Short Communication

Two unusual cases of *PLA2G6*-associated neurodegeneration from India

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Abstract

Phospholipase A2-associated neurodegeneration (PLAN) comprises of three disorders with overlapping presentations. The most common of these is classical or infantile-onset phospholipase A2-associated neurodegeneration, also known as infantile neuroaxonal dystrophy (INAD). Only 1 case of INAD has been reported from India till now. We report two genetically confirmed patients seen at a tertiary care pediatric hospital. Both these patients presented with infantile onset of neuroregression. We believe that INAD is underrecognized and underreported from India.

Key Words

Infantile neuroaxonal dystrophy (INAD), neurodegeneration with brain iron accumulation (NBIA), neuroregression, phospholipase A2-associated neurodegeneration (PLAN)

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Introduction

Neurodegeneration with brain iron accumulation (NBIA) comprises an expanding group of heterogeneous diseases characterized by progressive brain iron accumulation presenting as neuronal degeneration and complex movement disorders.[1] This group includes pantothenate kinase-associated neurodegeneration (PKAN, 50%), phospholipase A2-associated neurodegeneration (PLAN, 20%), fatty acid hydroxylase-associated neurodegeneration (FAHN, 1%), mitochondrial membrane protein-associated neurodegeneration (MPAN, 10%), beta-propeller protein-associated neurodegeneration (BPAN, 7%), and a few other, rarer disorders comprising 2% of NBIA. Finally, there is an idiopathic group (8%) for which the underlying genetic mutation has not yet been delineated.[2] PLAN comprises three diseases with overlapping presentations, of which infantile neuroaxonal dystrophy (INAD) is the most common,[1] but only 1 case has been reported from India till now.[3] We report 2 cases seen in our tertiary care pediatric hospital.

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Case 1

A 3-year-old female child, first issue of a third-degree consanguineous union, presented to us with history of developmental delay and recent loss of achieved milestones. She had a normal birth history and history of two episodes of pneumonia, at 2 months and at 1 year of age, both requiring inpatient treatment. She achieved head holding at 5 months, sitting at 1 year, standing with support at nearly 18 months, transfer of objects at 1 year, and scribbling at 22 months. She also had social language delay with social smile at 4 months, stranger anxiety after 1 year, speaking bisyllables after 14 months, and two words with meaning at nearly 22 months of age. She stopped gaining new milestones after 22 months, and at 2 years she lost her ability to stand and became progressively unable to sit, speak meaningfully, scribble, or hold objects. She developed abnormal eye

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movements and auditory inattention. There were no seizures. There was no family history of neurological disease. On examination, her head circumference was normal and she did not have any dysmorphic features. Ophthalmological examination showed rotatory and horizontal nystagmus with optic disc atrophy in both eyes. She had hearing loss. She had titubations, and was hypotonic and hyporeflexic, with a normal plantar response.

Investigations showed normal basic metabolic tests, creatine kinase, blood ammonia, serum lactate, alpha fetoprotein, lipid profile, and vitamin E and B12 levels. Neuroimaging showed mild cerebellar atrophy [Figure 1a]. Brainstem evoked response audiometry (BERA) showed sensorineural hearing loss. Nerve conduction velocity (NCV) was normal at this stage, but on electromyography (EMG), chronic partial denervation was seen in the tibialis anterior muscle bilaterally.

The child was started on physical therapy and nutritional supplementation and was followed up. She showed steady deterioration with loss of head control, vocalization, and hearing, and also developed ataxia and pyramidal signs. *PLA2G6* sequencing was performed and a homozygous mutation was found for c2047A > T at p. K683X, which confirmed the diagnosis of INAD in the child. The patient was continued on physical therapy, baclofen, and nutritional support but has, by now, progressed to a vegetative state.

Case 2

A 4-year-old boy, second issue of a nonconsanguineous union, presented with history of loss of achieved milestones. He had a normal birth history and achieved age-appropriate milestones till 1 year. At 11 months, his mother first noticed swaying while sitting, and by 15 months he had frequent falls while standing up or trying to walk. He became increasingly hypotonic and sequentially lost achieved milestones with gradual loss of sitting, head control, social milestones, vision, and hearing by 4 years. On examination, he had normal facial features and his head circumference was appropriate for his age. Ophthalmological examination showed nystagmus with bilateral disc pallor. There was hearing loss. He was hypotonic with absent deep tendon reflexes and mute plantar reflexes. He did not have any abnormal movements.

