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MRI Spectrum of Neurodegeneration with Brain Iron Accumulation: A Case Series of Varied Clinical Phenotypes

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Abstract: ***Background**: Neurodegeneration with brain iron accumulation (NBIA) is a group of inherited neurodegenerative disorders characterized by basal ganglia iron deposition and variable neurological manifestations. **Aim**: To describe the clinical presentations and characteristic MRI findings in patients with NBIA. **Materials and Methods**: This retrospective case series included ten patients with NBIA diagnosed based on clinical features and characteristic MRI findings. Neurological examination and MRI brain were evaluated for basal ganglia iron deposition and the "eye-of-the-tiger" sign. Genetic testing and family history were documented where available. **Results**: Patients aged 12–60 years had an equal male-to-female ratio. Clinical features included behavioral and psychiatric symptoms, cognitive decline, dystonia, bradykinesia, tremor, and ataxia. The "eye-of-the-tiger" sign was present in six patients. Three patients were from the same family, and one asymptomatic patient had characteristic MRI abnormalities. One patient had Kayser-Fleischer rings. Genetic testing identified PKAN mutations in six patients and an ADCY5 mutation in one. **Conclusion**: NBIA has a diverse clinical presentation, while characteristic MRI findings can provide important diagnostic clues. Recognition of basal ganglia iron deposition, along with genetic testing and family evaluation, facilitates diagnosis and counseling.*

Keywords: NBIA; MRI; Eye-of-the-Tiger sign; PKAN; Brain iron accumulation

1. Introduction

Neurodegeneration with brain iron accumulation (NBIA) comprises a genetically heterogeneous group of neurodegenerative disorders characterized by abnormal iron deposition, predominantly in the globus pallidus and substantia nigra. Clinical manifestations are variable and may include dystonia, parkinsonism, ataxia, spasticity, cognitive impairment, behavioral changes, and psychiatric symptoms, with onset ranging from childhood to adulthood.

Pantothenate kinase-associated neurodegeneration (PKAN), caused by pathogenic variants in **PANK2**, is one of the most well-characterized NBIA disorders. MRI plays a central role in diagnosis, particularly by demonstrating basal ganglia iron accumulation. The characteristic **eye-of-the-tiger" sign**, consisting of central T2 hyperintensity surrounded by T2 hypointensity in the globus pallidus, is strongly associated with PKAN. However, clinical presentations may be atypical, and similar imaging findings may occasionally occur in other disorders.

Familial occurrence and genetic testing can further support the diagnosis and facilitate identification of affected or presymptomatic relatives. This case series describes the clinical and MRI features of ten patients with NBIA and highlights the role of neuroimaging and genetic evaluation in diagnosis.

2. Materials and Methods

2.1 Study Design

This retrospective descriptive case series included ten patients diagnosed with NBIA based on clinical assessment and characteristic MRI findings.

2.2 Clinical Assessment

Clinical data including age, presenting symptoms, behavioral and psychiatric manifestations, cognitive impairment, and movement disorders were reviewed. Neurological examination focused on extrapyramidal and cerebellar features such as dystonia, bradykinesia, tremor, and ataxia.

2.3 Neuroimaging Assessment

MRI brain was evaluated for basal ganglia iron deposition, particularly involving the globus pallidus and substantia nigra, with specific attention to the characteristic **eye-of-the-tiger" sign**.

2.4 Genetic and Family Evaluation

Genetic testing was performed where available, with assessment for **PANK2** and other relevant mutations. Family history and consanguinity were documented to identify possible familial disease patterns.

3. Results

Ten patients with NBIA were included, aged **12–60 years**, with an equal male-to-female ratio. Clinical manifestations were heterogeneous and included behavioral and psychiatric abnormalities, cognitive decline, dystonia, bradykinesia, tremor, and ataxia.

MRI demonstrated the characteristic **eye-of-the-tiger" sign** in six patients, reflecting basal ganglia iron accumulation.

