HHS Public Access

Author manuscript

Am J Med Genet A. Author manuscript; available in PMC 2025 February 01.

Published in final edited form as:

Am J Med Genet A. 2024 February ; 194(2): 301–310. doi:10.1002/ajmg.a.63428.

Epilepsy in cardiofaciocutaneous syndrome: clinical burden and response to anti-seizure medication

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Abstract

Aim: Treatment-resistant epilepsy is among the most serious complications of cardiofaciocutaneous syndrome (CFCS), a rare disorder caused by germline variants in the RAS-MAPK signaling pathway. This study analyzed the clinical characteristics of epilepsy and response to anti-seizure medications (ASMs) in a multinational CFCS cohort.

Methods: A caregiver survey provided data regarding seizure history, use of ASMs and other treatment approaches, adverse effects, caregiver perception of treatment response, and neurological disease burden impact among individuals with CFCS. Results from 138 survey responses were quantitatively analyzed in conjunction with molecular genetic results and neurological records.

Results: The disease burden impact of CFCS was higher among individuals with epilepsy (n=74/138), especially those with more severe seizure presentation. Oxcarbazepine, a sodium-channel blocker, had the best seizure control profile with relatively infrequent adverse effects. The

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Contributions

DKJ: study conception and design, data acquisition, manuscript drafting and revision. JCL: data analysis, data interpretation, preparation of tables and figures, manuscript drafting and revision. DJR: data analysis, data interpretation, preparation of tables and figures, manuscript revision. RS: statistical analysis, preparation of tables and figures, manuscript drafting and revision. AZ: study conception, data acquisition, data interpretation, manuscript revision. AW: data acquisition, data interpretation, manuscript revision. AER: data acquisition, data interpretation, manuscript revision; MZ: data acquisition, data interpretation, manuscript revision. EIP: study conception and design, data acquisition, data analysis and interpretation, manuscript drafting and revision.

Conflict of Interest Disclosure: The authors have no relevant conflicts of interest to declare.

Ethics Approval Statement: The study was approved by the University of Minnesota Institutional Review Board (STUDY00006097).

Patient Consent Statement: Informed consent was obtained from all research participants prior to enrollment.

most commonly prescribed ASM, levetiracetam, demonstrated comparatively poor seizure control. ASM efficacy was generally similar for individuals with *BRAF* and *MAP2K1* gene variants.

Interpretation: The high proportion of patients with CFCS who experienced poor seizure control despite use of multiple ASMs highlights a substantial unmet treatment need. Prospective study of ASM efficacy and clinical trials of therapies to attenuate RAS-MAPK signaling may improve avenues for clinical management.

Keywords

RASopathies; seizures; treatment; *BRAF*; *MAP2K1*

Introduction

Germline variants that dysregulate signaling through the RAS-mitogen activated protein kinase (RAS-MAPK) pathway cause cardiofaciocutaneous syndrome (CFCS), a rare genetic disorder associated with craniofacial, skin, cardiac, growth and neurological features (Pierpont et al., 2014; Rodriguez-Viciana et al., 2006). Pathogenic changes affecting different components of the RAS-MAPK pathway can also cause other genetic syndromes ("RASopathies") that are phenotypically similar to CFCS, including Noonan and Costello syndromes. The RAS-MAPK pathway is expressed in tissues throughout the body and is vital in the development and function of the brain. This pathway regulates proliferation, differentiation and migration of neurons and oligodendrocytes; it also plays a role in synaptic plasticity and release of neurotransmitters (Kim & Baek, 2019; Ryu & Lee, 2016). Although neurological features vary widely, people with RASopathies are at heightened risk for epilepsy, structural brain anomalies, hypotonia, cognitive impairment, and characteristics of autism and other neurodevelopmental disorders (Geoffray et al., 2021; Green et al., 2017; Kontaridis et al.; Yoon et al., 2007). Several studies report correlations between neurological findings such as epilepsy or intellectual disability and specific genes or risk alleles that modulate RAS-MAPK signaling (Battaglia et al., 2021; Cesarini et al., 2009; Kenney-Jung et al., 2022; Pierpont et al., 2022).