In this patient, too, basic metabolic tests were normal. BERA showed profound hearing loss and electroencephalogram (EEG) was normal. EMG showed proximal and distal denervation in all four limbs, and NCV showed axonal sensory and motor neuropathy. Electroretinogram (ERG) was normal and visual evoked potential (VEP) showed normal latencies with small amplitudes.

Magnetic resonance imaging (MRI) brain done at 4 years showed severe cerebellar atrophy involving both cerebellar hemispheres and vermis with atrophic superior cerebellar peduncle [Figure 1b]. Ill-defined, subtle T2 hyperintensities were found in the corpus striatum, internal capsule, parietooccipital lobes, and cerebellar white matter. The striking feature was the hypointensity of globus pallidi on T2-weighted images [Figure 1c]. *PLA2G6* sequencing was performed and a homozygous mutation was found for c671T > C at p. L224P, which confirmed the diagnosis of INAD in this child. The child was started on physical therapy and nutritional and other supportive management, but deteriorated rapidly.

Discussion

The phenotypic spectrum of *PLA2G6*-related disorders is divided into three phenotypes: INAD or classical PLAN, childhood or atypical PLAN (also known as atypical neuroaxonal dystrophy, including Karak syndrome) and adult-onset PLAN (early onset dystonia-parkinsonism).[4] The *PLA2G6* gene encodes a calcium-independent phospholipase A2 enzyme, which plays an important role in phospholipid remodelling and cell membrane homeostasis.[5] The mode of inheritance is autosomal recessive. The mechanism of pathological brain iron deposition in patients with *PLA2G6* mutations is unclear.[6] The disease prevalence is estimated to be approximately 1:1,000,000.[7]

Patients affected with classic INAD are usually normal after birth, with no dysmorphism and with normal early milestones.

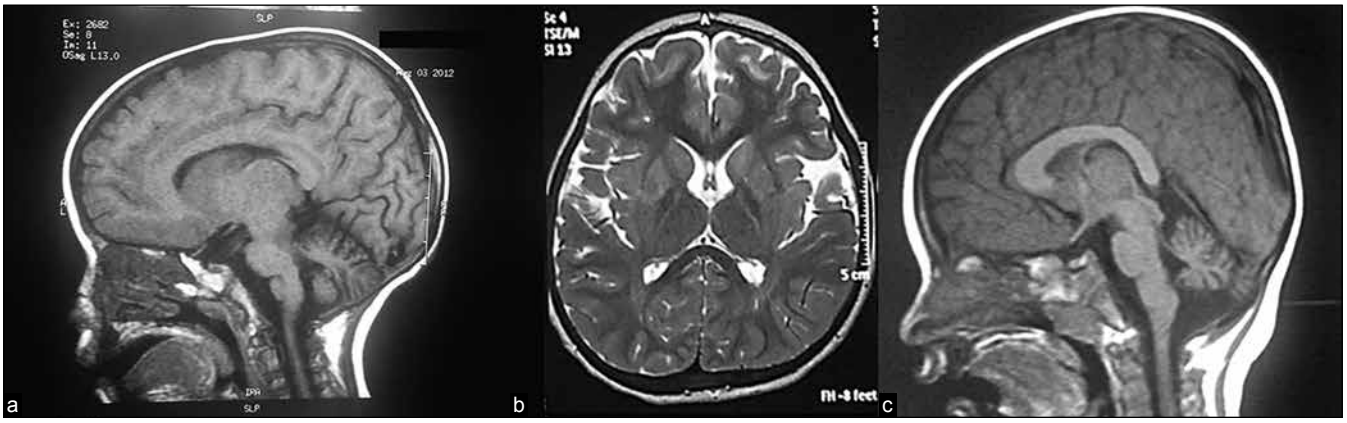

Figure 1: MRI images of the brain (a) T2-weighted sagittal section (Patient 1) showing mild cerebellar atrophy (b) T2-weighted axial section (Patient 2) showing hypointense globus pallidi indicative of brain iron accumulation (c) T2-weighted sagittal section (Patient 2) showing severe cerebellar atrophy

