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Developmental and Epileptic Encephalopathy-5 (DEE5) & Aicardi Syndrome associated with A Novel Mutation in SPTAN1 Gene, a Case report

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Abstract

Introduction: Heterozygous mutation in the SPTAN1 gene on chromosome 9q34 causes developmental and epileptic encephalopathy-5 (DEE5) characterized by global developmental delay and the onset of tonic seizures or infantile spasms in the first months of life. Aicardi syndrome is a rare neurodevelopmental disorder characterized by the triad of infantile spasms, central chorioretinal lacunae and agenesis of the corpus callosum. It is considered mysterious due to its unknown aetiology; the causative mutation might be related to the X chromosome as only females are affected, yet no studies have identified pathogenic variants on the X chromosome to date.

Case Report: A female infant presented with myoclonic seizures and global developmental delay, right eye anophthalmus, left eye microphthalmos, cleft lip, cleft palate, marked hypomyelination of brain and absence of corpus callosum and abnormal sleep EEG and missense variant NM-001130438.3(SPTAN1): c.3034C>T (p.Arg1012Cys) reported by whole genome exon sequencing, which has not been reported previously as a pathogenic variant nor as a benign variant to the best of our knowledge.

Conclusion: This report will contribute to the phenotype associated with the SPTAN1 gene mutations and developmental and epileptic encephalopathy-5. Newer Genome sequencing studies might identify the underlying genetic cause and may help in better managing rare genetic disorders. Additional studies are needed to determine whether this missense mutation is associated with such a specific phenotype.

Keywords: Developmental And Epileptic Encephalopathy (DEE); Epileptic Encephalopathy (EE); SPTAN1; p.Arg1012Cys

Abbreviations

DEE5: Developmental and epileptic encephalopathy -5; SPTAN1: Spectrin Alpha, Non-Erythrocytic1; ARG : Arginine; CYS :cysteine; DEE : Developmental And Epileptic Encephalopathy; EE: Epileptic encephalopathy; ID: Intellectual Disability; IS: Infantile Spasms; ILAE: International League Against Leprosy; EEG: Electro

Encephalography; MRI: Magnetic Resonance Imaging; HC: Head Circumference; Hb: Hemoglobin; PHPV: Persistent Hyperplastic Primary Vitreous; 2D ECHO: 2Dimensional Echocardiography; SD: Standard Deviation; OMIM: Online Mendalian Inheritance in Men; ExAC: Exome Aggregation Consortium; SIFT: Sorting Intolerant From Tolerant; GERP: Genomic Evolutionary Rate Profiling; ACMG: American College of Medical Genetics.

Introduction

Targeting and maintenance of groups of proteins at specific membrane domains of neurons like axons and synapses and assembling of these membrane domains by spectrin has key importance for brain function and development. Heterozygous mutation in the SPTAN1(Spectrin Alpha, Non-Erythrocytic 1) gene on chromosome 9q34 results in developmental and epileptic encephalopathy-5 (DEE5); a neurologic disorder characterized by global developmental delay and onset of tonic seizures or infantile spasms in early infancy & severely impaired psychomotor development with the lack of visual attention, poor head control, feeding difficulties, microcephaly, and spastic quadriplegia and refractory seizures. EEG shows hypsarrhythmia or other abnormalities leading to electroclinical diagnoses of West syndrome or otherwise [1]. Brain imaging may show marked cerebral atrophy, hypomyelination or partial or complete agenesis of the corpus callosum consistent with the diagnosis of Aicardi syndrome. As per the ILAE classification of epilepsies 2017, the conditions in which cognitive development and behaviour are impaired independent of the epilepsy onset and epilepsy is characterized by a high frequency of seizures and abundant epileptiform abnormalities, the term "developmental and epileptic encephalopathy'' (DEE) is more appropriate [2].

Aicardi syndrome (OMIM 304050) is a rare condition with a worldwide incidence of ~ 1 in 100 000 live births affecting only females [3] & few males with 47XXY chromosomes [4]. Technologies examining candidate genes, copy number variation, skewing of X-chromosome inactivation, and whole-exome sequences could not identify strong genetic candidates as etiology of Aicardi syndrome to date.

