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Case Report

Correlation between ARV1 Mutation and Early Infantile Epileptic Encephalopathy: A Second Case Worldwide

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Abstract

Early infantile epileptic encephalopathy (EIEE) syndrome occurs during early infancy, up to 3 months of age, and typically within the first 2 weeks. Previous data link EIEE-38 in humans to a deficiency of the ARV1 gene (ACAT related enzyme 2 required for viability 1; ACAT for Acyl-CoA:cholesterol acyltransferases). ARV1 is needed in sphingolipid metabolism and implies an important role for ARV1 in lipid/membrane homeostasis. Here we report the second case worldwide of ARV1 c.294+1G>A in a Lebanese infant (a homozygous girl diagnosed at the age of one year) inducing EIEE type 38. This severe phenotype is explained by the exon 2 skipping that encodes 40 amino acids in N-terminal zinc-binding motif in the AHD (the conserved ARV1 homology domain). By comparing the phenotypes of these In 2 individuals, we noticed almost identical phenotypes with some differences regarding the ophthalmic exam and the brain MRI (Table 1). However, these differences result most probably from genotypic or environmental elements that are not related to the intronic mutation itself.

Keywords: Early Infantile Epileptic Encephalopathy (EIEE); ARV1; Magnetic Resonance Imaging (MRI)

Introduction

Early infantile epileptic encephalopathy (EIEE) occurs during early infancy, up to 3 months of age and typically within the first 2 weeks [1]. EIEE is a rare disease including structural brain abnormalities and some monogenetic diseases (autosomal recessive disease). The former is highly damaging and associated with overlapping and severe phenotypes [2]. EIEE syndrome has different types, most commonly hemiconvulsions, focal motor seizures, or generalized tonic-clonic seizures (Yamatogi and Ohtahara 2002). The electroencephalograms of EIEE show a suppression burst pattern, consisting of polyspikes and bursts of high-amplitude spikes that alternate regularly with the periods of electric suppression. The tonic spasms concur with the mentioned bursts [3]. During both sleep and awake times, the pattern often stays the same. In most cases of epileptic encephalopathy syndromes, Patients die during infancy; thus, the prognosis is very poor.

In this article, we report the second case of a Lebanese girl diagnosed at the age of one year to have EIEE type 38, homozygous for an ARV1 variant c.294+1G>A. This second case is detected in a different family, with no relation with the Lebanese Australian family described by [4].

Case Report

This is a one-year-old girl patient, born vigorously at full term with a birth weight of 3.2 kg, by a repeat cesarean section to a G4P4A0L4 mother, second degree consanguineous parents, smooth pregnancy and delivery were noted, but excessive movements noticed in the last trimester.

The proband was the fourth child and the second daughter to consanguineous Lebanese parents. Family history revealed the paternal grandmother has a second-degree consanguineous parents. The maternal grandmother had three children (two male infants and one female infant) who died in the newborn period. Moreover, the mother and the father have second-degree consanguineous parents.

At two hours of life, she started to have eyes over and up rolling associated with tonic movement in both upper extremities; she had feeding difficulties with oral cyanosis; she was noted to have severe central hypotonia and head lag; At three months of age, she had a severe developmental delay with persistent eyes up rolling; Magnetic resonance imaging (MRI) brain and electroencephalogram (EEG) done and both were negative; Metabolic workup including serum and CSF amino acids, lactic acid, pyruvate and serum ammonia, acylcarnitine profile, neonatal screen and urine organic acids were all negative; Congenital Disorders of Glycosylation screening by serum transferrin isoelectric focusing was not available.

On her physical exam she had a head circumference on the 10th percentile, weight, and length on the 5th percentile; No dysmorphic features, pupils are mid dilated, not reactive to light with no tracking; Severe central hypotonia with peripheral spasticity mainly in the upper extremities with obligatory fisting hands; Deep Tendon Reflexes (DTR) +2 in all extremities; No evidence of organomegaly or skin marks.

At the age of four months, she presented with febrile status epilepticus and cerebrospinal fluids studies revealed Herpes simplex virus type 1. She received acyclovir for 6 months duration and was started at the age of 4 months on Levetiracetam (20 mg /kg/day and increased to 60 mg/kg/day) because of frequent intermittent focal tonic, myoclonic and tonic-clonic seizures; Seizures were partially controlled for one month, then at the age of five months Topiramate (8 mg/Kg/ day) was added with significant improvement.

An electroencephalogram (EEG) at 4 months of age showed diffuse generalized slowing and superimposed slowing in the left posterior head region and scattered left temporal and parietal spikes. At the age of 10 months, she started to have infantile spasms, and EEG showed modified hypsarrhythmia (Figure 1).