CFCS is one of the rarest RASopathies, with a prevalence estimated at 1 in 810,000 individuals (Abe et al., 2012). It can occur due to germline variants in the *BRAF*, *MAP2K1*, *MAP2K2, KRAS*, and possibly *YWHAZ* genes (Rauen, 2022). CFCS is also among the most neurologically complex of the RASopathies. Up to 64% of individuals with CFCS have been reported to experience epilepsy, with the most severe forms occurring among those with specific *BRAF* or *MAP2K1* variants (Battaglia et al., 2021; Pierpont et al., 2022). Epilepsy in CFCS is often resistant to treatment and has been reported to cause early death in some patients (Pierpont et al., 2022). Polytherapy with multiple anti-seizure medications (ASMs) is common, leaving patients susceptible to significant medication-related adverse effects that could exacerbate CFCS complications and impair quality of life (Pierpont et al., 2014; Yoon et al., 2007). The failure of epilepsy treatment could also lead to the use of alternative pharmacological and non-pharmacological approaches such as surgical intervention, dietary therapies and/or neuromodulation (Aizaki et al., 2011; Laxer et al., 2014). While the deleterious effects of epilepsy in CFCS are apparent, less is known about treatment responsiveness to specific ASMs or other interventions. With the goal of better

informing treatment decisions and future therapeutic trials, the present study aimed to characterize seizure history and semiology in patients with CFCS, quantify the neurologic disease burden of CFCS, and evaluate the caregiver-perceived efficacy and adverse effects of ASMs.

Methods

Participants

Study participants were recruited internationally through email listservs and social media postings by CFCS patient advocacy groups and at the CFC International conference. Inclusion criteria required that participants were the parent/legal guardian of a living or deceased person (minimum age 3 months) with CFCS; had English, Spanish, or German language fluency; and provided access to documentation confirming their child's CFCS diagnosis via molecular genetic testing. Written informed consent was obtained from parents/caregivers prior to enrollment. The consent forms and survey were available in English and German languages. Spanish-speaking participants completed the English forms with interpreter assistance. Participants from 14 different countries were enrolled; associations between genotype variants and the neurological and neurodevelopmental features of study participants in this cohort have previously been published (Pierpont et al., 2022). The study was approved by the University of Minnesota Institutional Review Board (STUDY00006097). Study data were collected between June 2019 and December 2021.

Survey design

Caregivers provided legal authorizations compliant with the Health Insurance Portability and Accountability Act (HIPAA) to release retrospective medical records from genetic and neurological health care providers of their child with CFCS, and completed an electronic survey administered and stored within a Research Electronic Data Capture (REDCap) database. Using similar survey methods to other published studies assessing epilepsy phenotypes and treatment response in individuals with genetic conditions, questions on the caregiver survey were designed to assess the presence, type, and frequency of seizures among children and young adults with CFCS (Conant et al., 2014; Ho et al., 2018). When available, seizure semiology was confirmed with review of medical records by a board-certified neurologist (D.L.K.). Participants provided a chronological record of all ASMs used and response to treatment. To enable comparison across medications, an ordinal "efficacy score" for each medication episode (i.e., span during which a medication was used) was assigned along on a five-point scale (5-complete seizure control; 4-greater than 50% control of seizures; 3-less than 50% control; 2-no change in seizure control; 1-seizures worsened, or the medication was discontinued due to adverse effects). In addition, a binary metric was used to capture the frequency of a positive treatment response. A "good response" to an ASM was recorded when caregivers reported >50% decrease in seizures in response to medication; a "poor response" was recorded when caregivers reported no improvement at all or worsening of seizures.

Seizure severity scoring

A seizure severity score was calculated based on parent responses to survey questions and review of medical records. Scores were derived using the Early Childhood Epilepsy Severity Scale (E-Chess; Humphrey et al., 2008). This scale quantifies seizure burden based on the following parameters: the time period of seizure activity; seizure frequency in the past year; number of seizure types in the past year; number of lifetime ASMs trialed; and current response to ASMs or other treatments. Higher scores indicated greater severity of seizures.

Neurologic disease burden

A version of the Impact of Childhood Neurological Disability (ICND) scale adapted for CFCS was used to assess the disease burden impact on participation in major aspects of life. This caregiver questionnaire measures the impact of a neurologic disability condition across 11 domains (e.g., health, relationships, participation in social and family activities, school performance, caregiver's hopes for their child's future).(Camfield et al., 2003) Caregivers provided ratings along a 5-point scale to indicate how significantly CFCS affected each facet of life. An average ICND score was computed across all items relevant to each participant. Higher scores indicated a more substantial disease impact on life activities.

