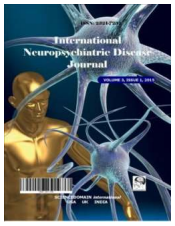

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Nbia-neurodegeneration with Brain Iron Accumulation: A Rare Case Report with Review of Literature

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Authors' contributions

This work was carried out in collaboration between all the authors. Author GC designed the study and wrote the format. Author IS managed the literature search and wrote the first draft of the manuscript with assistance from authors AKB and AS. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

NBIA (Neurodegeneration with Brain Iron Accumulation) is a rare disorder with varied age group of presentation but mostly detected in childhood. It is a progressive disease with basic extra-pyramidal symptoms and an autosomal recessive nature. The incidence is found to be very low depending on the various subtypes in this group, most common being PKAN (Pantothenate Kinase Associated Neurodegeneration). We here highlight a case of a 16 years old male, radiologically proven as NBIA and currently on regular follow up at our institute.

Keywords: Autosomal recessive; MRI; NBIA; PKAN.

1. INTRODUCTION

Childhood NBIA syndrome comprises a clinically and genetically heterogeneous group of disorders, characterized predominantly by a progressive extrapyramidal phenotype and an associated excess deposition of iron in brain [1]. Though various neurodegenerative disorders

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have been described in texts, NBIA is uncommon with very low incidence. There are two major NBIA phenotypes – PKAN (Pantothenate Kinase - Associated Degeneration) and PLAN (Phospholipase A2 group 6 – Associated Neurodegeneration) [2,3]. Brain MRI (Magnetic Resonance Imaging) is currently the standard radiological modality used for the diagnostic evaluation of all forms of NBIA.

2. CASE REPORT

A 16 year old male child presented to our outpatient department with chief complaints of abnormal gait since 2 and a half years and a gradual decrease in overall muscle mass. The present history dated to around two years back when his father noticed tightening of foot with gradual increase in abnormal walking on toes and associated difficulty in sitting/squatting. The child could manage his daily activities and chores only with proper support and showed a tendency to fall with profound gait imbalance.

Family history revealed that the eldest brother had somewhat similar complaints with significant limping, which started around 11-12 years, but without any preceding history of trauma or insult. The other two younger siblings, a sister and a brother aged 9 and 8 years respectively, are normal as of now.

On examination, the vitals were normal and the child had no distress on room air. General physical examination revealed no pallor, icterus, clubbing, cyanosis or lymphadenopathy. Complete neurological examination revealed bilateral symmetrically reduced muscle bulk in both upper and lower limbs. The tone was increased in lower limbs but power was normal in all four limbs. The deep tendon reflexes were exaggerated in both upper and lower limbs with significant clasp knife spasticity in lower limbs and presence of a classical ankle clonus. The higher mental functions were normal. Other systems including respiratory, cardiovascular system and per abdomen were found to be normal. No external spine injury or any other abnormality was seen.

A Provisional diagnosis of upper motor neuron (UMN) lesion made and a MRI dorso-lumbar spine was advised which showed no significant abnormality. Muscular dystrophy was also ruled out with a normal plasma creatinine kinase level of 39 mg/dl. MRI Brain was further advised which revealed abnormal symmetrical mineral deposition in bilateral Globus Pallidi and Substantia Niagara. Both the above regions appeared hypo intense on T2W images and with evidence of blooming on FFE images (see Image 1). Mild atrophy of Cerebellar hemispheres and Vermis was also noted along with a prominent