Figure 1

Note that she had recurrent viral infections, mainly respiratory and focal seizures were triggered by fever and infections.

MRI brain repeated at the age of 6 months and remains negative.

As follow up, the patient was maintained on Clonazepam (0.3 mg/Kg/day), Levetiracetam (60 mg/kg/day), and Topiramate (8mg/kg/day); Seizures were more of the form of tonic and focal in the upper and lower extremities. The patient had a persistent fever since the age of 6 months of 38.5 degree Celsius, and severe dehydration, chronic constipation, and then she passed away at the age of 2 Years 3 months.

Since the extended metabolic workup available in our institution was performed and was negative, we had to do the whole-exome sequencing, where we found a homozygous variant in the ARV1 gene c. 294+1G>A supporting the diagnosis of EIEE38.

Discussion

Early infantile epileptic encephalopathy 38, is a severe form of encephalopathy and it affects individuals with central hypotonia, refractory epilepsy, mental retardation, visual impairment and ataxia [5].

Previous data link EIEE in humans to a deficiency of the ARV1 gene (ACAT related enzyme 2 required for viability 1: MIM *611647). Human ARV1, located at 1q42.2, encodes a 271 amino acid transmembrane protein of the endoplasmic reticulum (ER) that plays an important role in lipid/membrane homeostasis. Two mutations in the ARV1 gene is already described in a male born to consanguineous Saudi Arabian parents and a female infant, born of consanguineous Lebanese parents. Both variants showed early infantile epileptic encephalopathy-38 (EIEE38). 3 children of a highly consanguineous Saudi Arabian family (08DGRC00077), with a homozygous missense variant (c. 565G>A; p.Gly189Arg) had early-onset epileptic encephalopathy, profound intellectual disability, ataxia, and unspecified visual impairment [6]. The Lebanese female infant with a homozygous splicing variant (c.294+1G>A, p.Lys59_Asn98del) presented a severe neurodevelopmental disorder [4].

ARV1-related disease should be distinguished from other EIES due to mutations in different genes, e.g. KCNQ2, SCN2A, SLC25A1, VARS, and PACS2. These disorders may share some clinical features including drug-resistant seizures within the first week of life, interictal epileptiform discharges, poor neurocognitive development and poor response to drugs.

Over time, EIEE can develop into West syndrome, and can furthermore be transformed into Lennox-Gastaut syndrome. The transition from one disorder to another is marked by a change in the electroencephalographic pattern; West syndrome is characterized by a transition from suppression burst to dysrhythmia, and further development to Lennox-Gastaut syndrome is associated with the appearance of a generalized, slow spike-wave. This interesting relationship among these three syndromes has conducted to the theory that they can be organized together as the age-dependent epileptic encephalopathies and that they include age-specific reactions in the brain to similar exogenous triggers [1,7,8].

ARV 1 is a putative lipid transporter of the endoplasmic reticulum that is conserved across eukaryotic species. The ARV1 protein contains a conserved N-terminal cytosolic zinc ribbon motif is the ARV1 homology domain, followed by multiple transmembrane regions anchoring it in the ER [9].

Acyl-CoA: cholesterol acyltransferases (ACAT) play key roles in the regulation of cellular cholesterol homeostasis and converts cholesterol to cholesteryl esters. ACATs are the most unusual enzymes because (i) they metabolize diverse substrates including both sterols and certain steroids; (ii) they contain two different binding sites for steroidal molecules. In mammals, there are two ACAT genes that encode two different enzymes, ACAT1 and ACAT2. Both are allosteric enzymes that can be activated by a variety of sterols. All sterols that possess the iso-octyl side chain including cholesterol, oxysterols, and various plant sterols could all be activators of ACAT [10]. It has been demonstrated that ARV1 (ACAT-related enzyme 2 required for viability 1) is required for sterol uptake and distribution in yeast [11] which implies an important role for ARV1 in lipid/membrane homeostasis [4]. ARV1 is a putative lipid transporter of the ER that is conserved in plants, yeasts, and mammals [11,12] and is expressed at a low level in all tissues [4,11]. ARV1 protein is integrated inside the ER membrane by three transmembrane domains. The protein is also characterized by a cytosolic N-terminal zinc ribbon motif (includes the 'ARV1 homology domain,' (AHD)). The first two domains are separated by a large loop region located inside the ER lumen. The C-terminus of ARV1 extends into the ER. Biochemical membrane studies performed on yeast deficient in ARV1 showed a reduction of sterol content in the plasma membrane [11,13,14]. The yeasts lacking ARV1 accumulate sterols in the ER and present defects in lipids synthesis [15]. In fact, ARV1 is needed in sphingolipid metabolism, a process known to be defective in other neurodegenerative diseases such as Niemann-Pick disease [6].