Statistical analysis

Standard descriptive statistics and t-test confidence intervals (CIs) were computed and tabulated using R software (v.4.2.1). When comparing efficacy scores of ASMs, only medications used by 10 or more individuals were considered. Although in some instances combinations of ASMs were taken together, the goal was to estimate overall efficacy of individual drugs; therefore, analyses were performed on each ASM regardless of the chronological order it was taken and whether it was used alone or in combination. An efficacy score was considered missing if the response to the seizure control survey question was "I don't know/remember." Medication efficacy was calculated by considering all scorable uses of each ASM.

Results

Completed surveys were obtained for 138 individuals with CFC syndrome, ranging from 7 months-old to 28 years (mean age: 12.2 years, SD: 7.6). A lifetime history of seizures was reported for 76/138 (55%) individuals. Two patients (one with a *MAPK2* variant and seizure-like episodes; one with a *BRAF* variant and possible febrile seizure) had seizure semiology that could not be conclusively classified as epileptic. The following analyses focus primarily on the characteristics and treatment response for the remaining 74 individuals with confirmed epilepsy phenotypes. Demographic information and epilepsy-related characteristics are reported in Table 1. The following countries (*n*) were represented among patients with confirmed epilepsy: United States (50), Germany (9), United Kingdom (5), Canada (3), Australia (2), New Zealand (2), Belgium (1), Brazil (1) and Switzerland (1).

Seizure semiology

Seizure semiology was often complex; the majority of CFCS patients with epilepsy experienced more than one seizure type (47/74; 64%). Generalized tonic-clonic and focal

were the two most common seizure types observed, each affecting more than half of those with epilepsy. Figure 1 shows Spearman correlation coefficients for co-occurrence of the different seizure types. Generalized tonic-clonic seizures often co-occurred with focal seizures within the same individual. Similarly, myoclonic and drop seizures were commonly co-occurring with epileptic spasms; 8/16 patients with epileptic spasms had one of these other seizure types.

Burden of neurologic disease

Epilepsy in CFCS can lead to frequent hospitalizations; more than half of the cohort with epilepsy had multiple hospital admissions for seizures (Table 1). Status epilepticus, defined as a seizure lasting longer than five minutes, occurred in 53/73 patients (73%). Seizure control was not attained or maintained for many individuals at the time of the survey. Caregivers of 34/74 individuals (46%) estimated that seizures had occurred at least weekly, and up to multiple times per day, over the course of the past year. Given these statistics, the disease burden of CFCS was examined in relation to epilepsy status (Figure 2). The caregiver-rated disease burden of CFCS on daily life activities was greater among patients with a history of epilepsy (mean ICND: 3.7; SD: 0.9) than those without epilepsy (mean ICND: 3.1; SD 0.8), mean difference: 0.5; 99% CI: 0.1, 0.9; $p<0.01$. Furthermore, in patients who had experienced epilepsy, a higher E-CHESS seizure severity score was also associated with more substantial impact of CFCS on daily life activities (Pearson correlation 0.34; Figure 2).

Treatment response

Among patients with epilepsy, most (92%) had trialed one or more ASMs (Table 2). ASMs that were trialed at least 10 times within the cohort are listed in Table 3 from highest efficacy score to lowest efficacy score. In general, sodium-channel blockers (typically prescribed for chronic use) and benzodiazepines (typically prescribed as rescue medications) were most highly ranked. The ASM with the best reported efficacy score based on caregiver report was oxcarbazepine, with a good response (>50% reduction in seizures) reported in 16/21 (76%) individuals who used this medication. Two other sodium-channel blockers (zonisamide and lacosamide) had relatively high efficacy scores. Levetiracetam was the most frequently prescribed ASM, with 20/74 (27%) of patients with epilepsy taking it as their first ASM and 42/74 (57%) trialing it at some point in their medication history. Levetiracetam had a lower efficacy score than three of the sodium-channel blocking medications (oxcarbazepine, zonisamide and lacosamide). A good treatment response was indicated by caregivers in fewer than half of patients who took levetiracetam (14/39; 36%).

