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A new missense mutation in PLA2G6 gene among a family with infantile neuroaxonal dystrophy INAD ☆

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ABSTRACT

We report a family with two siblings having features of infantile neuroaxonal dystrophy (INAD), with first degree consanguineous parents. Rapid progressive loss of developing milestones (started from 18 months) and early infantile death of both siblings occurred. Brain magnetic resonance imaging (MRI) revealed severe rapidly progressive cerebellar atrophy initially reported as early as 18 months, with the younger brother suffered generalized tonic clonic seizures.

Next generation sequencing revealed a new mutation in PLA2G6 gene (c.319 del C, p. Leu107 Cyst), resulting in a premature stop codon with shift in the reading frame of resulting protein.

Conclusion: Early onset loss of developmental milestones with cerebellar atrophy and other described clinical findings ultimately warrant PLA2G6 gene sequencing. Here we report c.319 del. C of PLA2G6 detected by next generation sequencing to be responsible for severe early infantile neuroaxonal dystrophy with early infantile death. We conclude that various PLA2G6 gene sites sequencing need further investigation in INAD in line with clinical correlation. Also INAD seems to be an unrecognized disorder that needs more categorization for proper diagnosis and genetic counselling.

Background

Neurodegeneration associated with PLA2G6 mutations (PLAN) constitutes a broad spectrum of clinical entities which encompasses infantile neuroaxonal dystrophy (INAD1/NBIA2A, MIM # 256600), atypical neuroaxonal dystrophy (NAD), idiopathic neurodegeneration with brain iron accumulation including Karak syndrome (NBIA2B, # MIM 610217) and Dystonia Parkinsonism Complex (PPC).[2–8]

Infantile neuroaxonal dystrophy (INAD), is a severe progressive disorder with infantile onset, affecting the motor and cognitive status. Brain iron accumulation occurs in a subset of INAD patients, which represents the distinctive feature of the idiopathic neurodegeneration with brain iron accumulation, NBIA.[1] NBIA is a group of rare, genetic neurological disorders characterized by abnormal accumulation of iron in the basal ganglia. Ten established genes, with their causative mutations, are recognized as causatives for sub types of NBIA, with Pantothenate-Kinase associated neurodegeneration (PKAN) being a well known category.[9] Most NBIA syndromes have a classic Mendelian inheritance (mostly autosomal Recessive type).

The globus pallidus is the mostly affected by iron deposition and the main symptoms include dystonia, choreoathetosis, legs spacticity, symptoms of parkinsonism and sometimes retinal and optic nerve degeneration. Psychiatric symptoms and cognitive decline are predominant features with cerebellar atrophy being a major finding in MRI in some types of NBIA.

The other disorder INAD is also known as Seitelberger's disease or neurodegeneration with brain iron accumulation 2A (NBIA2A). Presence of axonal spheroids throughout the central and peripheral nervous systems is a common feature of this group of psychomotor disorders. A predominant causative gene, PLA2G6, encoding iPLA2-VIA, a calcium-independent phospholipase is considered the main molecular background.

Suggestions assume that mutations leading to a complete absence of the protein are associated with a severe INAD, while compound heterozygous mutations with a residual protein activity are associated with the less severe NBIA phenotype. INAD caused by mutations in PLA2G6 gene manifests typically between ages 6 months and 3 years with rapid progression of truncal hypotonia, progressive psychomotor delay, cerebellar ataxia, symmetric pyramidal tract signs, tetraparesis, with lost walking ability or

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unachieved walking ability is a main finding.[3] Nystagmus, strabismus and optic atrophy are also common features.

Atypical NAD has a later onset than INAD (about 4 years of age). Gait instability, delayed speech, progressive dystonia, dysarthria, optic atrophy, tetraparesis (spastic or areflexic), and neurobehavioral disturbances are the common manifestations. Cerebellar atrophy is evident at 2–3 years of age but later brain iron deposition in the brain becomes evident.[5] Karak syndrome was described in adolescents, with manifestations started at 6 years of age, with progressive ataxia, cognitive decline, ending in lost ambulation by around 10 years. MRI shows moderate cerebellar atrophy, accumulation of iron in the substantia nigra, and central hyperintensity in the medial globus pallidus (the eye of-the-tiger-sign).[2]

From the histopathological point of view, INAD patients show axonal spheroids in the brain, spinal cord and in the peripheral nervous system.[10]

PLA2G6 has a pivotal role in membrane phospholipid metabolism in various cell types through a calcium-independent PLA2 enzyme.[11] The biological role of PLA2-VIA enzyme is linked to its glycine-rich nucleotide binding motif, a lipase motif (GTSTG) and a calmodulin binding site at the C-terminus.[1] The N-terminus domain has seven ankyrin-like repeats involved in enzymes oligomerization, and hence full enzymatic activity.[11]

Deficiency of PLA2- VIA enzyme activity alters the phospholipid composition of cellular and subcellular membranes, improper repair of oxidative damage with changes of membrane permeability, fluidity and ion homeostasis. The ultimate result would be apoptosis and cell damage.[12]

Cases description

Here we present a family presented to us at Clinic of children with Special Needs, National Research Centre, Cairo, Egypt, with 2 affected siblings. Parents are first degree cousins with no history of previous abortions (Fig 1).

