Clinical Spectrum of Voltage-gated Sodium Channelopaties; One-center Experience

Hale Atalay Celik[1], Abdullah Sezer[2], Ülkühan Öztoprak[1], Erhan Aksoy[1], Deniz Yüksel[1]

[1] University of Health Sciences Turkey, Dr Sami Ulus Maternity and Child Health and Diseases Research and Training Hospital, Department of Pediatric Neurology

[2] University of Health Sciences Turkey, Dr Sami Ulus Maternity and Child Health and Diseases Research and Training Hospital, Department of Medical Genetics

ICNC 2022 17th INTERNATIONAL CHILD NEUROLOGY CONGRESS
ANTALYA, TURKEY | OCTOBER 3-7, 2022

Introduction

Voltage-gated sodium channels(VGSC) can be found mainly in the central nervous system(CNS), peripheral nervous system(PNS), skeletal and cardiac muscles. Structurally, VGSCs are composed by an alpha and one or more beta subunits. There are nine different sodium channel α-subunit genes that code for Nav1.1 to Nav1.9 channel proteins. SCN1A to SCN5A encode Nav1.1-Nav1.5 proteins, while SCN8A to SCN11A encode Nav1.6-Nav1.9 proteins, respectively. On the other hand, five different ß-subunit proteins have been reported, namely: ß1 (product of SCN1B), ß1B (product of SCN1B splice variant), ß2 (SCN2B), ß3 (SCN3B), and ß4 (SCN4B). The mutations at these genes named as sodium chanelopathies. In this study, we aimed to describe the clinical spectrum of voltage-gated sodium channelopathies in our patients.

Material & Method

We investigated recordings of the patiens in the University of Health Sciences Turkey, Dr Sami Ulus Maternity and Child Health Diseases Training & Research Hospital, department of the Pediatric Neurology, retrospectively. The patients with sodium chanelopathies, whose diagnoses' were genetically confirmated were included in the study.

Results

We identified 26 patients with VGSC mutations. The most common mutation was SCN1A(69% n:18) and SCN1B(n:2), SCN3A(n:2), SCN4A(n:1), SCN8A(n:1), SCN9A(n:1) and SCN11A(n:1) were also detected(figure1). %57(n:15) of the cases were male.

The most common phenotype was Dravet Syndrome(DS)(75% n:14) in the 24 cases(SCN1A, SCN1B, SCN3A, SCN8A and SCN9A) whose mutations are related with epilepsy. Furthermore, developmental and epileptic encephalopathy(n:5), Genetic Epilepsy with Febrile Seizures plus (GEFS+)(n:3), complicated febrile seizure(n:1) and epilepsy(n:1) were also identified. Although, 6 of them were genetically benign/variant of uncertain significance(VUS), they were clinically compatible with their mutations. Developmental milestones were delayed/regressed in the majority of cases (%75(n:18)), however 6 of them were developmentally normal(figure 2 and figure 3). Accompanying disorders were spesific learning disability, attention deficit and hyperactivity disorder and autism spectrum disorder.

There were 2 more cases who were identified peripheric neuropathy and penduler nystagmus in the SCN4A and SCN11A mutation, respectively.

Discussion

SCN1A mutations are the most prevalent amongst all VGSCs mutations in epilepsy and most DS and GEFS+ cases have mutations in SCN1A, as in this study.

In one study, 50% of all DS cases arise from missense mutation, the most common mutation could be detected in this study was missense mutation, similarly.

Zhang et al. detected that, only 15% of the patients had abnormal brain imaging results, while most of them had normal electroencephalographic (EEG) activity. The consideration for genetic diagnosis in patients with epilepsy should not be teased out despite the absence of definite EEG results. Valproic acid(VPA), stiripentol, clobazam, combination of them and ketogenic diet were proven therapies, and the sodium channel blockers should be avoided in the patients with SCN1A mutations. Majority of our cases were benefited from same drugs, unlikely, 3 of SCN1A cases were benefited from carbamazepin/oxcarbazepin. Functional studies should be performed to understand the drug responses.

Mutations in SCN1B have been reported in patients having GEFS+ phenotype, DS and Temporal lobe epilepsy (TLE). The role of SCN1B was recently demonstrated in developmental and epileptic encephalopathy, as in our study.

In the SCN3A mutations, GEFS+, focal epilepsy could be observed, clinically. Although, both of our SCN3A mutaions were not pathogenic variant, they were compatible with their mutatiıns, phenotypically.

Early infantile epileptic encephalopathy Type 13 (also called SCN8A encephalopathy) is caused by mutations of the SCN8A gene. Additionally, de novo mutations of SCN8A in singleton patients with epilepsy with or without intellectual disability were identified also, as in our study.