There were no clear genotype-phenotype relationships regarding efficacy of ASMs, although a slightly higher efficacy score and frequency of good response was calculated for levetiracetam among the subcohort of patients with *BRAF* variants as compared to those with *MAP2K1* variants (Table 3; 99% CI: −0.5, 1.7). Both subcohorts appeared to have relatively good treatment response with respect to sodium-channel blockers, with oxcarbazepine having the highest efficacy score.

Adverse effects of ASMs reported by caregivers are tabulated in Supplementary Table 1. Lethargy, drowsiness, hypersomnolence, irritability, and aggression were some of the most commonly reported adverse effects and were frequently cited as a reason for discontinuing medication. Among chronic ASMs, the least tolerated was valproate, with 58% of participants (18/32) reporting adverse effects and 19% (6/32) stopping the medication due to those effects. Three of the sodium-channel blockers (oxcarbazepine, lacosamide, and zonisamide), as well as clonazepam and diazepam, were all reported as having a relatively low rate of adverse effects (<30% of users). For levetiracetam, adverse effects occurred in 33% (14/42) of users, with 10% (4/42) discontinuing medication due to adverse effects.

Nonpharmacologic therapy approaches were reported among 19/74 participants. Two patients underwent temporal lobe epilepsy surgery, with one caregiver noting post-surgical improvement. For this patient, seizures began in infancy and worsened around age 6 with resistance to multiple ASMs. Medical records indicate that MRI-guided stereotactic laser ablation of the mesial temporal lobe at age 7 reduced seizure frequency from an average of two focal seizures per day to being seizure-free without use of ASMs. For the second patient, intractable focal epilepsy was treated with left anterior temporal lobectomy at age 7 and subsequent lobectomy revision at age 8. Refractory seizures continued after both surgeries. Vagus nerve stimulation (VNS) was another treatment approach used for six patients. Among these patients, >50% reduction in seizure frequency was reported for two cases (33%); short-term improvement followed by gradual reduction in effectiveness occurred in one case (17%); and no improvement at all with continued refractory seizures was observed for three cases (50%). Thirteen patients trialed a ketogenic diet, of which caregiver responses and medicals records indicated that only 4/13 (31%) experienced some clinical benefit, i.e., reduction in seizures. Several caregivers provided free response information regarding alternative therapies tried, including nutritional supplements, neurofeedback, and cannabidiol, but responses for these approaches were not sufficiently well-documented to inform efficacy.

Discussion

Between the neonatal period and young adulthood, the majority of individuals with CFCS will develop epilepsy, often in the first years of life. (Battaglia et al., 2021; Pierpont et al., 2022). The association between seizure severity in CFCS and functional outcomes in key neurodevelopmental domains such as communication and mobility independence underscores the need to attain seizure control as early and as completely as possible (Kenney-Jung et al., 2022; Pierpont et al., 2022). Our investigation utilized data derived from caregiver surveys and review of medical records to characterize the semiology and impact of epilepsy in CFCS and to assess the tolerability and efficacy of currently available treatments. The results confirm previous reports that many individuals with CFCS experience a high clinical burden from seizures. Epilepsy frequently involved multiple seizure types, repeated hospitalizations, prolonged seizures, and/or adverse effects of ASMs. Moreover, the presence and severity of seizures was associated with a higher disability impact, i.e., more limitations regarding overall participation in family, social, and academic activities. These findings highlight the inadequacies of existing treatment approaches to prevent significant neurologic burden from epilepsy in CFCS.

