Evaluation of genetic, electrophysiological and clinical characteristics of patients followed up with the diagnosis of Developmental Epileptic Encephalopathy: A single center experience

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INTRODUCTION

The term 'developmental and epileptic encephalopathy (DEE) is defined as a group of diseases in which underlying genetic cause leads to both developmental delay and epileptic activity. The classification of underlying genetic causes has provided individualized targeted treatments and the identification of novel drug targets for pathogenic mutations. .

OBJECTIVES

The aim of this study was to evaluate the clinical, electrographic and genetic characteristics of patients with DEE and also to discuss treatment suggestions for targeted mutations.

MATERIALS & METHODS

We retrospectively evaluated 44 consecutive children with monogenic DEE whose genotype-phenotype relationship was shown at the pediatric neurology division of Baskent University, Adana Hospital between 2012-2022. Patients with ALDH7A1, TSC1, TSC2 and SCN1A-related DEE, Rett Syndrome and metabolic DEE were excluded as they were a part of different projects.

AGE AND SEX		
Sex Total:44	Female n:22 (%50)	Male n:22 (%50)
Age	Mean 56.9 months ± 34.8 months	
Age of onset the seizure	Median: 6 months (25-75. quarter; 2-12.7 months) (min-max; Newborn-108 months)	
Age of genetic diagnosis	Median: 36 months (25-75. quarter; 18-54 months) (min-max; 3-132 months)	

RESULTS

DIAGNOSTIC METHOD						
aCGH n:1 (%2,27)	Inherited diseases panel n:2 (%4,54)	Single gene n:1 (%2,27)	Epileptic encephalopathy gene panel n: 15 (%34)			WES n:25 (%56,8)
GENETIC RESULTS						
KCNQ2 n:4 (%9)	CACNA1A n:3 (%6,8)	SCN2A n:3 (%6,8)	SCN9A n:3 (%6,8)	STXBP1 n:3 (%6,8)	GABRB3 n:2 (%5)	CDKL5 n:2 (%5)
EEF1A2 n:1 (%2,2)	NECAP1 n:1 (%2,2)	SPTAN1 n:1 (%2,2)	TUBB2A n:1 (%2,2)	PRICKLE2 N:1 (%2,2)	CHD2 n:1 (%2,2)	FGF12 n:1 (%2,2)
ITPA n:1 (%2,2)	SIK1 n:1 (%2,2)	YWHAG n:1 (%2,2)	KCNB1 n:1 (%2,2)	ST3GAL5 n:1 (%2,2)	FOXG1 n:1 (%2,2)	PLAG26 n:1 (%2,2)
SCN1B n:1 (%2,2)	PRRT2 n:1 (%2,2)	PCDH19 n:1 (%2,2)	ATXN2 n:1 (%2,2)	ARX n:1 (%2,2)	GRIA2 n:1 (%2,2)	CACNA1H n:1 (%2,2)
GRIN2D n:1 (%2,2)	GABBR2 n:1 (%2,2)	BRAT1 n:1 (%2,2)				

DISCUSSION

Lacosamide is a newer AED, enhances slow inactivation of voltage-gated channels and is mostly used for partial seizures. In the literature, monotherapy response with lacosamide has been demonstrated in the CHD2-related Jeavons syndrome even if lacosamide response in DEE has not been specified yet. Our patient with de novo heterozygous mutation in CHD2 gene was followed up seizure-free after lacosamide was added then the other AED were gradually discontinued. In our study, we had 3 patients with STXBP1 mutation, but we experienced seizure-free status in only 1 of them with lacosamide.

Folinic acid is an activated form of folic acid/vitamin B9, which is required for methylation and purine synthesis, and plays a role in the initiation of mitochondrial protein synthesis. NECAP1 is a key element in clathrin-mediated endocytosis and has been reported previously to cause DEE type 21. However, there are only 4 articles in the literature about epilepsy and NECAP1. We encountered a folinic acid response in the patient with NECAP1 mutation dramatically and she is seizure-free for about 3 years. However, NECAP1 mutation of our patient had a heterozygous variant, considering that in-familial penetrance may differ in WES analyses and no other genetic cause could be shown to explain the clinic, we thought that we could explain the patient's clinical condition with this mutation.

DISCUSSION

However, since we could not find any pathogenetic mechanism explaining the relationship between folinic acid and NECAP1 mutation, further studies should be done for the NECAP1 mutation and its pathogenesis. On the other hand, we suggest that folinic acid should be tried in cases with NECAP1 mutation, and the presence of response should be tested in more cases. In another interesting patient, the clinical findings were consistent with DEE and a heterozygous mutation in PRICKLE2 gene was found, and this mutation was not previously associated with DEE in the literature. We also observed folinic acid response in this patient. PRICKLE2 localizes to the post-synaptic density, and interacts with post-synaptic density protein 95 and the NMDA receptor. Bayat et al reported that PRICKLE2 is involved in human neuronal development and pathogenic variants cause neurodevelopmental delay, behavioral difficulties and epilepsy in humans. Seizures in Bayat et al human subjects were not a recurrent feature but when present they were also easily treatable. It has been suggested that the PRICKLE2 homolog is consistently expressed in postmitotic neurons in early embryogenesis and plays a role in neuron formation during brain development. For this observation, whether PRICKLE2 is a good candidate gene in the context of folate deficiency and neural tube defects (NTD) is being investigated. Therefore, it may be speculated that a folinic acid response in our patient is due to the possible effects of this gene on the folate mechanism. However, additional studies are needed to further support this claim, to delineate the phenotypic spectrum, to inform genotype-phenotype correlation and to pave the way toward precision medicine for PRICKLE2-related illness.

Primidone is a first-generation barbiturate type AED. The mechanism of action is not well-demarcated, but it appears to bind centrally with voltage-gated sodium channels and inhibits the monotonous firing of action potentials. We thought that primidone response in one of our patients with SCN2A mutation also might be occur through this pathway, and we want to share our experience as a contribution to the literature.

CONCLUSION

Advanced genetic studies contribute to a better understanding of the course of the disease by identifying targeted treatment options in DEE**. In this study, the relationship between heterozygous PRICKLE2 mutation and DEE was shown for the first time** and **we report the first case of DEE associated with the heterozygous NECAP1 mutation in literature. Moreover, the most important contribution of this study is the effective drug experience that has been reported for the first time that can be a targeted treatment options for CHD2, STXBP1, NECAP2, PRICKLE2 and SCN2A mutations**.

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