In a study patients with SCN8A mutations, the authors discovered that sodium channel antagonists at high therapeutic doses effectively manage SCN8A seizures.

Although SCN9A mutations are related with pain disorders,but febrile seizures, epilepsy and GEFS+ were also detected.

Conclusion

With the clinical and genetic characteristics of VGSC described in the literature, recognising the spectrum of this disease is important for a targeted treatment plan. Genetic investigation improves diagnosis and may help in selecting better effective combination therapies in epilepsy management.

Figure 1:Genotype&Phenotype relationship (n:26)

	Gene	Classification	Disease
1	SCN1A	VUS/LP	DS
2	SCN1A	P	DS
3	SCN1A	P	Complicated febrile seizure
4	SCN1A	LP	DS
5	SCN1A	LP	GEFS+
6	SCN1A	VUS/LP	GEFS+
7	SCN1A	P	DEE
8	SCN1A	P	DS
9	SCN1A	LP	DS
10	SCN1A	P	DS
11	SCN1A	P	GEFS+
12	SCN4A	LP	SCN4A-associated myotonia
13	SCN8A	P	epilepsy
14	SCN9A	VUS/LB	DEE
15	SCN3A	VUS/LB	DEE
16	SCN3A	VUS/LB	DEE
17	SCN1A	VUS/LB/B	DS
18	SCN1B	VUS/LB	GEFS+
19	SCN1B	B	DEE
20	SCN1A	P	DS
21	SCN1A	P	DS
22	SCN1A	P	DS
23	SCN1A	P	DS
24	SCN1A	P	DS
25	SCN11A	P	Sensory loss
26	SCN1A	VUS/B	DS

Figure 3: results of epileptic cases (n:24)

The mean age at the onset(month)	11,96±21,6 (0-108)
The mean age at the diagnosis(month)	47,17±38,2 (3-144)
The time with the admission and the diagnosis(month)	35,96±29 (7-108)

Figure 2: Results of epileptic cases (n:24)

Patient history(prematurity, small for gestational age)	
Yes	5
No	19 (79%)
Family history(epilepsy, VGSC mutation)	
Yes	14
No	10
The seizure semiology	
Focal	4
Generalised	17 (70%)
Focal to bilateral tonic clonic	1
Epileptic spasm	2
The epilepsy semiology	
Focal	3
Generalised	19 (79%)
Epileptic syndrome	2
The seizure frequency	
Daily	4
Weekly	5
Monthly	5
Yearly	7
Seizure free	3
EEG	
Normal	13 (54%)
Abnormal(focal, multifocal, generalised)	11
Cranial MRI	
Normal	16 (66%)
Abnormal(Periventricular leukomalacia, corpu callosum abnormality)	8
Developmental outcome	
Normal	6
Delay/retardation	18 (75%)
Language	10
Motor	8
Mental	17(70%)
Global developmental delay	4

References

1. Holland, K. D., Kearney, J. A., Glauser, T. A., Buck, G., Keddache, M., Blankston, J. R., ... & Meisler, M. H. (2008). Mutation of sodium channel SCN3A in a patient with cryptogenic pediatric partial epilepsy. *Neuroscience letters*, *433*(1), 65-70.
2. Catterall, W. A., Kalume, F., & Oakley, J. C. (2010). NaV1. 1 channels and epilepsy. *The Journal of physiology*, *588*(11), 1849-1859.
3. Brackenbury, W. J., & Isom, L. L. (2011). Na+ channel β subunits: overachievers of the ion channel family. *Frontiers in pharmacology*, *2*, 53.
4. Rangel-Barajas, C., Silva, I., Lopéz-Santiago, L. M., Aceves, J., Erlij, D., & Florán, B. (2011). L-DOPA-induced dyskinesia in hemiparkinsonian rats is associated with up-regulation of adenylyl cyclase type V/VI and increased GABA release in the substantia nigra reticulata. *Neurobiology of disease*, *41*(1), 51-61.
5. Marini, C., Scheffer, I. E., Nabbout, R., Suls, A., De Jonghe, P., Zara, F., & Guerrini, R. (2011). The genetics of Dravet syndrome. *Epilepsia*, *52*, 24-29.
6. . Wallace RH, Wang DW, Singh R, Scheffer IE, George ALJ, Phillips HA, et al. Febrile seizures and generalized epilepsy associated with a mutation in the Naþ-channel beta1 subunit gene SCN1B. Nat Genetics. (1998) 19:366e70. doi: 10.1038/1252
7. . Ogiwara I, Nakayama T, Yamagata T, Ohtani H, Mazaki E, Tsuchiya S, et al. A homozygous mutation of voltage-gated sodium channel beta(I) gene SCN1B in a patient with Dravet syndrome. Epilepsy. (2012) 53:e200e3. doi: 10.1111/epi.12040