X linked Infantile Epileptic Encephalopathy due to SMC1A Truncating Mutation

Dear Sir,

Till date, PCDH19 was the only well described X linked disorder associated with the syndrome of 'Epilepsy with Mental Retardation limited to Females (EFMR).[1] Recently pathogenic truncating variants in SMC1A gene have been reported in females with similar presentation. Their characteristic phenotype differs from SMC1A related Cornelia de Lange syndrome (CdLS).[2,3] We report a patient with a novel de novo pathogenic SMC1A truncating variant.

Case Report

A 3-year-old girl born to nonconsanguineous parents, with normal birth and motor development till 8 months of age, presented with multiple seizures starting at the age of 8 months. Initially, she had few brief generalized tonic, clonic (GTC) seizures. They were followed by flexor spasms involving head and upper extremity, with squirming of face. The spasms occurred every 10 seconds in clusters lasting for few hours, at irregular intervals. She also had multiple episodes of behavioural arrest with impaired awareness lasting for few seconds daily. She regressed developmentally after seizure onset.

On examination, she had short stature, microcephaly, coarse facies, bushy eyebrows with long eyelashes, broad depressed nasal bridge, short shallow philtrum, low set posteriorly rotated ears with flattened midface, hypertrichosis, and short hands [Figure 1a-c]. Her developmental quotient was 55, with autistic features, and did not have any receptive or expressive language. Her systemic examination was normal.

Her first sleep EEG showed frequent generalised bursts of spike and wave complexes with background suppression [Figure 1d] suggestive of modified hypsarrhythmia. Audiometry, metabolic screening (TMS) and MRI were normal. We classified her seizures as focal and generalized seizures and epilepsy as epileptic and developmental encephalopathy.[4] We started her on ACTH which resulted in seizure reduction and improvement on EEG [Figure 1e]. Thereafter despite adding Topiramate, Levetiracetam, Vigabatrin and Valproate consecutively, seizure were only partially controlled. She achieved complete seizure freedom only after starting Modified Atkins Diet (MAD) along with Zonisamide and Valproic acid and remained seizure free for a year. Recently she had seizure recurrence with cluster of GTC seizures. She regained some of the lost mile stones during the seizure free period but continued to have developmental delay with maximum impairment in speech and communication.

In view of pharmacoresistent seizures, genetic test in form of a neurology panel was conducted at a commercial laboratory. A novel pathogenic heterozygous deletion in the SMC1A gene was identified by this focused next generation sequencing on the illumina (MiSeq and NextSeq) platform. The variant (c. 3305_3312del) was predicted to cause a frameshift and consequent premature termination of the protein (p.Asn1102ArgfsTer53) resulting in loss-of-function. Moreover, due to introduction of premature stop codon, this aberrant transcript would likely be targeted by nonsense mediated mRNA decay mechanism. The variant was considered to be de novo as both parents tested negative on Sanger sequencing.

Discussion

The PCDH19 phenotype is a well-defined X linked inherited epilepsy syndrome. It is characterized by normal early development, infantile onset epilepsy with fever sensitive, convulsive seizure clusters at the onset and multiple seizure types later.[1] Some cases may show developmental stagnation or regression while rest (40%) develop normally.[2] Dysmorphism and congenital anomalies have not been reported in any.

