



Focal epilepsy in *SCN1A*-mutation carrying patients: is there a role for epilepsy surgery?

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*Members of the Epilepsy Surgery in *SCN1A* Study Group are listed in the Acknowledgements.

PUBLICATION DATA

Accepted for publication 27th April 2020.

Published online 15th June 2020.

ABBREVIATIONS

GEFS+ Genetic epilepsy with febrile seizures plus
GTCS Generalized tonic-clonic seizures

Variants in the gene *SCN1A* are a common genetic cause for a wide range of epilepsy phenotypes ranging from febrile seizures to Dravet syndrome. Focal onset seizures and structural lesions can be present in these patients and the question arises whether epilepsy surgery should be considered. We report eight patients (mean age 13y 11mo [SD 8y 1mo], range 3–26y; four females, four males) with *SCN1A* variants, who underwent epilepsy surgery. Outcomes were variable and seemed to be directly related to the patient's anatomico-electroclinical epilepsy phenotype. Patients with Dravet syndrome had unfavourable outcomes, whilst patients with focal epilepsy, proven to arise from a single structural lesion, had good results. We conclude that the value of epilepsy surgery in patients with an *SCN1A* variant rests on two issues: understanding whether the variant is pathogenic and the patient's anatomico-electroclinical phenotype. Careful evaluation of epilepsy phenotype integrated with understanding the significance of genetic variants is essential in determining a patient's suitability for epilepsy surgery. Patients with focal onset epilepsy may benefit from epilepsy surgery, whereas those with Dravet syndrome do not.

Pathogenic variants in *SCN1A*, the gene encoding the alpha 1 pore-forming subunit of the sodium channel, are the most common genetic cause for Dravet syndrome and the wider genetic epilepsy with febrile seizures plus (GEFS+) spectrum. GEFS+ includes clinical phenotypes ranging from classical febrile seizures in typically developing individuals to Dravet syndrome with drug-resistant epilepsy and intellectual disability.¹ Even though febrile seizures are the characteristic initial seizure type of Dravet syndrome and GEFS+, focal seizures occur in both GEFS+ and Dravet syndrome.²

Most patients with an *SCN1A* variant have normal magnetic resonance imaging (MRI),³ although diffuse, cerebral or cerebellar, atrophy, increased white matter signal, and focal abnormalities are reported. Hippocampal sclerosis has been reported in Dravet syndrome, even though the incidence is unclear.^{4–6} Further, Barba et al.⁷ reported six patients with Dravet syndrome and *SCN1A* variants who had cortical malformations.

The co-occurrence of focal onset seizures and focal MRI findings in patients with *SCN1A* variants raises the question of whether these patients could benefit from resective

epilepsy surgery, or whether the presence of a genetic abnormality implies an unfavourable outcome. Previous reports of postoperative outcome in patients with Dravet syndrome have been discouraging.⁸

We report a series of eight individuals with *SCN1A* variants who underwent resective epilepsy surgery.

CASE SERIES

Method

We conducted a retrospective note review in five epilepsy surgery centres on eight patients with drug-resistant epilepsy and *SCN1A* variants who underwent resective epilepsy surgery. In order to identify the epileptogenic zone and in line with current recommendations,⁹ all patients underwent a full presurgical evaluation; this included MRI, ictal video-electroencephalogram (EEG) monitoring, and neuropsychological assessment. Three patients also underwent positron emission tomography, one an ictal single-photon emission computerized tomography, and one a stereo-EEG recording. Histopathology was assessed on all surgical specimens. The Engel classification was used to assess postsurgical outcome.¹⁰ We classified seizures

according to the recent International League Against Epilepsy classification.¹¹

Clinical genetic testing was performed. In order to evaluate the pathogenicity of missense variants in *SCN1A*, in silico prediction algorithms were used: SIFT (sorting tolerant from intolerant),¹² PolyPhen-2 (polymorphism phenotyping v2),¹³ and MutationTaster.¹⁴ We determined if variants were present in control exomes (150 000 exomes in the Genome Aggregation Database [gnomAD, gnomad.broadinstitute.org/]) and performed a literature search to determine if they were recurrent and reported in affected individuals. In one case (patient 8), in vitro functional testing was undertaken. Whole-cell patch-clamp recordings of tsA201 cells transfected with either wildtype or mutant alpha 1 subunits together with β_1 - and β_2 -subunits were performed as described previously.^{15,16}

Patients

Mean age at surgery was 13 years 11 months (SD 8y 1mo, range: 3–26y). Mean age at seizure onset was 8.25 months (SD 4mo, range: 2–14mo). Four patients were female and four male. Patient characteristics and investigation results are summarized in Table 1. According to their electroclinical phenotype, patients were divided into three groups.

