ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

https://iap-kpj.org

Karnataka Paediatric Journal

Original Article

Epileptic Spasms-West syndrome secondary to Dravet syndrome due to *SCN* gene mutation from India

Vykuntaraju K. Gowda[1], Hemadri Vegda[1], Raghavendraswami Amoghimath[2], Manojna Battina[1], Sanjay K. Shivappa[3], Naveen Benakappa[3]

[1]Department of Pediatric Neurology, Indira Gandhi Institute of Child Health, Bengaluru, [2]Department of Pediatrics, Karnataka Institute of Medical Sciences, Hubli, [3]Department of Pediatrics, Indira Gandhi Institute of Child Health, Bengaluru, Karnataka, India.

***Corresponding author:**
Vykuntaraju K. Gowda, Department of Pediatric Neurology, Indira Gandhi Institute of Child Health, Bengaluru, Karnataka, India.

drknvraju08@gmail.com

Received : 20 December 2020
Accepted : 10 January 2021
Published : 02 June 2021

DOI
10.25259/KPJ_36_2020

Quick Response Code:

ABSTRACT

Objectives: West syndrome (WS) is a triad of epileptic spasms, developmental delay/regression, and hypsarrhythmia. SCN related epileptic encephalopathy is a rare epilepsy syndrome characterized by an early-onset, severe, and epileptic encephalopathy. The causes of WS are multiple and diverse ranging from genetic to structural, metabolic, and unknown causes. The objectives of the study were to report SCN related epileptic encephalopathies with epileptic spasms.

Materials and Methods: This is retrospective chart review of children presenting with epileptic spasms secondary to *SCN* gene variants from January 2015 to March 2020 in a tertiary care referral center.

Results: Out of 15 children, ten were boys. The mean age of presentation was 5 months. Thirteen children had preceded seizures before epileptic spasms in the 1st year of life, two children presented initially with epileptic spasms. No neuro-deficits were noted in all the children. In all the cases electroencephalogram was suggestive of hypsarrhythmia. Routine testing, neuroimaging, and metabolic tests were normal in all the cases. Various pathogenic variants seen in next-generation sequencing were *SCN1A* in 11, *SCN1B* and *SCN2A* in two children each. Three children responded for vigabatrin and five children responded for steroids but all of them had relapse and were refractory to other antiepileptic drugs.

Conclusion: *SCN* related epileptic encephalopathy should be considered in the differential diagnosis of epileptic spasms. These infants present earlier compare to classical Dravet syndrome children.

Keywords: Epileptic spasms, West syndrome, *SCN* mutation, Epileptic encephalopathy

INTRODUCTION

Dravet syndrome (DS) and *SCN* related encephalopathies are genetically determined severe early onset epileptic encephalopathy (EOEE), which begins in the 1st year of life in an otherwise normal infant.[1] Initial seizures, often induced by a fever, tend to be prolonged generalized or unilateral tonic and/or clonic seizures, are more frequent and come in clusters. Beyond the 1st year, multiple seizure types often develop such as myoclonic, atypical absence, and focal seizures. West syndrome (WS) is the most common epilepsy syndrome in infancy, which is characterized by triad of infantile spasms, developmental deterioration, and hypsarrhythmia.[2] It can be due to structural, genetic, infectious, immune, metabolic and unknown cases. Several genes, such as,

SCN1A, *SCN2A*, *SCN1B*, *ATXN2*, *NR3C1*, *KPNA7*, *STXBP1*, *ABCB1*, *GRIN1*, *ARX*, and *TSC2,* were found to be associated with the pathogenesis of epileptic spasms.[3] Variants in the gene encoding voltage-gated sodium channel (*SCN1A*) are associated with several epilepsy syndromes. Here, we report children of *SCN* related epileptic encephalopathies who presented with epileptic spasms.