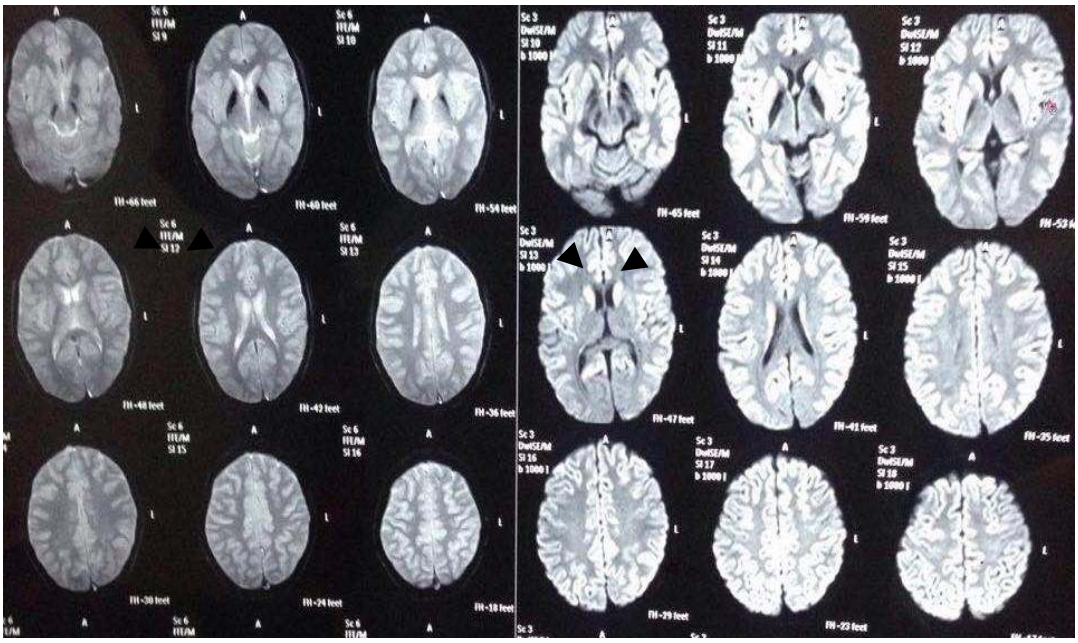

Image 1. Symmetrical mineral deposition in bilateral globus pallida

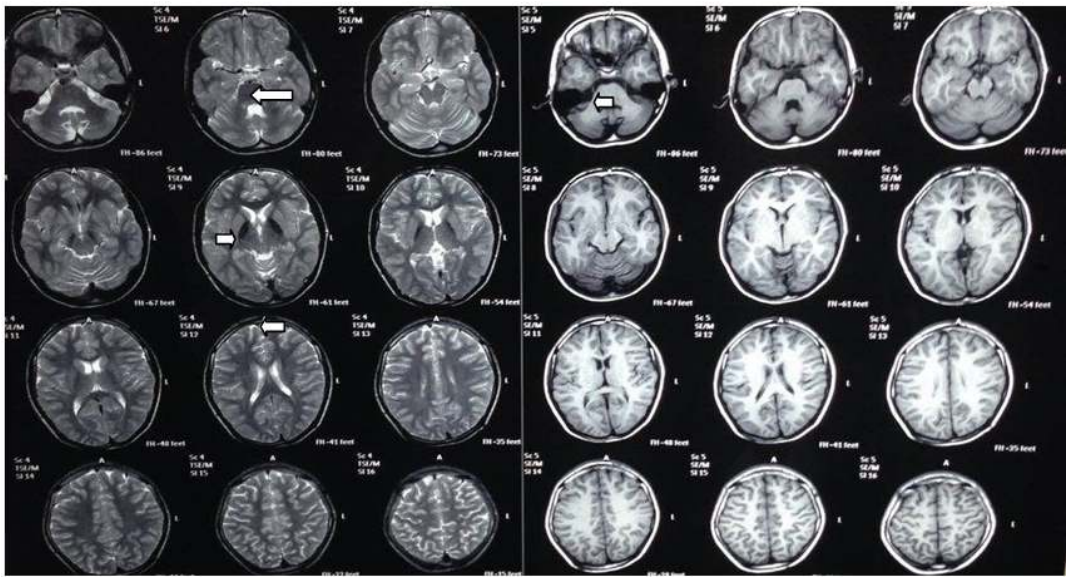

Image 2. Mild atrophy of cerebellar hemispheres and vermis with a prominent fourth ventricle

fourth ventricle (see Image 2). These findings were classically suggestive of NBIA with a likely possibility of PKAN (Pathothenate Kinase Associated Degeneration) subtype.

The child was managed symptomatically with tab baclofen and levodopa. An oral iron chelating agent (Deferasirox) was also started.

3. DISCUSSION

As per existing literature data, approximately half of the patients with a clinical diagnosis of NBIA are found to have identifiable mutations in the PKAN-2 gene which causes PKAN [4]. The genetic mutation in the gene was first described in detail by Zhou et al in [2]. The condition has a proposed prevalence rate of between 1 and 3 million population [1].

PKAN further can have a classical/ typical or atypical variant. Majority of the cases have an age of onset before 6 years, but there is a great variability in age of presentation (range 6 months to 12 years) as per existing case reports [1]. Extra-pyramidal features are known to predominate the clinical presentation and range from gait disturbances to dystonias, muscular rigidity and athetotic movements. The two variants of PKAN are better categorized by age of onset, rate of disease progression and the clinical and radiological features (see Table 1) [5]. MRI can distinguish changes that are more specifically recognized as indicative of PKAN with 'eye of the tiger' sign. This is a characteristic radiographic sign defined on coronal or transverse T2 weighted images of the Globus pallidus as a central region of hyper intensity surrounded by a rim of hypo intensity [6]. But in our index case this classical sign was missing with presence of a more uniform pattern of abnormal mineralization in bilateral Globus pallidi. Moreover, presence of functional and radiographic abnormalities in other regions of brain, particularly atrophy of cerebellar hemispheres and vermis with prominent fourth ventricle are relatively rare in PKAN. However, NBIA includes patients who meet the diagnostic criteria for PKAN with the exception of the 'eye of the tiger' sign and mutations in the PKAN-2 gene or the other two genes known to cause NBIA. Thus in our index case, diagnosing the child as PKAN (classical variant) at present is not appropriate due to lack of PKAN-2 gene testing results and also because of the MRI findings which were suggestive only of NBIA.

For appropriate symptomatic management, oral and intrathecal baclofen, stereotactic pallidotomy and anti- cholinergic treatments are available, but they have no long term known disease modifying effects [7,8]. While iron chelation represents the most feasible and promising therapy for NBIA today, it remains unclear to what extent iron removal affects the phenotype and in what dose and duration the treatment to be continued [9]. Our patient has been put on baclofen, levodopa and iron chelation and is present on regular follow up.

Table 1. Highlights the features used to differentiate the two variants of PKAN

Features	Classical PKAN	Atypical PKAN
Onset of symptoms	Early, within first decade after birth or early adolescence.	Second or third decade after birth
Progression of disease	10 years after onset	15-40 years after onset
Neurological symptoms	Gait abnormalities, extra pyramidal dysfunction such as dystonia and choreo athetosis, corticospinal tract involvement	Speech disorders, extrapyramidal dysfunction such as dystonia and rigidity
Psychiatric disorders	Rare	Depression, personality splits (30% of cases), obstructive obsessions and compulsions.
Retinitis Pigmentosa or optic atrophy	Often	Rare
MRI findings	'Eye of tiger' sign	'Eye of tiger' sign

4. CONCLUSION

NBIA is a rare entity, detected in childhood with extrapyramidal symptoms and progressive neurological damage. MRI is the standard diagnostic modality of choice to identify mineralization in deep grey nuclei of brain. Treatment is usually symptomatic and aimed at chelation of iron as well as replenishment with levodopa to provide relief from extrapyramidal symptoms.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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