“PLA2G6 associated Neurodegeneration (PLAN)- Similar Mutation, Divergent phenotype”

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Introduction

- PLA2G6 gene encodes iPLA2β enzyme essential for phospholipid metabolism and neuronal membrane integrity, especially in the CNS.
- Mutations impair enzyme function, leading to phospholipid imbalance, axonal damage, and progressive neurodegeneration, associated with a group of autosomal recessive neurodegenerative disorders collectively known as PLA2G6-associated neurodegeneration (PLAN).
- PLAN includes a spectrum of autosomal recessive disorders: infantile neuroaxonal dystrophy (INAD), atypical NAD, adult-onset dystonia-parkinsonism (DP), and early-onset parkinsonism (AREP), showing vast clinical variability.
- Genotype-phenotype correlation is unclear; same mutation can produce distinct clinical presentations, reflecting disease complexity.
- Reporting 3 cases with identical mutations but distinct presentations sharpens understanding of disease complexity and aids tailored patient management.

Cases

Case-1; 23 years old male with 2-year progressive gait slowness and daily activity decline, developed resting tremor in both hands at 6 months. After 1 year, gait worsened to Parkinson's gait. Speech became soft and slow. Exam showed normal cognition, bilateral resting tremor, bradykinesia, grade 2 rigidity and exaggerated reflexes.

Case-2; 39 years old male presented with 5 years of behavioral changes (aggression, abusiveness, social-withdrawal), gradual progressive slowness in daily activities, hypokinetic dysarthria, and dystonic wrist movements. Over 3.5 years, he became wheelchair-bound with anarthria and fully dependent. Family history included Wilson's disease in a nephew and early death of a brother from liver failure. Exam showed bradykinesia, severe rigidity, truncal rigidity, oromandibular dystonia, and dystonic wrist posture.

Case-3 24-year-old male presented with 3 years of depression and visual hallucinations, followed by progressive slowness and limb stiffness after 8-9 months. Within 2 years, he developed cognitive decline, executive dysfunction and distractibility. Family history included two sisters with similar undiagnosed neuropsychiatric and parkinsonian features. Exam revealed severe inattention, bradykinesia, grade II rigidity, normal power, exaggerated reflexes, slow shuffling gait, and stooped posture.

Table- Clinical and demographic information of PLA2G6 mutation patients

Features	Case 1	Case 2	Case 3
Current age (in years)	23	39	24
Age at onset (in years)	21	34	21
Family History	No	History of Wilson's disease in nephew	Yes
First symptoms at onset	Bradykinesia (Motor)	Behavioral (Neuropsychiatric)	Psychiatric
Phenotypic Presentation	Early onset Parkinsonism	Dystonia-parkinsonism,	Psychiatric, cognitive, Early onset Parkinsonism
Cognition Involvement	No	Yes	Yes
Psychiatric features	No	No	Yes
Extrapyramidal symptoms			
Tremors	Yes	No	No
Bradykinesia	Yes	Yes	Yes
Dystonia	No	Yes	No
Levodopa response	++	+	++
Pyramidal, sensory and Cerebellar	Absent	Absent	Absent
Neuroimaging	Normal	Generalized Cortical and cerebellar atrophy	Normal
Mutation	c.2222G>A (p.Arg741Gln)	c.2222G>A (p.Arg741Gln)	c.2222G>A (p.Arg741Gln)

Discussion

- In this case series, we describe three adult-onset PLAN patients carrying the same rare homozygous c.2222G > A (p.Arg741Gln) mutation, previously reported mainly in South Asian populations.
- Despite sharing this mutation, their clinical presentations varied — one with dystonia-parkinsonism and two with early-onset parkinsonism. Two patients also presented with neuropsychiatric symptoms, consistent with previous studies showing high prevalence of psychiatric features in PLAN.
- We suggest that this clinical heterogeneity arises not only from mutation location within different iPLA2β domains but also from additional genetic, epigenetic, and environmental factors influencing disease expression.
- Such gene-gene and gene-environment interactions likely drive phenotype variability, highlighting the complexity of PLAN and shaping its pathogenesis. Understanding these interactions is crucial for developing targeted, disease-modifying therapies.