MATERIALS AND METHODS

This is a retrospective chart review of epileptic spasms due to *SCN* related epileptic encephalopathies from tertiary care referral center, from southern part of India. The medical records of children attending the pediatric neurology clinic and those who were admitted in pediatric neurology and pediatric ward from January 2015 to March 2020 were analyzed. Among them, only children who were confirmed to have a diagnosis of *SCN* related epileptic encephalopathies in genetic studies and presented with epileptic spasms were included and formed the study group. Those children with epileptic spasms and suspected *SCN* related epileptic encephalopathies without genetic confirmation were excluded from the study. The data were extracted as per-designed pro forma. Details of history including birth history, developmental history, clinical features including seizure semiology, precipitation of seizures with fever, investigations such as complete hemogram, liver function, renal function, serum calcium, serum ammonia, serum lactate, arterial blood gas, and neuroimaging MRI of brain were taken. Special investigations such as tandem mass spectrometry (TMS), electroencephalogram (EEG), and genetic analysis were also taken. Statistical analysis was performed with SPSS version 21. The results were analyzed. Ethical clearance was obtained, from institutional ethical committee.

RESULTS

A total of 50 children with *SCN* related epileptic encephalopathies were seen during this period, out of these 15 (35%) had epileptic spasms. The various clinical features, laboratory findings, and outcome of all the 15 children are mentioned in [Table 1]. Of the 15 children, ten (67%) were boys. All of them presented in 1st year of life except once child, with mean age of presentation being 5 months of age compare to 10 months in children with *SCN* related epileptic encephalopathies without epileptic spasms. All of them presented with other seizures in the form of focal or generalized seizures along with epileptic spams, and except two children who had only epileptic spasms as per history. Seven children presented with fever triggered seizures and spasms, four children presented with seizures after vaccination and four children had afebrile seizures before onset of spasms. Birth history was normal in all the children. Initial development was normal followed by severe developmental delay in all the children. Neuro imaging and TMS were normal in all the children. EEG showed hypsarrhythmia in all the children. EEG showing modified hypsarrhythmia in [Figure 1]. Targeted next generation sequencing showed *SCN1A* gene mutation in 11 children, *SCN1B* and *SCN2A* in two children each. Spasms were controlled initially with vigabatrin and steroids, but later seizures were refractory to treatment.

DISCUSSION

There are only few reports describing *SCN* related epileptic encephalopathies presenting with epileptic spasms secondary to mutation in *SCN* gene in the literature. Here, we are reporting 15 patients presenting as WS with mutation in *SCN* gene. Around 70–80% of children with *SCN* related epileptic encephalopathies have point mutations or gross rearrangements in the *SCN1A* gene. Over 1200 variants associated with epilepsy have been reported in *SCN1A*.[4] Truncating variants are associated with severe phenotypes. The missense variants are associated with a wide spectrum of phenotypes from DS to much milder forms of epilepsy, such as febrile seizures and "febrile seizures plus," which are often familial and part of a genetic epilepsy with febrile seizures plus.[5] Ten percent of *SCN* related epileptic encephalopathy patients have deletion, duplication, or amplification identified with multiplex ligation-dependent probe amplification. In 10–20% of cases, the genetic cause remains unknown, may be other genes are likely to be involved. Less than 1% of *SCN* related epileptic encephalopathy patients have homozygous mutation in *SCN1B*, and very few have *GABRG2* or *SCN2A* mutations.[6]

WS is an epileptic encephalopathy with onset typically around 6 months of age, characterized by epileptic spasms, hypsarrhythmia, and developmental delay or regression.

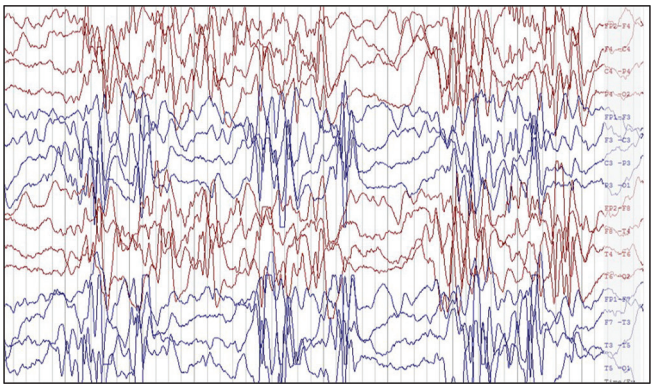

Figure 1: Electroencephalogram of bipolar longitudinal montage with a sensitivity of 20 μV showing high amplitude multifocal spikes, sharp waves with secondary generalization followed by suppression suggestive of modified hypsarrhythmia in a 8-months-old child with epileptic spasms due to *SCN1A* pathogenic variant.