Before 3 years of age (usually 6 months to 2 years), these children lose attained milestones and develop truncal hypotonia and progressive psychomotor regression. This is followed by the development of spastic quadriparesis and hyperreflexia and ultimately areflexia and a vegetative state by the end of the first decade. Ataxia, deformities, and bulbar dysfunction may be seen.[7] Ophthalmological abnormalities include nystgamus, strabismus, and optic disc pallor, suggestive of optic atrophy. MRI brain shows cerebellar atrophy with gliosis, vertically oriented thin corpus callosum, white matter abnormalities, and hypointense globus pallidi on T2-weighted images, suggestive of brain iron accumulation.[8] ERG is normal and VEP is delayed with reduced amplitudes. NCV shows distal axonal type sensorimotor neuropathy.[7] Although seizures are described as rare, one study has found the proportion of patient with seizures to be as high as 29%, and 70% of patients showed EEG abnormalities in the form of fast rhythms.[9] Before the advent of genetic testing, the histological features of axonal swelling and spheroid body formation evident on skin, sural nerve, conjunctival, rectal, or muscle biopsy were the hallmarks of this disease. Testing for mutations in the *PLA2G6* gene is the current basis for diagnosis of INAD, with 80–90% patients harboring this mutation in the classic INAD phenotype.[9] The genotype–phenotype correlations in PLAN have not been well elucidated till date.

Childhood-onset or atypical PLAN is a rare disease that presents late in childhood with movement abnormalities and social language regression followed by motor regression. Radiologically, these patients are always found to have involvement of globus pallidus.[9,10] PLAN can also present in young adults as a dystonia–parkinsonism complex associated with eye signs and rapid cognitive decline. These patients have a considerable overlap with Kukor–Rafeb syndrome.[11]

Patient 1 presented with features reminiscent of the INAD phenotype, except for the global developmental delay manifest from early infancy. Neonatal onset of INAD has been reported to manifest as neonatal hypotonia and weakness, with homozygous mutations of the *PLA2G6* gene.[12] However, our patient did not have neonatal complaints but had delayed milestones followed by regression and a typical INAD phenotype. Patient 2 presented with a typical history of INAD. With the clinical background of infantile-onset neuroregression with optic atrophy, sensorineural hearing loss, and features of peripheral neuropathy, we further investigated both these children. MRI brain in both cases showed cerebellar atrophy, which is the earliest sign in imaging and is seen in nearly all patients with INAD.[9] Hypointense Globi pallidi/Globus pallidus: Plural and singular forms, although much more striking, may be absent in a substantial number of patients. Abnormalities on electrophysiology further supported the diagnosis. This combination of infantile neuroregression with ataxia and peripheral neuropathy can be seen in a handful of conditions, including, but not limited to, metachromatic leukodystrophy, Krabbe disease, mitochondrial disorders, peroxisomal disorders, and INAD. All of these can be clearly differentiated based on clinical, biochemical, and radiological features.

Genetic testing provides a definitive diagnosis and was performed in both these patients. Genetic counselling was offered to both the families. Supportive management was provided but the outcome was dismal.

Infantile-onset PLAN has not been reported widely from India, as noted before. Given the diversity and the large population, it seems unlikely that the prevalence of this disease is very low. Limited diagnostic facilities, expensive testing, and lack of recognition make it likely that PLAN is grossly underreported in this country.

Conclusion

Infantile-onset PLAN is a devastating disease leading to severe psychomotor regression and early death in the majority of cases. Currently, only supportive and palliative care can be offered to these children. We think that the disease may present with developmental delay in infancy before the appearance of other signs, as in our patient. INAD, though a very rare disorder, should always be considered and investigated in a patient presenting with characteristic clinical and imaging features. Family screening and genetic counselling should be offered to the patients.

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Conflicts of interest
There are no conflicts of interest.

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