The older sister was born after a normal course pregnancy, no prenatal medications, except for routine pregnancy multivitamins. Normal pregnancy scans with average frequency and strength of fetal movements were reported. She was born by normal vaginal delivery in a private clinic, with 3.3 kg birth weight, length of 50 cm and normal head circumference. Serial body measurements till 2 years age for routine baby check showed normal figures.

She developed head support by 7 months, normal teething, and supported walking by one year age with taking few steps.

Onset of symptoms developed by 1 6/12 year with gradual progressive loss of developed milestones in a reversed order of their development. Mother noticed balance problems started first in sitting, then impaired balanced standing and walking were noticed. Central body tone and head support were markedly affected with the later being lost by 2 years and 6 months. By 3 years of age, she had limited movements of limbs and body and she was bed ridden. No history of convulsions or abnormal movements was reported. Mother described a normal cognitive skills for age till age of 1 year and 6 months.

Nerve conduction study was done at 21 months age, which did not reveal abnormalities. Gingival biopsy examination by electron microscopy at 30 months age showed many curvilinear structures, spheroid bodies and filamentous or membranous deposits. The histocystes fibroblasts and endothelial cells show scattered spheroid bodies and few curvilinear structures (Fig 2).

Brain MRI showed cerebellar cortical atrophy with involvement of vermis and hemisphere, cerebellar cortex hyperintensity on T2-weighted images is evident. No brain iron accumulation was seen (Fig 3).

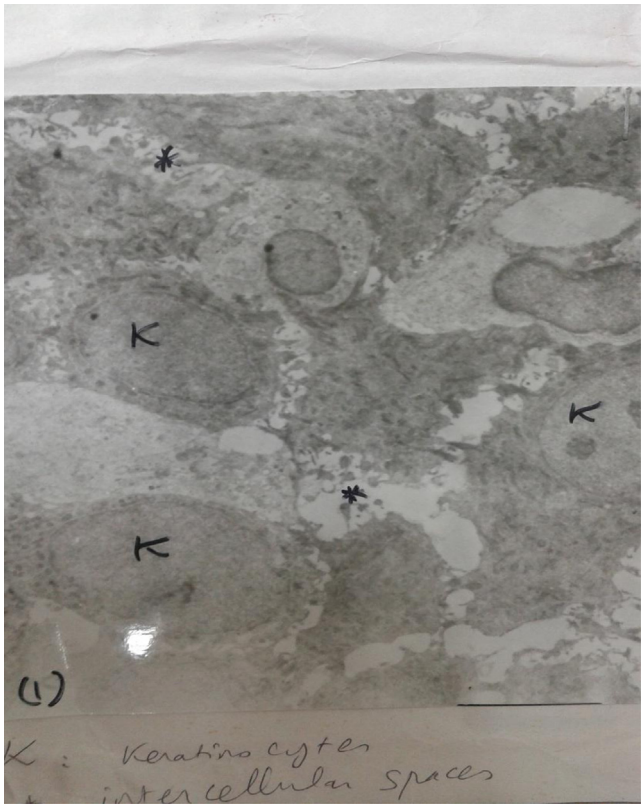

Fig. 2. Electron microscopic examination of gingival biopsy from the older sister showing many curvilinear structures, spheroid bodies and filamentous or membranous deposits.

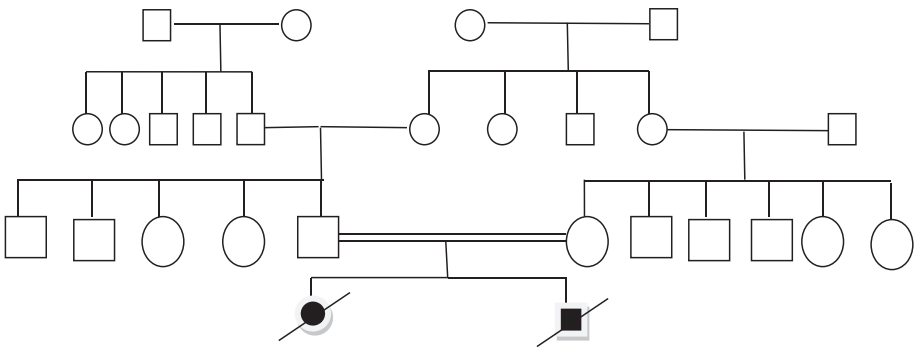

Fig. 1. Pedigree of studied family showing 1st degree consanguinity and affected two siblings.