Moreover, despite the essential roles of sterols in cellular and biochemical activities, their accumulation is cytotoxic [11]. This variant c.294+1G>A described here has been previously reported and studied by Palmer., *et al.* 2016 in a Lebanese female infant. In this study, the author highlighted the importance of reporting additional affected individuals to define the phenotypic-genotypic spectrum for ARV1 deficiency.

Here we report the second worldwide case of ARV1 c.294+1G>A in a Lebanese infant. By comparing the phenotypes of these 2 individuals carrying the same ARV1 a variant, we noticed almost identical phenotypes (Table 1) with some differences regarding the ophthalmic exam and the brain MRI. However, these differences result most probably from genotypic or environmental elements that are not related to the intronic mutation itself. At the molecular level, this severe phenotype, in the c.294+1G>A patients,

is explained by the exon 2 skipping that encodes 40 amino acids (p.(Lys59_Asn98del) in N-terminal zinc-binding motif in the AHD [4]. This truncated protein failed to be rescued at low temperature and was not expressed at detectable levels in mammalian cells. In opposition, the previously reported p.(Gly189Arg) ARV1 variant that also presents a null allele was partially rescued the temperature-dependent growth [4]. These findings support the critical role of the conserved ARV1 homology domain (AHD) domain in ARV1 protein. The AHD is a zinc-binding motif characterized by two CXXC motifs separated by 20 amino acids [14]. In contrast to wild type human ARV1, neither variant expressed detectable levels of protein in mammalian cells. Mice with a neuronal deletion of ARV1 recapitulated the human phenotype, exhibiting seizures, and a severe survival defect in adulthood. Our data support ARV1 deficiency as a cause of autosomal recessive epileptic encephalopathy [4]. Moreover, new therapy with drugs playing in cholesterol homeostasis could be tested [16,17].

	Our patient	**Palmer., et al. 2016**
Fetal Movements	Vigorous Irritable since birth	Vigorous Irritable since 6 weeks of age
Roving eye movements/ Ophtalmic exam	Since birth Normal eye exam	Since 6 months of age Retinal dystrophy consistent with Leber congenital amaurosis, Hypermetropia
Tonicity	Central hypotonia Peripheral hypertonia Dystonia	Central hypotonia Peripheral hypertonia Dystonia
Seizures onset	Febrile status epileptics at 4 months of age Encephalitis - Herpes simplex virus type 1	Status epileptics at 4 months
Seizures type	Tonic, clonic, tonic-clonic, myoclonic, Spasms Refractory to treatment	Clusters, multifocal Refractory to treatment
EEG pattern	3 months : normal 4 months: slowing with epileptiform activity (focal spikes) 10 months : Modifies hypsarryhtmia	6 weeks: normal 4 months: slow with focal epileptiform activity 9 months: Modified hypsarrythmia
Feeding - Growth	Nasogastric tube since 6 months of age because of severe poor suck. Severe Failure to thrive Chronic constipation	Enteral tube feeding due to gastro -esophageal reflux, poor suck, and oromotor control. Growth was appropriate for age with adequate caloric intake
Fever – Infections	Persistent fever since the age of 6 months Recurrent bronchiolitis and pneumonia	No persistent fever Recurrent respiratory infections secondary to aspiration
MRI brain :	Normal at 3 and 6 months of age	Hyperintense signal in cerebral central tegmental tract on T2-weighted MRI with restricted diffusion at 7 months of age
Muscle biopsy	Not performed	Increase of type 1 to type 2 of fibers proportion and relatively smaller type 2 fibers.
Death age	2 years 3 months in status epilepticus	12 months in status epileptics

Table 1

Conclusion

The mutation c.294+1G>A detected in this case in one consanguineous Lebanese family was first described in a highly consanguineous Lebanese family living in Australia, suggesting a similar origin. This is the second case in the world and the clinical symptoms are very similar.

Molecular genetics is useful to help epileptologists or neurologists to make the right diagnostic and therapeutic decisions for treating children when the results of EEGs are not specific.

Moreover, this study shows that the treatment used is not sufficient (Clonazepam, Levetiracetam, Pyridoxine, and Topiramate). Further studies will improve our understanding of early infantile epileptic encephalopathy-38 (EIEE38) and lead to improvements in genetic diagnosis, treatment, and development of new drugs for patients with neuropsychiatric diseases.

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