Infantile neuroaxonal dystrophy in a pair of Malaysian siblings with progressive cerebellar atrophy: Description of an expanded phenotype with novel PLA2G6 variants

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Infantile neuroaxonal dystrophy 1 (INAD) (OMIM #256600) is a rare infantile onset neurodegenerative disease characterised by neuroregression and hypotonia, evolving into generalized spasticity, blindness and dementia. We report our diagnostic approach of a pair of siblings with psychomotor regression, hypotonia, optic atrophy and auditory neuropathy. The brain magnetic resonance imaging (MRI) showed progressive cerebellar atrophy. Genetic testing of the PLA2G6 confirmed presence of compound heterozygous novel mutations. As the variant c. 196C>T (p.Gln66X) was a truncating variant, it was considered as pathogenic while the variant c. 2249G>A (p. Cys750Tyr) was considered as "likely pathogenic" by bioinformatics analyses. Our patient expands the clinical phenotype of INAD as it described the first South-East Asian patient with INAD-associated auditory neuropathy. Our report highlights the importance of increased awareness of this condition amongst clinicians, the use of deep phenotyping using neuroimaging and the clinical utility of gene sequencing test in the delineation of syndromes associated with infantile neurodegenerative disease.

1. Introduction

Infantile neuroaxonal dystrophy (INAD) (OMIM #256600) is a rare, autosomal recessive neurodegenerative disease, clinically characterised by psychomotor regression and marked hypotonia, gradual deterioration to spastic tetraplegia, visual impairment and dementia. Onset of disease occurs within the first 2 years of life. The course of the disease is rapidly progressive, culminating in death by the age of 10 years old. Patients demonstrate both extra-pyramidal and symmetrical pyramidal tract signs, hypotonia, and extensor plantar responses. Visual disturbances are evident early, which may be the earliest presentation of the disease. These include optic atrophy, strabismus, pendular or downbeat nystagmus [1]. As the disease progresses, patients are usually blind, bed-bound and demented at the terminal phase of the disease.

Characteristic neuroradiological features of INAD are marked progressive cerebellar atrophy with increased cerebellar cortex signal hyperintensity on T2-weighted magnetic resonance imaging (MRI) images. Whilst cerebellar atrophy is invariably present in all INAD cases, some INAD cases however may not show cerebellar cortex hyperintensity [1,2]. Hypointensity in the globus pallidus representing brain iron deposition has also been described [3–6]. Electromyography (EMG) may show early signs of denervation. Nerve conduction study (NCS) may be normal in early disease but often demonstrate distal axonal-type sensorimotor peripheral neuropathy in late disease. The pathological hallmark of INAD is the presence of widespread terminal axonal swellings called "spheroid bodies".

Before availability of molecular diagnosis, INAD was diagnosed clinically with demonstration of these spheroid bodies. In 2006, Morgan et al. identified recessive mutation in the PLA2G6 causing INAD [7]. PLA2G6 encodes calcium-independent phospholipase enzyme (iPLA2-VI), which plays an integral role in remodeling membrane phospholipids in axons and synapses.

Rare cases of INAD has been reported worldwide including Asia [4–6,8]. Since the recognition of the PLA2G6 mutation and increas-
ing accessibility to genetic testing, more cases of INAD are now being recognised and reported. However, none have been reported so far from the South East-Asia region. We report a case of genetically confirmed INAD in a pair of siblings in Malaysia and highlight the usefulness of utilizing the neuroradiological and clinical gene sequencing approach in making the diagnosis of INAD.

2. Case report

A 1-year 10-month-old boy was referred for psychomotor regression and progressive central hypotonia. He was the first child of healthy parents from a non-consanguineous marriage. He was born full term after healthy pregnancy and delivery. His developmental milestones were normal. Slowing rate of development was noticed after 1 year old with developmental regression starting from the age of 1 year 5 months. Neurological examination showed bilateral convergent strabismus, central hypotonia, dystonia, tremors, generalized hyper-reflexia and extensor plantar responses. Fundoscopy showed bilateral optic atrophy. He had a normal otoacoustic emissions (OAE) test but abnormal auditory brainstem evoked response (ABR) which indicated bilateral profound auditory neuropathy.

Two brain MRIs done 9 months apart revealed progressive cerebellar atrophy. (Fig. 1). Nerve conduction study was normal. Extensive metabolic and genetic investigations performed included microarray comparative genomic hybridization (CGH), inborn error of metabolism profile, serum very low chain fatty acid (VLCPA), serum pyhctic acid, transferrin isoform pattern studies, white cell enzyme studies, urine purine and pyrimidine and cerebrospinal fluid (CSF) neurotransmitter profile were all unrevealing.

By age of 2 years 8 months, his development had regressed significantly to that of a 3-month-old level. He was fed through a nasogastric tube as swallowing was impaired. He developed generalised seizures at 4 years old and continued to regress. We reviewed our patient’s clinical presentation using Al-Maawali et al.’s algorithm on diagnostic approach of childhood-onset cerebellar atrophy [3]. Based on the MRI findings of progressive cerebellar atrophy, differential diagnoses were shortlisted down to INAD, congenital disorders of glycosylation (CDG) and mitochondrial disorders. Amongst these differentials, INAD best fitted our patient’s clinical presentation.