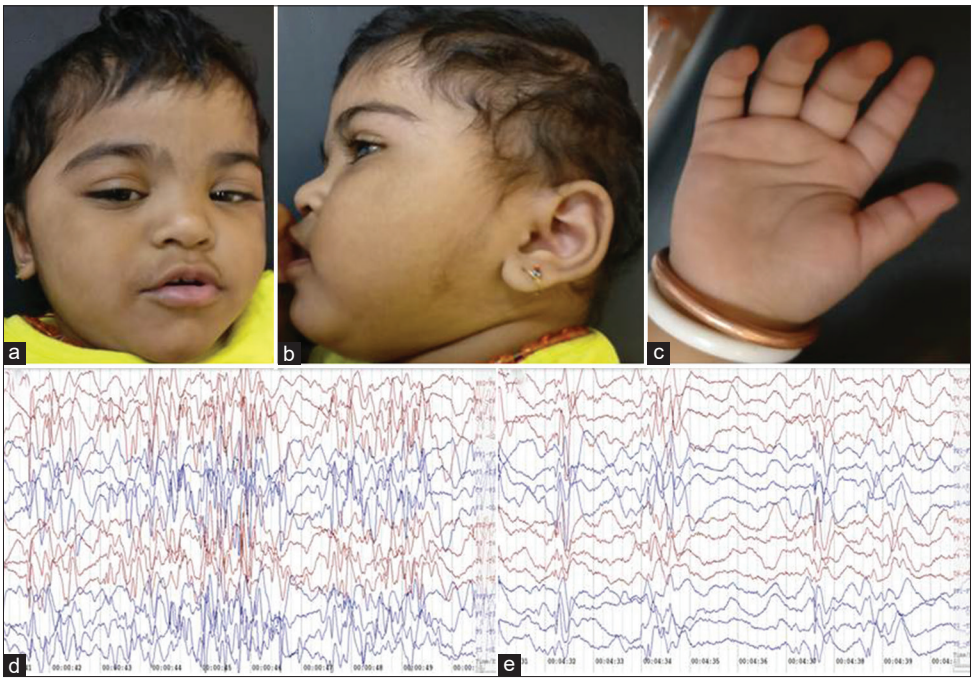

Figure 1: Phenotype and EEG study of the patient. Phenotype and EEG study of the patient: Facial appearance (a, b) and short hand (c) of the patient. First EEG (d) showing frequent generalized epileptic activity followed by suppression and subsequent EEG after starting ACTH (e) showing improved background and decreased epileptic activity

Table 1: Comparison of our patient with previously reported cases and differentials

Condition	EFMR 1	X-linked Cornelia de Lange syndrome 5	New phenotype Reported (2,3)	Our patient
Sex predisposition	Females only	Males & Females (Females have milder phenotype)	Females only	Female
Phenotype Severity	Moderate phenotype	Milder phenotype	Moderate to Severe phenotype	Moderate phenotype
Anthropometry	Nil	Microcephaly, Short stature, Small hands and feet	Microcephaly, Short stature, Small hands and feet	Microcephaly, Short stature, Small hands
Facial Gestalt	None described	synorphys, down slanting palpebral fissures, anteverted nares, hirsutism	straight thick eyebrows, anteverted nares, flattened midface, shallow philtrum, Hirsutism	Thick eyebrows, anteverted nares, Broad depressed nasal bridge, low set ears, flattened midface, hirsutism
Congenital Anomalies	Nil	Cardiac (hypertrophic cardiomyopathy, pulmonary stenosis) Vertebral, Gastrointestinal	Cardiac (ASD, VSD), Vertebral Palatal	Nil
Development	Developmental delay after seizure onset	Developmental delay since birth	Severe developmental delay since birth, No expressive language	Severe developmental delay since birth, No expressive language, Autistic traits
Epilepsy	Epileptic Encephalopathy (100%) Fever sensitive seizure clusters	Mild - moderate epilepsy (4 - 23%)	Epileptic Encephalopathy (100%), Afebrile seizure clusters	Epileptic Encephalopathy, Afebrile seizure clusters
Genotype	PCDH19 mutation	Missense/small in-frame deletions	Truncating mutation	Truncating mutation

Recently, 15 females with truncating pathogenic variants in SMC1A have been described with early infantile onset (median 4.5 months) drug resistant epilepsy. Generalized tonic, clonic seizures were predominant at onset. Multiple other generalized seizures like eyelid myoclonia, myoclonic, tonic, spasms, atypical absence, drop attacks and focal seizures including NCSE developed later. Majority of the seizures occurred in clusters and there was no fever sensitivity. All showed moderate to severe global developmental impairment prior to seizure onset and none developed expressive language. They had a distinct phenotype with short stature, microcephaly, flattened midface, short upturned nose and a shallow philtrum. Cardiac, vertebral and palatal anomalies were seen in few.[2,3]

Missense variants and small in frame deletions in SMC1A present with non-classic phenotype of CdLS. It is characterized by fuller eyebrows, rounder face and less prominent shortening of the nasal bridge with partial epilepsy amenable to standard therapy (45%) and mild cognitive delay.[5]

Our patient showed dysmorphisms, developmental impairment and epilepsy similar to previously described cases with pathogenic SMC1A truncating variants but did not have any congenital anomalies [Table 1]. She had generalized tonic, clonic seizures only at onset and at the time of recurrence but her predominant seizure type was epileptic spasms, which has been described only in 3 cases so far. As reported, her seizures were resistant to multiple AEDs, but she achieved seizure freedom with normalization of EEG on a combination of MAD and drugs. A similar response to Ketogenic Diet (KD) has been previously described in 2 cases.[2]

The MAD is a less restrictive alternative to the traditional ketogenic diet. It is started on an outpatient basis without a fast and well tolerated as it allows unlimited protein and fat, without restricting calories or fluids.[6] In resource constraint settings of a developing country like India, it can be easily used with limited dietician support, as it does not require tedious calculations.[7] A significant response has been documented in infantile spasm refractory to antiepileptics and steroids.[8] No statistical significance has been demonstrated in the beneficial outcomes of classical KD and MAD even in symptomatic etiologies including genetic disorders.[9] Ours is the first reported case of pathogenic SMC1A truncating variant from India and the only one amongst these SMC1A in literature where MAD has been tried and found beneficial.

Conclusion

Pathogenic truncating variants in SMC1A is an emerging X linked early onset epileptic and developmental encephalopathy. It should be considered as an important differential in females with severe developmental delay and drug resistant epilepsy in clusters, along with PCDH19 associated syndrome. We recommend early trial of MAD along with drugs in the management of epilepsy in these cases.

Acknowledgement

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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