrial Protein Associated Neurodegeneration (MPAN). No fundoscopic abnormalities have been observed in Kufor Rakeb syndrome and Beta-Propeller Protein Associated Neurodegeneration (BPAN). In Kufor Rakeb syndrome cerebral atrophy can be present. Woodhouse sakati syndrome is endocrinal disorder with hypogonadism, diabetes mellitus, alopecia, mental retardation and extrapyramidal symptoms.

Treatment

There is no specific treatment and management is only symptomatic² and requires multidisciplinary approach. Preconception counselling and genetic study can help in prevention. Baclofen and trihexyphenidyl remain the most

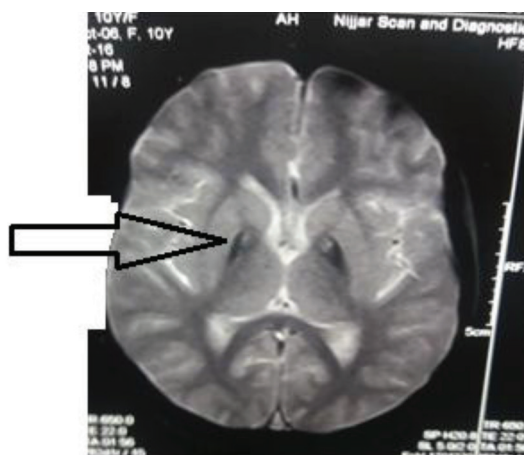


Figure-1: “Eye of the tiger sign” MRI image of Case no.1

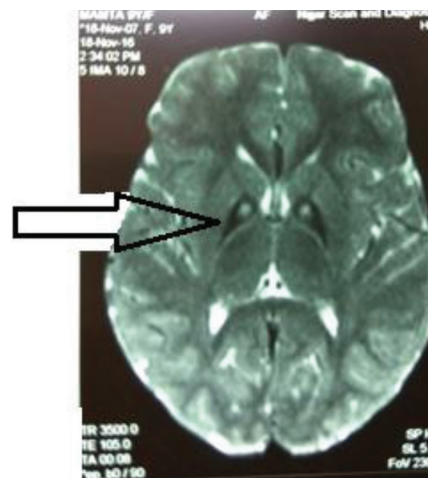


Figure-2: “Eye of the tiger sign” MRI image of Case no.2

effective drugs for dystonia and spasticity, intrathecal baclofen pumps⁷ can be considered for resistant cases. For localized muscle spasms injections of botulinum toxin are in use.

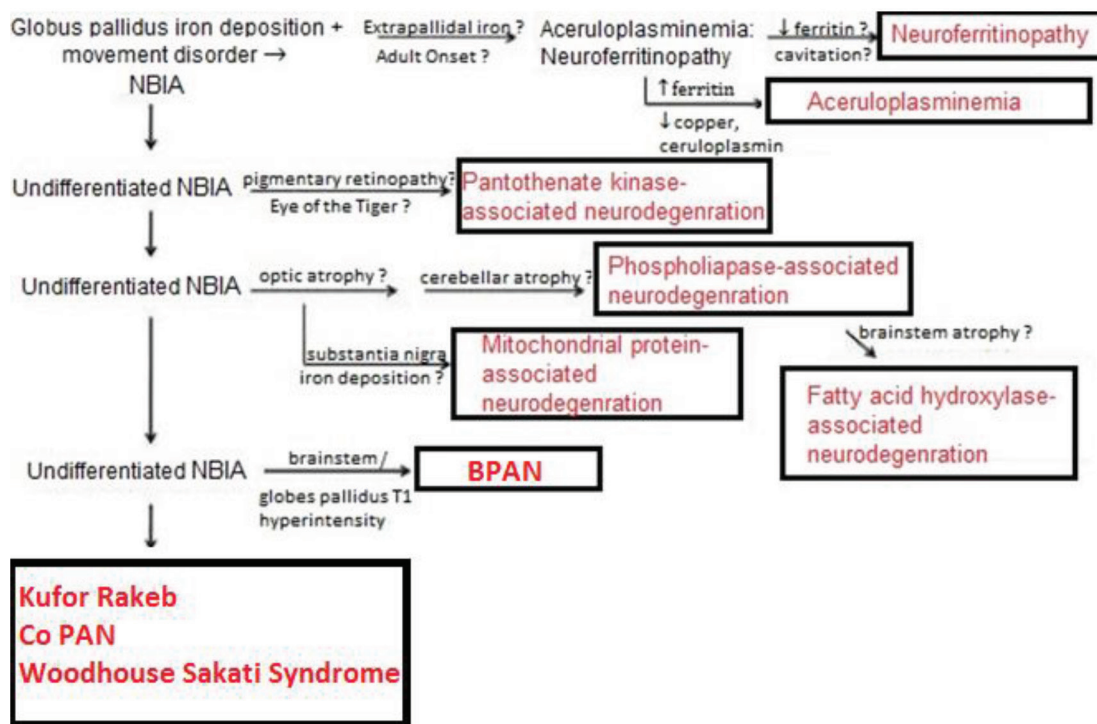
Deep brain stimulation therapy is a new modality of treatment performed by implanting electrodes in to brain with neurostimulator under the skin of chest and abdomen. It showed overall improvement in writing, speech, walking and global measures of motor skills.⁸ Gastrostomy placement is helpful in dysphagia and impaired nutrition. Glycopyrrolate and hyoscine patch may be beneficial for angular drooling.¹ Stereopallidotomy and thalamotomy have been used. Future management strategies involve iron chelators, direct delivery of phosphorylated pantothenate to the cells, bypassing pantothenate kinase.^{9,10}

CONCLUSION

Careful perusal of above flow chart shows that, in both cases clinical features, early onset, fundus changes of retinitis pigmentosa and MRI changes of “eye of the tiger sign” helped us to reach the diagnosis of PKAN. Family history of both patients also pointed to its genetic origin. By early onset and normal serum ferritin and ceruloplasmin levels we ruled out neuroferritinopathy and aceruloplasminemia. As there was no optic atrophy and no other significant finding in MRI except “eye of the tiger sign” helped us to rule out other forms of NBIA.

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Flowchart-1: Combined clinical and neuroimaging features, to confirm NBIA disorders and correctly characterize the subtypes of NBIA.⁶

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Source of Support: Nil; **Conflict of Interest:** None
Submitted: 25-01-2017; **Published online:** 03-03-2017