Neuro-degeneration with Brain Iron Accumulation in 18 Indian families: a case series highlighting phenotypic and genotypic diversity

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INTRODUCTION

- Neuronal Brain Iron Accumulation (NBIA) are a group of genetic disorders characterized by abnormal accumulation of iron in the basal ganglia.
- Progressive movement disorder with variable neuropsychiatric abnormalities, spasticity, ocular involvement and impaired cognition
- 10 genes are known to be associated with various subtypes of NBIA : *PANK2, PLA2G6, C19ORF12, FA2H, CRAT, FTL, COASY, WDR45, REPS1, ATP13A*.

OBJECTIVES

- To describe the clinical & radiological findings of patients with NBIA
- Molecular characterization of the underlying genetic etiology.

METHODOLOGY

Study design: Observational study at 2 tertiary level medical genetics centres in India.

Inclusion criteria: Patients with NBIA during the 2016-2021 period based on confirmed genetic studies .

Clinical data: Demographic details, family history, clinical details and neuroimaging findings were collected.

Genetic testing:

- Exome sequencing on genomic DNA of the proband
- Variant assessment as per ACMG-AMP guidelines
- Segregation of variants in family members by Sanger.

RESULTS

- 24 patients with NBIA from 18 unrelated families
- Age: 1 month- 18 years
- 5 sub-types of NBIA detected; PLAN most common
- Consanguinity: 4/18 (22%) & disease recurrence: 9/18 (50%)
- Iron deposition on MRI in only 6 out of 20 patients.

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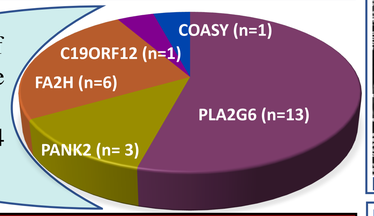
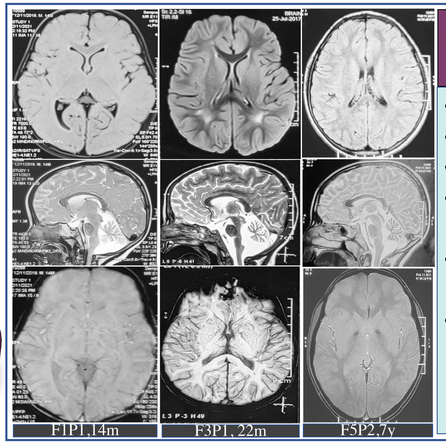
Subtypes of NBIA in the study cohort of 24 patients



Genotype profile of study cohort

ID	Gene	variants	zygosity	class
F1	*PLA2G6*	c.1799G>A / c.1974C>A	Comp het	P / LP
F2	*PLA2G6*	Exon 3-7 duplication*	Hom	P
F3	*PLA2G6*	c.1799G>A / c.2370T>G	Comp het	P / P
F4	*PLA2G6*	c.1690del*	Hom	LP
F5	*PLA2G6*	c.2200T>C* / c.2222G>A	Comp het	LP / P
F6	*PLA2G6*	c.1799G>A / c.2370T>G	Comp het	P / P
F7	*PLA2G6*	c.1982C>T	Hom	LP
F8	*PLA2G6*	c.2370T>G / c.668C>T	Comp het	P / LP
F9	*PLA2G6*	c.2128 del*	Hom	P
F10	*PANK2*	c.509_521 del* / c.1700T>A*	Comp het	P / P
F11	*PANK2*	c.1594C>T	Hom	VUS
F12	*PANK2*	c.652A>C*	Hom	VUS
F13	*FA2H*	c.491T>C*	Hom	VUS
F14	*FA2H*	c.589C>T	Hom	P
F15	*FA2H*	c.443C>T*	Hom	VUS
F16	*FA2H*	c.1039+2T>G / c.232G>A	Comp het	P / LP
F17	*C19ORF12*	c.161G>T	Hom	P
F18	*COASY*	c.1486-3C>G	Hom	LP

*novel; P-pathogenic; LP-likely pathogenic; VUS-variant of uncertain significance

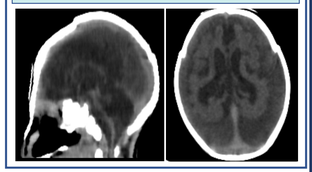


PLA2G6-associated neurodegeneration (PLAN)

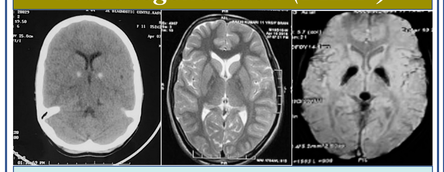
- 13 patients from 9 families
- Majority- Infantile neuroaxonal dystrophy
- 2 patients - Atypical Neuroaxonal dystrophy
- Features: neuroregression (11/13); dystonia (4/13); optic atrophy (8/11), seizures (4/13)
- Rapid disease progression; 3 patients died in early childhood.
- MRI: cerebellar atrophy universally ; variable white matter involvement and brainstem atrophy. Iron accumulation in only 1 patient with ANAD

COASY associated neurodegeneration (CoPAN)

Neonate with severe microcephaly, spasticity, arthrogryposis
Prenatal onset severe form of CoPAN



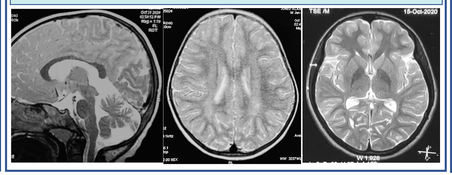
Pantothenate Kinase-Associated neurodegeneration (PKAN)



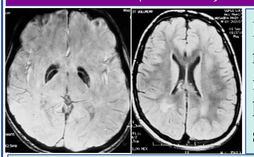
- 3 individuals, gait abnormality; dystonia; Behavioural disturbances visual deficit.
- Classic “eye of a tiger” sign in 2 pts.

Fatty acid hydroxylase-associated neurodegeneration (FAHN)

- 5 patients from 3 families
- Gait abnormality; dystonia ; abnormal cognition
- Iron accumulation in 1pt (13y) only.



Mitochondrial membrane-associated neurodegeneration (MPAN)



Iron accumulation in GP, PV hyperintensities

Juvenile-onset gait abnormality; rapid cognitive decline; focal dystonia, choreoathetosis; bradykinesia

CONCLUSION

Largest cohort of molecularly characterized pediatric patients with NBIA from Indian subcontinent.

- Clinical presentation is varied and not restricted to extrapyramidal signs
- PLAN is underdiagnosed due to early onset & atypical features
- Iron accumulation on MRI –considered hallmark but inconsistent feature
- 21 variants across 5 genes described adding 9 novel variants.

References:
1. Gregory A et al., *J Med Genet*. 2009;46(2):73-80. 2. Richards et al., *Genet. Med*. 2015;17; 405–424. ; 3. Bharadwaj NK et al., Brain Dev. 2021;43(10):1013-1022.