Table 1: Various clinical and laboratory profile of study population.

Case number	Sex	Age of onset (m.)	Fever triggered seizures	Seizure type	Last follow-up (mo.) and Dev	Gene	Variant	AED tried	Response to AED
1.	M	3	No	GTCS, ES	45 NA	*SCN1A*	Ex16.c.3199G>A/p. Ala1067Thr	VPA, LEV,CZM, TPM, ZSM, VB, ACTH	VB
2.	M	3	Yes	Focal, ES	42 NA	*SCN1A*	Ex8.c.3199G>A/p. Ala1067Thr	VPA, LEV,CZM, TPM, ZSM, VB, ACTH	ACTH
3.	M	16	Yes	ES	37 Amb Autistic	*SCN2A*	Ex7.c.823C>T/p. Arg275Ter	VPA, CBZ, LEV, CZM, TPM, ZSM, VB,ACTH	VB
4.	M	3	No	GTCS, F, ES	60 NA	*SCN1A*	c.6013C>T/p. Arg2005Cys	VPA, SP, LEV, CZM, TPM, ZSM, VB, ACTH	None
5.	F	2	Yes	GTCS, F, ES	13 NA	*SCN1A*	Ex8.c.3199G>A/p. Ala1067Thr	VPA, LEV, CZM, TPM, ZSM, VB, ACTH	ACTH
6.	F	3	Yes	GTCS, F, ES	07 Amb Autistic	*SCN1B*	c.253C>T/p.Arg85 Cys	VPA, SP, LEV, CZM, TPM, ZSM, VB, ACTH	SP
7.	F	3	Yes	GTCS, F, ES	48 NA	*SCN1A*	c.3199G>A/p. Ala1067Thr	VPA, SP, LEV, CZM, TPM, ZSM, VB,ACTH	None
8.	M	3	Yes	GTCS, F, ES	12 Autistic	*SCN1A*	c.3199G>A/p. Ala1067Thr	VPA, LEV, CZM, TPM, ZSM, VB, ACTH	ACTH
9.	M	9	Yes	GTCS, F, ES	33 NA	*SCN2A*	c.823C>T/p. Arg275Ter	VPA, CBZ, LEV, CZM, TPM, ZSM, VB, ACTH	CBZ
10.	M	3	Yes	GTCS, F, ES	28 Amb Autistic	*SCN1A*	c.695G>T/p. Gly232Val	VPA, LEV, CZM, TPM, ZSM, VB, ACTH	ACTH
11.	M	5	Yes	GTCS, F, ES	25 NA Autistic	*SCN1A*	c.3199G>A/p. Ala1067Thr	VPA, SP, LEV, CZM, TPM, ZSM, VB, ACTH	SP
12.	F	1	Yes	GTCS, F, ES	12 NA Autistic	*SCN1A*	Ex26.c.4907G>A/p. Arg1636Gln	VPA, SP, LEV,CZM, TPM,ZSM, VB,ACTH	None
13.	F	7	Yes	GTCS, F, ES	21, Amb Autistic	*SCN1A*	Ex26.c.4855A>G/p. Met1619Val	VPA, LEV, CZM, TPM, ZSM, VB, ACTH	ACTH
14.	M	6	Yes	GTCS, F, ES	24 NA Autistic	*SCN1A*	Ex15.c.2712dupT/p. Ala905Cysfs	VPA, SP, LEV, CZM, TPM, ZSM, VB, ACTH	None
15.	M	8	Yes	ES	18 NA, Autistic	*SCN1B*	c.560delG/p. Arg187profs	VPA, LEV, CZM, TPM, ZSM, VB, ACTH	VB

ACTH: Adrenocorticotropic hormone, AEDs: Antiepileptic drugs, Amb: Ambulatory, CLB: Clobazam, CBZ: Carbamazepine, DEV: Development, ES: Epileptic Spasms, F: Focal, GTCS: Generalized tonic-clonic seizures, LEV: Levetiracetam, NA: Non ambulatory, SP: Stiripentol, VPA: Valproate, TPM; Topiramate, VB: Vigabatrin, ZNS: Zonisamide