Group 1 consisted of four patients who presented with infantile febrile seizures, who subsequently developed unilateral seizures with mesial temporal semiology and temporal onset on EEG. Two patients (patients 1, 3) also had preoperative generalized tonic-clonic seizures (GTCS) and interictal generalized spike wave discharges. No other seizure types were documented. All four patients had hippocampal sclerosis and underwent anterior temporal lobectomy.

Group 2 consisted of three patients with a clinical diagnosis of Dravet syndrome, characterized by multiple seizure types and multifocal, as well as generalized, EEG findings. MRI demonstrated focal cortical dysplasia in two and hippocampal sclerosis in one. In an attempt to ease their seizure burden, patients 5 and 6 underwent resection of the focal cortical dysplasia, and patient 7 an anterior temporal lobe resection.

Group 3 consisted of one patient (patient 8) with focal seizures involving the occipital lobe and negative MRI who underwent an occipital lobe resection. This patient had a personal and family history of uncomplicated febrile seizures, and a wider family history, through the maternal line, of occipital lobe epilepsy.

Molecular genetics

All patients had heterozygous variants in *SCN1A* (Table 2); none were present in gnomAD. Patient 5 and 7 had recurrent nonsense variants.^{17–19} The remaining six patients had missense variants, with four recurrent^{20–22} and two novel. Variant c.985G>T (p.Gly329Cys) (patient 6) is predicted to be disease-causing by SIFT, MutationTaster, and Polyphen 2. Variant c.1804G>A (p.Glu602Lys) (patient 8) is predicted to be damaging by MutationTaster, tolerated by

What this paper adds

- Patients should not automatically be excluded from epilepsy surgery evaluation if they carry an *SCN1A* variant.
- Patients with focal epilepsy may benefit from epilepsy surgery; those with Dravet syndrome do not.

SIFT, and benign by Polyphen 2; the variant was present in the mother and sister, who both had febrile seizures, but not in the wider family with occipital lobe epilepsy. In vitro functional testing demonstrated that the variant caused a clear loss of function by significantly reducing the current density (Fig. S1, online supporting information). Patient 3 has previously been published as case 3 in Livingston et al.,²² patient 7 has been described as patient 9 in Cooper et al.¹⁹

Surgical outcome

Patients in groups 1 and 3 benefited from surgery: outcomes were Engel class IA (patient 8), IB (patient 2), ID (patient 1 and 4), and IIA (patient 3). All patients in these groups experienced no further focal seizures after surgery but some had occasional or isolated GTCS (Engel class ID and IIA). Histopathology confirmed hippocampal sclerosis in all four group 1 patients postoperatively. Patients with Dravet syndrome in group 2 did not improve with surgery: outcomes were Engel class III (patient 7) and IV (patients 5 and 6). Patient 7 preoperatively experienced seizures semiologically and electrographically consistent with right temporal origin as well as GTCS. She underwent surgery at 3 years of age. The focal seizures initially ceased after her right temporal lobectomy, but GTCS continued and additional myoclonic seizures developed. She died of sudden unexpected death in epilepsy 4 years after surgery.

DISCUSSION

There is increasing interest in whether a pathogenic variant in *SCN1A* precludes successful epilepsy surgery. Interpretation of the significance of a genetic variant in individuals undergoing presurgical evaluation, their relevance to the patient's phenotype, and implications for surgical outcome require careful consideration. We describe a series of eight patients with *SCN1A* variants who underwent epilepsy surgery. Those who had focal onset seizures with concordant preoperative investigations benefited from focal resection, whereas those with a clinical phenotype of Dravet syndrome had poor postoperative outcome, despite resection of a structural lesion.

Little has been published about the outcome of epilepsy surgery in patients with *SCN1A* variants. Barba et al.⁷ described two patients with Dravet syndrome and *SCN1A* pathogenic variants who underwent epilepsy surgery for associated structural lesions, both with poor outcomes. Skjei et al.⁸ reported six patients with *SCN1A* variants who had epilepsy surgery, again with poor outcomes. Five patients had classical Dravet syndrome and one had GEFS+ with a history of severe head trauma.