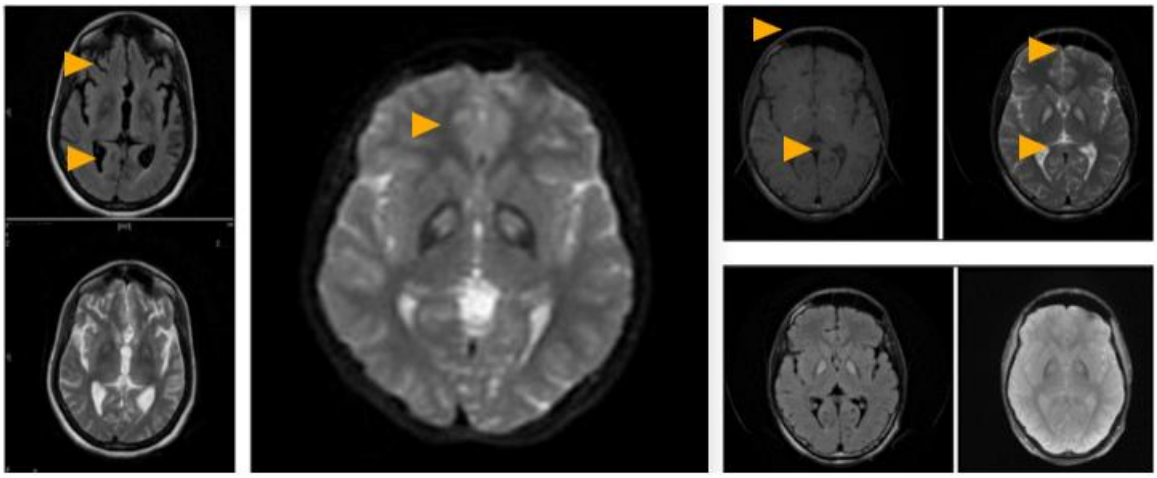

Figure 1: Representative MRI brain showing Eye of Tiger appearance

Three patients belonged to the same family, suggesting a familial pattern. One patient was asymptomatic despite characteristic MRI abnormalities, indicating the potential role of neuroimaging in identifying presymptomatic disease. One patient had **Kayser-Fleischer rings**, highlighting the diagnostic overlap with Wilson disease.

Genetic testing identified **PKAN mutations in six patients** and an **ADCY5 mutation in one patient**.

Table 1: Summary of clinical, imaging, and genetic findings

Parameter	Finding
Number of patients	10
Age range	12–60 years
Male-to-female ratio	01:01
Eye-of-the-tiger sign	6 patients
Same family	3 patients
Asymptomatic with MRI abnormalities	1 patient
Kayser-Fleischer rings	1 patient
PKAN mutation	6 patients
ADCY5 mutation	1 patient

4. Discussion

NBIA comprises a heterogeneous group of neurodegenerative disorders with variable genetic and clinical phenotypes. In the present series, patients ranged from 12 to 60 years and presented with behavioral, psychiatric, cognitive, and movement abnormalities, highlighting that NBIA can occur across a wide age range and may have diverse presentations.

The **eye-of-the-tiger" sign** was present in six patients and was the most characteristic MRI finding. This pattern is classically associated with PKAN and reflects iron accumulation within the globus pallidus. However, the finding is not entirely specific for PKAN and should be interpreted alongside the clinical phenotype and genetic results.

The familial clustering observed in three patients emphasizes the importance of obtaining a detailed family history. Identification of familial disease may facilitate genetic evaluation, counseling, and screening of potentially affected relatives. The presence of characteristic MRI abnormalities in an asymptomatic patient also suggests the potential role of neuroimaging in identifying presymptomatic disease, particularly in familial cases.

The presence of **Kayser-Fleischer rings** in one patient highlights the diagnostic overlap between NBIA and Wilson disease. Wilson disease remains an important differential diagnosis in younger patients with movement disorders and basal ganglia abnormalities, and appropriate evaluation of copper metabolism should be considered when clinically indicated.

Genetic testing identified **PKAN mutations in six patients**, supporting the important role of *PANK2* in NBIA. Molecular testing is particularly valuable when characteristic MRI findings are present and can help distinguish among genetically distinct NBIA disorders with overlapping phenotypes. The **ADCY5 mutation** identified in one patient should be interpreted cautiously, with correlation to the exact variant, zygosity, pathogenicity classification, and clinical phenotype.

Overall, this series highlights the importance of recognizing NBIA in patients with unexplained movement or neuropsychiatric disorders. Characteristic MRI findings, particularly basal ganglia iron deposition and the eye-of-the-tiger" sign, can guide genetic evaluation and facilitate diagnosis, family assessment, and genetic counseling.

5. Conclusion

NBIA is a clinically and genetically heterogeneous group of neurodegenerative disorders with characteristic MRI abnormalities. In this series, patients showed varied neurological and neuropsychiatric manifestations, with the **eye-of-the-tiger" sign** present in six patients. Familial clustering and an asymptomatic patient with characteristic MRI findings further emphasize the importance of recognizing inherited disease.

MRI, supported by appropriate genetic testing, remains central to the diagnosis of NBIA. A high index of suspicion, detailed neurological and family assessment, and molecular evaluation can facilitate early diagnosis and genetic counseling.

6. Limitations

This was a small retrospective case series of ten patients, limiting the generalizability of the findings. Detailed patient-level data regarding clinical course, MRI characteristics, treatment, and long-term outcomes were limited. Genetic findings also require further characterization, including the specific variants and their pathogenicity, where available.

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