Etiology of epileptic spasms is widely heterogeneous, with acquired and congenital causes. Advances in the genetic investigations have led to discovery of new genes in WS in the past few decades. More than ten genes had been shown to be associated with epileptic spasms.[7] More recently, copy-number variations and mutations in *STXBP1*, *SCN2A*, and *KCNQ2*, which were previously associated with EOEE, have been found in patients with epileptic spasms.[8] Despite these advances, in many cases the cause still remained hidden.[9] The study done by Wallace *et al*. extends the phenotypic heterogeneity of mutations in *SCN1A* to include epileptic spasms.[10]

In seven children initial seizures were noticed following DPT vaccine and subsequently developed epileptic spasms, this finding was consistent with other studies of seizures following vaccinations which were reported in 7–57% of children with DS.[11,12] Two children presented with epileptic spasms one had *SCN2A* and the other with *SCN1B* mutation.

Ogiwara *et al*.[13] reported mutation in *SCN2A-E1211K*, causing epileptic spasms. Nakamura *et al*.[14] reported, nine of 67 Ohtahara syndrome (OS) cases (13.4%) and one of 150 WS cases (0.67%) were secondary to *SCN2A* mutation. All nine mutations in patients with OS were in linger regions between two transmembrane segments. In seven of the nine patients

with OS, EEG findings transitioned from suppression-burst pattern to hypsarrhythmia.

Harkin *et al*.[15] described missense *SCN1A* variant, Nav1.1-p. Thr226Met (T226M) is associated with a far more profound clinical phenotype than typical DS, represents a new class of early infantile epileptic encephalopathy (EIEE) located even beyond DS on the classical severity spectrum of *SCN1A*-linked disorder. Sadleir *et al*.[16] described the clinical presentation of more severe *SCN1A*-linked "early infantile *SCN1A* encephalopathy." They identified eight unrelated cases with an identical, presumed *de novo* missense variants resulting from c.677C > T in *SCN1A* exon 5. A ninth unrelated child, with the *de novo SCN1A* missense variant p.Pro1345Ser (c.4033C > T), was also included in the series due to the similarities in symptomology to the T226M patients indicates that early infantile *SCN1A* encephalopathy can arise from more than one particular variant. In our study, none of them had T226M variant, but most common variant is A1067T.

The mean age of presentation is our study was 5 months; however, mean age of presentation for A1057T variant is 3 months. Mean age of presentation of 50 children with *SCN* related epileptic encephalopathies with or without epileptic spasms was 10 months. Males are most affected. Only four of them are ambulatory, ten of them had autistic features. Epilepsy is refractory in all children, however epileptic spasms responded for steroids in five and vigabatrin in three children but later relapsed and refractory requiring polytherapy. Six children received stiripentol but only partial response that is more than 50% reduction in seizures noted in two children. We tried carbamazepine, sodium channel blocker in *SCN2A* subtype but only partial improvement was noted.

Traditional DS can be differentiated from early infantile *SCN1A* encephalopathy in several ways.[16] Early infantile *SCN1A* encephalopathy has an earlier age of onset, with seizures arising at an average of 9 weeks of age, more profound developmental impairments; and the majority required feeding tubes. Early infantile *SCN1A* encephalopathy presents with hyperkinetic movements, as early as 9 weeks of age and epileptic spasms, neither of which are seen in patients with DS, while hyperkinetic movements are not characteristic of *SCN1A* linked DS. However, similar movements are described with *SCN2A* and *SCN8A*-linked EIEEs; this overlap in symptomology led Sadleir *et al*. to speculate that the early infantile *SCN1A* encephalopathy, such as *SCN2A* and *SCN8A*-linked EIEEs, may be associated with a gain-of-function variant.

Epileptic spasms can be present in *SCN* mutations. They present earlier than classical DS with more severe developmental delay and refractory to treatment. Most common pathogenic variant noted in this study is A1057T in *SCN1A*.