Table 1: Patient characteristics

Patient	Sex	First seizure	Seizure types	Epilepsy classification	Ictal/interictal EEG	MRI	Further investigations	Age at surgery (y)	Surgery type	Histology	FU (y)	Engel class	Cognition
1	F	Febrile hemiclonic right 15min	Focal, left temporal semiology, GTCS	Combined generalized and FTME with HS and SCN7A variant	Left temporal seizure onset, interictal, general bilateral SW	Left HS	PET: left temporal hypometabolism SPECT: not done	13	Left temporal lobectomy	HS	12	ID	IQ 66, improvement after surgery
2	F	Hemiclonic right >30min	Focal, left temporal semiology	FTME with HS and SCN7A variant	Left temporal seizure onset	Left HS	PET: left temporal hypometabolism SPECT: not done	25	Left temporal lobectomy	HS	8	IB	IQ 63, stable after surgery
3	M	Febrile 25min	Focal, left temporal semiology, GTCS	Combined generalized and FTME with HS and SCN7A variant	Left temporal seizure onset, interictal general bilateral SW	Left HS	Not done	13	Left temporal lobectomy	HS	1	IIA	IQ <50, stable after surgery
4	F	Febrile GTCS >60min	Focal, right temp semiology	FTME with HS and SCN7A variant	Right temporal seizure onset	Right HS	Not done	9	Right temporal lobectomy	HS	6	ID	IQ 59, stable after surgery
5	M	Afebrile GTCS >20min	GTCS, atonic seizures, AA, MS	Dravet syndrome	Multifocal, documented left and right seizure onset	Right temporo-anterior FCD	Not done	15	Right temporal lobectomy	FCD lb	10	IVA	IQ <30, stable after surgery
6	M	Febrile hemiclonic left	GTCS, atonic seizures, AA, MS	Dravet syndrome	Multifocal, documented left and right seizure onset	Left temporo-occipital FCD	PET: left temporo-parietal hypometabolism Ictal SPECT: left hemispheric hyperperfusion excl. temporal lobe	7	Extended left temporo-occipito-mesial lesionectomy+ AHE	FCD	12	IVB	IQ <50, deteriorating after surgery
7 ^a	F	Febrile hemiclonic 40min	Focal, right temporal semiology, MS	Dravet syndrome	Right temporal seizure onset, generalized bilateral SW	Right HS	Not done	3	Right temporal lobectomy	HS	4	III/	SUDEP
8	M	Febrile seizure	Focal, right occipital semiology, frequently evolving to bilateral GTCS	Focal occipital epilepsy with SCN7A variant	Right occipital seizure onset	Negative	Stereo-EEG: right occipital seizure onset	26	Partial right occipital lobectomy	Negative	2	IA	Normal cognition

^aDeceased. Group 1=patients 1–4. Group 2=patients 5–7. Group 3=patient 8. Neurological examination was normal for all patients, except for patient 5, who was hypotonic and ataxic and patient 6, who was hypotonic. EEG, electroencephalography; MRI, magnetic resonance imaging; FU, follow-up; GTCS, generalized tonic-clonic seizure; FTME, focal temporal mesial epilepsy; HS, hippocampal sclerosis; SW, spike waves; PET, positron emission tomography; SPECT, single-photon emission computerized tomography; AA, atypical absences; MS, myoclonic seizures; FCD, focal cortical dysplasia; AHE, amygdalohippocampectomy; SUDEP, sudden unexplained death in epilepsy.

Table 2: *SCN1A* variants in our cohort

Patient	GRCh37/ hg19 position	Allele change	Genomic refer- ence sequence	Protein position	AA change	Variant effect	SIFT	Mutation taster	Polyphen 2	Previously published
1	2:166850722	G/A	c.4786C>T	1596	R/C	Missense	Deleterious (0)	Disease causing	Probably damaging (1.000)	Harkin et al. ²⁰
2+4	2:166848897	C/T	c.4888G>A	1630	V/M	Missense	Deleterious (0)	Disease causing	Probably damaging (0.99)	Marini et al. ²¹
3	2:166909404	A/G	c.652T>C	218	F/L	Missense	Deleterious (0)	Disease causing	Probably damaging (0.997)	Livingston et al. ²²
5	2:166894639	G/A	c.2593C>T	865	R/*	Nonsense	n/a	Disease causing	n/a	Xu et al. ¹⁷
6	2:166905439	C/A	c.985G>T	329	G/C	Missense	Deleterious (0)	Disease causing	Probably damaging (1.000)	n/a
7	2: 166900385	G/A	c.1837C>T	613	R/*	Nonsense	n/a	Disease causing	n/a	Kearney et al. ¹⁸ Cooper et al. ¹⁹
8	2:166900418	C/T	c.1804G>A	602	E/K	Missense	Tolerated (0.18)	Disease causing	Benign (0.038)	n/a

The table shows genomic location of the variants, protein position, and anticipated AA change, as well as the predicted effect of this change on protein function by in silico tools SIFT, polyphen 2, and mutation taster. In variants that have been previously published, the first paper describing the variant is cited. AA, aminoacid, SIFT, sorting tolerant from intolerant; Polyphen 2, polymorphism phenotyping v2.