Aicardi syndrome, characterized initially by a triad of signs: agenesis or dysgenesis of the corpus callosum, distinctive chorioretinal lacunae, and infantile spasms, has now been known to have complex neurological and peripheral manifestations including heterotopias, polymicrogyria, intracranial cysts, cerebellar abnormalities, and severe and often intractable complex seizures, optic nerve defects and anophthalmia [5]. A variety of other neuronal migration defects, eye anomalies and somatic features, including skin, skeletal, and craniofacial systems have also been reported with Aicardi syndrome. Excess skewing of X-inactivation in females with Aicardi syndrome, suggests that X-linked gene(s) are involved in Aicardi syndrome phenotypes [6]. No studies have identified pathogenic variants on the X chromosome to date. Changes in genes TEAD1 and OCEL1 in two girls with Aicardi suggested in one report were not confirmed in a large cohort of other girls with Aicardi syndrome, hence these genes do not seem to be the aetiology of this extremely rare disorder [7,8].

We report a case with SPTAN1NM_001130438.3 gene transcript having a mutation on chromosome 9, Exom 22 with missense variant NM-001130438.3(SPTAN1): c.3034C>T (p.Arg1012Cys), which has not been reported previously as a pathogenic variant nor as a benign variant to the best of our knowledge; with the phenotype of Aicardi syndrome.

Case Report

A full-term appropriate for gestational age female infant; born at our hospital (birthweight 2.5 kg, HC 34cm) out of a non-consanguineous marriage, to a 24-year-old mother by normal vaginal delivery with an unremarkable antenatal history, admitted at birth for feeding difficulty due to cleft lip and cleft palate and discharged after 2 days; presented at 3 months of age with complaints of infrequent seizure-like activity (lasting for 2-3 minutes) In form of flexion at neck and extension at arms with hips and knees flexed; since last 1 ½ month; labelled as myoclonic seizures after observation (Figure 1).

Figure 1: Ocular Abnormalities, Cleft Lip.

On admission her weight was 3.5 kg, HC- 37 cm, and no neck holding or social smile; occasional cooing and developmental delay were noted. She did not have any neurocutaneous stigmata. On neurological examination, she was not fixing or following objects and had hypotonia and partial neck holding. Her father said that she reacts to loud noises.

Complete blood count of the child suggested Hemoglobin (Hb) 11.7 g/dL, platelet count 490×109/L, total leukocyte

count 11.43×109/L with polymorphs 49% lymphocytes 46% and eosinophils 2%. Blood sugar (85 mg/dL), urea (21 mg/dL), creatinine (0.58 mg/dL) & electrolytes were normal. SGOT (47 U/L), SGPT (18 U/L), alkaline phosphatase (604 U/L), and S Calcium (10.1 mg/dL) phosphorus were normal. C-reactive protein was reactive. Metabolic workup, including liver panel, serum lactate and pyruvate, plasma ammonia, serum and urine amino acids, urine organic acids, serum biotinidase, Cerebrospinal fluid analysis for cell count, glucose, protein, bacterial and viral culture, lactate, pyruvate, and amino acids Blood, urine, and cerebrospinal fluid cultures were normal.

Chest X-ray & 2D ECHO were normal. Ultrasound abdomen revealed mesenteric lymphadenopathy. Ultrasound B scan revealed right eye anophthalmus and left eye microphthalmos with Persistent Hyperplastic Primary Vitreous (PHPV). Sagittal T1-weighted MRI Brain revealed shows complete absence of the corpus callosum. The cingulate sulcus is absent, and the medial hemispheric sulci reaches the third ventricle radially. Axial T1-weighted MRI revealed that the lateral ventricles parallel and continuation of the interhemispheric fissure with the third ventricle; colpocephaly with the occipital horn of the right ventricle suggestive of agenesis of the corpus callosum (Figures 2a-d).