Genetic counselling and clinical exome sequencing study was done. The result showed the presence of compound heterozygote mutations in PLA2G6 gene, where novel mutations c. 196C>T (p. Gln66X) and c. 2249G>A (p. Cys750Tyr) were found. As the p. Gln66X is a truncating variant, it is considered as pathogenic. The variant p.Cys750Tyr was considered as “likely pathogenic” by using InterVar, a bioinformatics software tool for clinical interpretation of genetic variants which followed the ACMG/AMP 2015 guidelines. Computer prediction was performed with the Alamut Visual software v.2.7.2 from the Interactive Biosoftware which showed these were highly conserved nucleotides and there was a large physicochemical difference between Cys and Tyr. This variant was located in the protein domain: Acyl transferase/acyl hydro-lase/liposyphospholipase with various bioinformatics tool reports as followed: Align GVDG: C0, SIFT: Deleterious and MutationTaster: disease causing. These two compound heterozygous mutations of the PLA2G6 was compatible with the patient’s clinical phenotype of INAD. He died at the age of 6 years old. His younger female sibling developed similar presentation starting 1 year 6 months and also had the same compound heterozygous mutation in the PLA2G6. She was also found to have auditory neuropathy.

3. Discussion

To the best of our knowledge, this is the first reported case of INAD in South-East Asia. Neurophysiological findings are often normal or non-specific during early disease. Non-specific MRI abnormalities of progressive cerebellar atrophy like in our patient may be the only positive finding but can play an important role in guiding diagnosis.

The concept of selective vulnerability and pattern recognition on neuroimaging was first introduced by van der Knaap and Valk in 1991 [8]. This had led to the emergence of publications emphasizing the importance of pattern recognition on neuroimaging in the diagnostic approach to childhood-onset cerebellar atrophy and abnormalities. In 2013, Al-Maawali et al. proposed a diagnostic approach to childhood-onset cerebellar atrophy based on the integration of specific neuroimaging patterns with clinical features [3]. After which, the commonest conditions associated with different neuroradiological patterns were identified. This approach helped guide selection of appropriate genetic and metabolic investigations with a successful diagnosis yield rate of 47% of patients in the study.

We utilized this approach on our patient. Ophthalmology examination, baseline metabolic and neurophysiological studies were performed in tandem with brain MRI. Following unremarkable first-tier investigation results, we then proceeded to microarray CGH in view of presence of developmental delay and seizures as recommended in the algorithm. When the microarray CGH result was also reported as normal, we repeated the brain MRI and identified progressive cerebellar atrophy. Under the classification of progressive cerebellar atrophy, mitochondrial disorders, CDG and INAD were listed as possible differential diagnoses, of which, INAD best suited to our patient’s clinical features. Subsequent exome sequencing helped confirmed the diagnosis of INAD. Our case highlights the clinical utility of Al-Maawali’s diagnostic approach to cerebellar atrophy in children. Our case also highlights that progressive cerebellar atrophy can serve as a useful starting point for the investigation of underlying primary neurodegenerative disease. This is particularly useful in resource limited developing countries. This report also demonstrates the clinical utility of exome sequencing in rare undiagnosed diseases in the Asian population. Making an early diagnosis using this new diagnostic tool shortens the diagnostic odyssey for the affected patients and their families. This will help in the process of genetic counselling and potentially help in prenatal diagnosis for future pregnancies.

Recent research studies have reported that PLA2G6 is expressed in neuronal and non-neuronal embryonic tissues, suggesting that the gene has an integral role in brain development and neuronal maturation [9]. Genotype-phenotype correlation has been speculated but never clearly proved. It has been postulated that patients with severe INAD carry two null mutations in PLA2G6 which resulted in complete absence of protein, whereas patients who carry compound heterozygous missense mutations consistent with residual protein function exhibit a milder phenotype of the condition [9,10]. Our patient however carried a nonsense mutation and a missense mutation, thus it is likely these variants resulted in complete functional loss of iPLA2-VI enzyme and resulting in severe INAD.

Our case has also expanded the clinical phenotype of INAD as auditory neuropathy has not been previously reported as an associated feature of INAD. Auditory neuropathy was associated with and previously reported in other hereditary neurological conditions such as Charcot-Marie-Tooth (CMT) disease, Leber’s Hereditary Optic Neuropathy (LHON), Friedreich’s Ataxia and mitochondrial disease. An abnormal ABR test suggests impaired function at the level of inner hair cells, type 1 auditory neurons.
Fig. 1. Brain MRI index patient of sagittal T2-weighted (A1), coronal T2-weighted (B1) and axial T2-weighted (C1) at age 1 year 5 months old and repeat sagittal T2-weighted (A2), coronal FLAIR (B2) and axial T2-weighted (C2) at 2 years 2 months old (A2, B2, C2). The serial MRI showed progressive cerebellar atrophy evidenced by reduced cerebellar volume and increased interfolial spaces.
or auditory nerve. Therefore, damage and degeneration of the cochlear nerve and ascending auditory nerve itself may be the possible pathological reason for auditory neuropathy in INAD.

4. Conclusion

Our report reiterates the importance of having a systematic diagnostic approach in the investigation of children with neurodegenerative disease associated with cerebellar atrophy enabling targeted genetic analysis in these children. Our case also expands the clinical phenotype of INAD as it is the first case to describe a South-east Asian patient with INAD associated with auditory neuropathy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References