CONCLUSION

In all cases of unexplained epileptic spasms, one should consider possibility of *SCN* gene mutation and genetic testing should be considered. Most common type of *SCN1A* mutation is A1057T variant. Early identifications are useful to select antiepileptic drugs for this subgroup of epileptic spasms.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Hwang SK, Kwon S. Early-onset epileptic encephalopathies and the diagnostic approach to underlying causes. Korean J Pediatr 2015;58:407-14.
2. Pellock JM, Hrachovy R, Shinnar S, Baram TZ, Bettis D, Dlugos DJ, *et al*. Infantile spasms: A US consensus report. Epilepsia 2010;51:2175-89.
3. Hirose S, Scheffer IE, Marini C, de Jonghe P, Andermann E, Goldman AM, *et al*. SCN1A testing for epilepsy: Application in clinical practice. Epilepsia 2013;54:946-52.
4. Catterall WA. From ionic currents to molecular mechanisms: The structure and function of voltage-gated sodium channels. Neuron 2000;26:13-25.
5. Meng H, Xu HQ, Yu L, Lin GW, He N, Su T, *et al*. The SCN1A mutation database: Updating information and analysis of the relationships among genotype, functional alteration, and phenotype. Hum Mutat 2015;36:573-80.
6. Catterall WA. Sodium channel mutations and epilepsy. In Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, editors. Jasper's Basic Mechanisms of the Epilepsies. Bethesda, MD: National Center for Biotechnology Information; 2012. p. 675-87.
7. Pavone P, Striano P, Falsaperla R, Pavone L, Ruggieri M. Infantile spasms syndrome, west syndrome and related phenotypes: What we know in 2013. Brain Dev 2014;36:739-51.
8. Tiwari VN, Sundaram SK, Chugani HT, Huq AH. Infantile spasms are associated with abnormal copy number variations. J Child Neurol 2013;28:1191-6.
9. Dimassi S, Labalme A, Ville D, Calender A, Mignot C, Boutry-Kryza N, *et al*. Whole-exome sequencing improves the diagnosis yield in sporadic infantile spasm syndrome. Clin Genet 2016;89:198-204.
10. Wallace RH, Hodgson BL, Grinton BE, Gardiner RM, Robinson R, Rodriguez-Casero V, *et al*. Sodium channel

alpha1-subunit mutations in severe myoclonic epilepsy of infancy and infantile spasms. Neurology 2003;61:765-9.
11. Tro-Baumann B, von Spiczak S, Lotte J, Bast T, Haberlandt E, Sassen R, *et al*. A retrospective study of the relation between vaccination and occurrence of seizures in dravet syndrome. Epilepsia 2011;52:175-8.
12. Verbeek NE, van der Maas NA, Jansen FE, van Kempen MJ, Lindhout D, Brilstra EH. Prevalence of SCN1A-related dravet syndrome among children reported with seizures following vaccination: A population-based ten-year cohort study. PLoS One 2013;8:e65758.
13. Ogiwara I, Ito K, Sawaishi Y, Osaka H, Mazaki E, Inoue I, *et al*. *De novo* mutations of voltage-gated sodium channel alphaII gene SCN2A in intractable epilepsies. Neurology 2009;73:1046-53.
14. Nakamura K, Kato M, Osaka H, Yamashita S, Nakagawa E, Haginoya K, *et al*. Clinical spectrum of SCN2A mutations expanding to ohtahara syndrome. Neurology 2013;11:992-8.
15. Harkin LA, McMahon JM, Iona X, Dibbens L, Pelekanos JT, Zuberi SM, *et al*. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain 2007;130:843-52.
16. Sadleir LG, Mountier EI, Gill D, Davis S, Joshi C, DeVile C, *et al*. Not all SCN1A epileptic encephalopathies are dravet syndrome: Early profound Thr226Met phenotype. Neurology 2017;89:1035-42.

How to cite this article: Gowda VK, Vegda H, Amoghimath R, Battina M, Shivappa SK, Benakappa N. Epileptic Spasms-West syndrome secondary to dravet syndrome due to *SCN* gene mutation from India. Karnataka Paediatr J 2021;36(1):49-53.