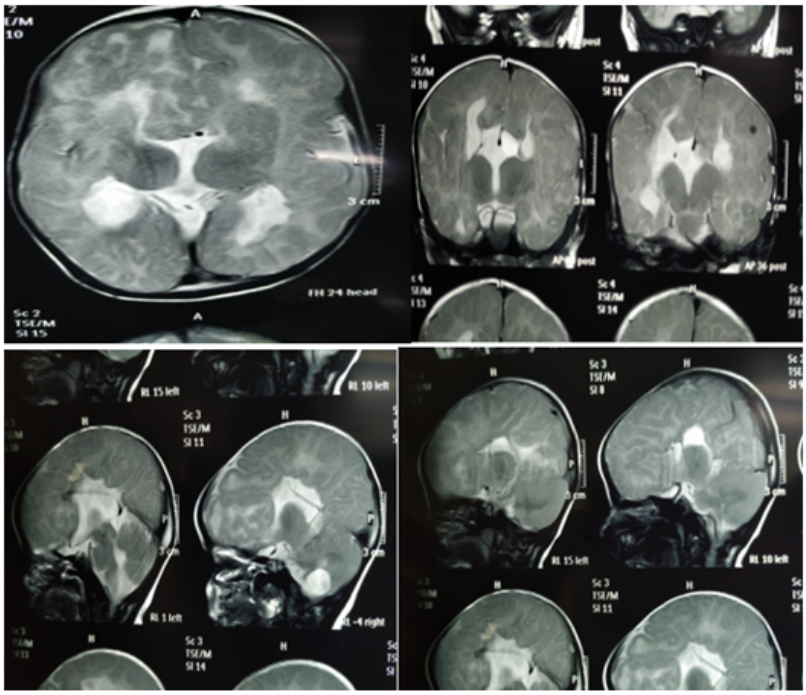

Figure 2: Mri Brain Showing Hypomyelination and Absence of Corpus Callosum; **A,B:** Sagittal T1-weighted MRI Brain; **CD:** Axial T1-weighted MRI.

Sleeping EEG was abnormal suggesting symmetrical synchronous 2-4 Hz, 40-60 δ activity intermixed with 4-8 Hz, 30-40 UV θ rhythm with centro-temporal continuous slow spike-and-wave discharges bilaterally and intermittent-sharp and slow spike and wave discharges. she was discharged with clinical diagnosis of Aicardi Syndrome and whole genome exome sequencing sent.

She again presented at 5 months of age with a history of respiratory distress in the form of increased respiratory rate for 3 days and similar seizures; though less often. She was being fed buffalo milk with a spoon & underweight (< 2SD - 4 kg). She had tachypnea and crepitations on auscultation. She had a global developmental delay.

Complete blood count of the child suggested Hb 11.8 g/dL, platelet count 2×109/L, leuco-cytosis (total leukocyte count 30.28×109/L), polymorphs 80% lymphocytes 15%, monocytes 4% and eosinophils 1%. Blood sugar (85 mg/dL), urea (74 mg/dL), creatinine (0.65 mg/dL) & electrolytes were normal. SGOT (107 U/L), SGPT (42 U/L), alkaline phosphatase (604 U/L), and S Calcium (10.1 mg/dL) phosphorus were normal. HRCT chest revealed confluent areas of ground glass opacities and consolidation in dependent regions in both lungs. Multiple enhancing soft tissue density lesions were noted in the right paratracheal region and subcarinal region largest measuring 15x10mm in the right paratracheal region and 17x10mm in the subcarinal region – likely lymph nodes. Suggestive of infective aetiology likely – COVID pneumonia. Whole genome exon sequencing (Table 1).

No pathogenic or likely pathogenic variants causative of the reported phenotype were identified						
Genes and transcript	**Variant**	**Location**	**Zygosity**	**Disorder (OMIM)**	**Inheritance**	**Classification**
SPTAN1 NM_001130438.3	c.3034C>T (p.Arg1012Cys)	Exon 22	Heterozygous	Developmental and Epileptic Encephalopathy5 -613477	Autosomal Dominant	Uncertain Significance

Table 1: summarizes the Whole genome exon sequencing reporting the missense variant. The child was managed and discharged as per protocol and is now under follow-up.

Discussion

SPTAN1 was cloned in 1987 and termed alpha-fodrin from a human lung fibroblast cDNA library as duplication and rapid divergence of an ancestral alpha-fodrin-like gene were supposed to result in the evolution of mammalian erythroid alpha-spectrin. A de novo heterozygous 3-bp in-frame deletion (c.6619_6621delGAG) in exon 50 of the SPTAN1 gene was identified In a Japanese girl with DEE5 with the clinical diagnosis of West syndrome [9]. In a Japanese boy with DEE5 with West syndrome, Saitsu H, et al. [8] identified de novo heterozygous in-frame duplication (nucleotides 6923-6928) in exon 53 of the SPTAN1 gene, resulting in arg2308 and met2309 duplications within the last spectrin repeat. There was profound mental retardation, poor visual attention, lack of speech development, and spastic quadriplegia in the patient. MRI brain showed widespread hypomyelination and atrophy in the cortex, corpus callosum, brain stem, and cerebellum [9].