In contrast, epilepsy surgery was beneficial in five out of eight patients in our series (Engel class I and II outcomes). These included all four patients in group 1 who had early prolonged febrile seizures with later development of temporal lobe seizures. They all had anatomico-electroclinical findings consistent with mesial temporal epilepsy with hippocampal sclerosis, rather than Dravet syndrome. Patients 1 and 3 also had experienced GTCS with interictal generalized spike wave and these two patients had ongoing rare GTCS postoperatively (Engel class ID and IIA). After 4 years of postoperative seizure freedom, patient 4 experienced two GTCS. After adjusting her antiepileptic medication she has been seizure free for a further 2 years. One could speculate, as Tiefes et al.²³ suggest, that the initial prolonged seizures, due to the *SCN1A* pathogenic variant, resulted in hippocampal sclerosis which, in turn, led to temporal lobe epilepsy. The GTCS in patients 1, 3, and 4, as well as the cognitive impairment of the four patients in group 1, could be the result of the *SCN1A* pathogenic variant.²

An excellent surgical outcome was observed in patient 8 (Engel class IA) who did not have a lesion on MRI, or on postoperative histopathology. He had occipital seizures with concordant surface and stereo-EEG findings. The *SCN1A* variant he carried was proven to cause a marked loss of function in an in vitro model system, but was not the cause of his familial occipital lobe epilepsy on clinical genetic grounds, and did not influence his postsurgical outcome. It can be argued that it may have caused the nuclear familial febrile seizures, but was not the cause of his familial occipital lobe epilepsy. Despite this, we decided to include him in this series to stress the point that the

presence of an *SCN1A* variant, even if confirmed pathogenic and especially if not, should not automatically preclude a patient from presurgical assessment for epilepsy surgery. Critical assessment of the pathogenicity of the variant²⁴ is essential.

Patients in group 2 with classical Dravet syndrome showed an unfavourable surgical outcome. Seizures failed to improve, or even worsened, after resection of a lesion (Engel class III/IV). For patients 5 and 6, their clinical semiology and EEG findings were not concordant with the MRI lesion. Arguably, based on clinical information, at the time of her surgery, patient 7 resembled patients 1 and 3 with GTCS and temporal onset focal seizures although the clinician suspected Dravet syndrome. She underwent surgery at 3 years, a time early in her natural history, and later went on to establish a full Dravet phenotype with ongoing GTCS and further seizure types (myoclonic seizures). Acknowledging the Dravet diagnosis was made in retrospect, it has to be recognized the surgery at an early age did not allow time for the full electroclinical phenotype to emerge, and might be a risk in patients with a likely pathogenic *SCN1A* variant. In analysis of this patient group, it has to be recognized the full phenotype of Dravet syndrome may not emerge until 4 years,¹ and consequently when suspected should be considered in presurgical evaluation at this time.

We conclude that patients with the electroclinical phenotype of Dravet syndrome are not epilepsy surgery candidates, even in the presence of a single structural lesion, supporting the observations of Barba et al.⁷ and Skjei et al.⁸ In the absence of electroclinical Dravet syndrome, when the presurgical evaluation reveals a single stereotyped

focal seizure semiology with concordant EEG and imaging findings, patients may profit from epilepsy surgery even in the presence of a *SCN1A* pathogenic variant. However, the presence of preoperative generalized spike waves may be associated with ongoing GTCS, suggesting that a more guarded surgical prognosis with regard to seizure freedom should be offered. Clinicians should be cautious about postoperative antiseizure medicine withdrawal, maintaining pharmacological treatments likely to be effective for generalized seizures.

ACKNOWLEDGEMENTS

The members of the Epilepsy Surgery in *SCN1A* Study Group are as follows: Dr Anita Devlin (Department of Paediatric Neurology,

Great North Children's Hospital, Newcastle Upon Tyne, UK), Dr Ulrike B.S. Hedrich and Professor Holger Lerche (Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany).

This research was supported by the National Institute of Health Research Biomedical Research Centre at Great Ormond Street Hospital.

The authors have stated they had no interests that might be perceived as posing a conflict or bias.

SUPPORTING INFORMATION

The following additional material may be found online:

Figure S1: Transient Na⁺ currents recorded from transfected tsA201 cells.

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Title:

Focal epilepsy inSCN1A-mutation carrying patients: is there a role for epilepsy surgery?

Date:

2020-11-01

Citation:

Vezyroglou, A., Varadkar, S., Bast, T., Hirsch, E., Strobl, K., Harvey, A. S., Scheffer, I. E., Sisodiya, S. M. & Cross, J. H. (2020). Focal epilepsy inSCN1A-mutation carrying patients: is there a role for epilepsy surgery?. DEVELOPMENTAL MEDICINE AND CHILD NEUROLOGY, 62 (11), pp.1331-1335. <https://doi.org/10.1111/dmcn.14588>.

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