Hamdan FF, et al. [10] reported a 3-bp in-frame deletion (6605_6607) in the SPTAN1 gene in an 11-year-old French Canadian boy with DEE5. The patient did not have a history of early infantile spasms except febrile seizures at 16 months of age & later developed mild generalized epilepsy and severe intellectual disability. Brain MRI revealed severe atrophy of the cerebellum and mild atrophy of the brainstem [10]. In a Japanese boy with DEE5 with West syndrome, Nonoda Y, et al. [11] identified a de novo 9-bp duplication in the SPTAN1 gene (c.6908_6916dup), which resulted in a 3-residue duplication (Asp2303_Leu2305dup) in the last spectrin repeat (Asp2303_Leu2305dup). The patient had onset of epileptic spasms at age 3 months [12]. The spectrin are cytoskeletal proteins with a highly conserved 106-amino acid repeat structure; the arginine residue at codon 1012 of SPTAN1 is conserved in all mammalian species & the nucleotide c.3034 in SPTAN1 is predicted conserved by GERP++ and PhyloP across 100 vertebrates [12].

Eight pathogenic missense variants are present in SPTAN1, indicating that missense variants play a significant role in disease. The p.Arg1012Cys missense variants are predicted to be Damaging by both SIFT and polyphan 2 [12,13]. Using the ExAC dataset, missense badness is calculated as the normalized fold difference between observed and expected substitutions. MPC (for missense badness, polyphan 2, and constraint) is a score that combines orthogonal deleteriousness metrics to determine whether a missense variant is deleterious. Variants with MPC >2 have a rate nearly 6 times higher in cases than in controls. The MPCs with an intermediate value (1<_ MPC <2) have a more modest excess in cases. With a Z score of 5.52, missense badness score of 0.68, and MPC score of 2.14, SPTAN1 has a high number of missense variants.

The genotype-phenotype correlation in the SPTAN1 gene is being explored with newer cases being reported. Even the severest patient with SPTAN1 mutation did not show the agenesis of the corpus callosum or ocular hypoplasia. The p.Arg1012Cys variant is novel (not in any individual) in gnom AD in 1kG. The missense mutation reported in our case has been classified as having uncertain significance (SPTAN1chr9:131353783C>T-Uncertain Significance). The mutation observed in our patient likely affects the function of the SPTAN1. However, since her symptoms were quite different from other patients with SPTAN1 mutation, using historical mutation databases or in silico validation is not enough to prove that this SPTAN1 mutation caused this patient's symptoms.

Our patient had distinct phenotypes with ocular abnormalities such as right eye Anophthalmus and left eye microphthalmos, cleft lip and cleft palate. No other case of Aicardi syndrome with this phenotype has been reported in the pretext of this genotype to the best of our knowledge. The diagnosis of Aicardi syndrome is based exclusively on clinical findings. Modified diagnostic criteria include either the presence of the classic triad or the presence of two of the classic triad plus at least two other major or supporting features. Diagnostic criteria of Aicardi syndrome have been modified [12]. Neurological findings now include cortical

malformations, cysts, gross cerebral asymmetry, and 'split-brain' on electroencephalography. Ophthalmic features now recognised are optic nerve coloboma or hypoplasia and microphthalmia [13]. The interpretations of this exon sequencing report result should be done in the context of this individual's clinical and biochemical profile. Sanger sequencing in future is recommended for parents to confirm the significance of the identified variant. Variants identified were classified as VOUS based on the available evidence and as per ACMG Guidelines [14]. Prenatal testing is not recommended due to limited/ conflicting evidence of association with the disease. If the variant is reclassified in the future as pathogenic or likely pathogenic variants, prenatal testing or pre-implantation genetic diagnosis may be available.

A multidisciplinary approach including a paediatric neurologist experienced in managing infantile spasms and medically refractory epilepsy is essential for treatment. Aicardi syndrome is not known to transmit horizontally, and the recurrence risk to siblings is less than 1%. While prenatal ultrasound or intrauterine MRI are not diagnostic. Conclusion- If developmental impairment and epileptic activity are associated with encephalopathy and epileptic discharges on EEG - developmental and epileptic encephalopathy should be considered. Early recognition often improves outcomes by selecting the best treatments timely. Recommendations for prenatal testing must be discussed with a clinical geneticist or a genetic counsellor. Genetic counselling is recommended. Confirmation of the above missense mutation by future studies is important in the pretext of yet undefined aetiology of this syndrome. Genes are not the destiny; environment, epigenetics and newer sophisticated diagnostic techniques may play a vital role in prevention, appropriate management, better quality of life and prognosis. Underlying genetic factors often result in developmental delay following the defects but epileptic encephalopathy affects the development furthermore. Timely and effective treatment of epileptic encephalopathy is key to developmental progress.

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