In terms of treatment response to ASMs, this study demonstrates that epilepsy in CFCS can be extremely drug-resistant, with more than half of individuals trialing three or more ASMs, and more than a third trialing at least five ASMs. Survey results indicate that the most commonly prescribed initial medications at seizure onset were levetiracetam (n=20), oxcarbazepine (n=10) and phenobarbital (n=6). Analysis of efficacy scores across ASMs suggested that certain medications conferred better seizure control than others. Oxcarbazepine was rated as the most effective in decreasing seizures and had a low frequency of patients discontinuing treatment due to adverse effects (1/24; 4%). Along with oxcarbazepine, two other medications with sodium-channel blocking activity (zonisamide and lacosamide) showed a relatively high efficacy score with similarly low rates of adverse effects. Although levetiracetam was a common first-choice medication, it emerged as less effective in terms of seizure reduction and had a similar rate of adverse events as oxcarbazepine. These results suggest that clinicians may want to consider early use of a sodium-channel blocking agent for seizure control in CFCS. Although findings vary widely across other genetic syndromes associated with epilepsy, a similar pattern has been observed in other genetically-defined cohorts (Cutts et al., 2022). These findings are also consistent with recent large-scale trials reporting better clinical effectiveness of oxcarbazepine relative to levetiracetam for infantile focal epilepsy and newly diagnosed focal epilepsy (Marson et al., 2021; Zhao et al., 2022). Finally, while two benzodiazepines (diazepam, clonazepam) showed relatively favorable response in our CFCS cohort in terms of seizure control, it is important to note that these ASMs are frequently used as “rescue medications” for people with epilepsy rather than chronically – a distinction our survey was unable to make. Risk of sedation, overdose, and dependence can be observed with prolonged use.

Given the potential for severe consequences that include early fatality, the failure of conventional treatment approaches to remit seizures motivates exploration of potential therapies targeting the underlying molecular pathology in CFCS. Although CFCS is very rare, it is caused by germline pathogenic variants in a well-defined and widely active cellular signaling pathway. In previous genotype-phenotype analyses, a higher likelihood of severe seizures was mapped to the protein kinase domain of *BRAF* as well as the common p.Y130 variant of *MAP2K1* (Pierpont et al., 2022). Battaglia et al. also reported that variants affecting the inhibitory turn region of *BRAF*, which destabilizes the autoinhibited state of B-raf, seem to be associated with the most severe epilepsy phenotypes (Battaglia et al., 2021). These studies provide important prognostic information for newly diagnosed individuals and suggest relevant loci to consider for preclinical models to test potential epilepsy-targeted therapeutics. Notably, our research suggests that individuals with *MAP2K1* variants and *KRAS* variants are at lower risk of severe epilepsy. At the time of the survey, few of the patients with variants in these genes (*MAP2K1*=2/10; *KRAS*=0/2) had confirmed epilepsy, and none were having frequent seizures (i.e., at least monthly) or had been prescribed ASMs in the past year. These findings are consistent with review of cases in the literature showing infrequent reporting of epilepsy in these genotypes (Pierpont et al., 2022).

Disruption of RAS-MAPK signaling via somatic and germline variants has been well-researched for its association with tumors and other cancers, with significant efforts into therapeutic development (Dunnett-Kane et al., 2020). Recently, a connection has been made between brain somatic variants affecting the RAS-MAPK pathway and focal epilepsies

(Sran & Bedrosian, 2023). In one study, activating somatic variants in *BRAF, PTPN11,* and other genes along the RAS-MAPK pathway were seen in 10/105 (10%) hippocampal resections from mesial temporal lobe epilepsy patients (Khoshkhoo et al., 2023). This connection between epilepsy more broadly and the RAS-MAPK pathway has considerable implications for understanding how aberrant signaling in different brain regions and cell types may result in different phenotypic consequences. The potential for targeted therapeutic approaches has also been demonstrated in recent studies. Animal models involving *BRAF* p.V600E mosaicism have demonstrated resolution of seizure activity upon treatment with a BRAF inhibitor (i.e., vemurafenib; Koh et al., 2018); however, the generalizability of this finding to the CFCS population is unclear given that this particular variant is not seen in CFCS. A mouse model of the *MAP2K1* Y130C variant has been developed with a phenotype involving neuropathology (i.e., changes in cranial parameters; astrogliosis), which could be useful for testing hypotheses regarding neurological treatment approaches (Aoidi et al., 2018). In terms of clinical findings, a recent case report described use of the MEK inhibitor (i.e., selumetinib) to treat a progressive optic pathway glioma in child with neurofibromatosis type 1 who also had medically refractory epilepsy. This patient showed resolution of seizures upon initiation of therapy with re-emergence of seizures after dose reduction and subsequent cessation of seizures upon return to full dose (Cantor et al., 2022). These findings suggest potentially exciting future avenues for epilepsy management in those with RAS-MAPK variants.

Limitations

Use of caregiver surveys, along with retrospective chart review, is an increasingly common research strategy to understand the treatment experience in genetically well-defined but rare conditions (Cutts et al., 2022). This methodology enables multinational participation, larger samples sizes, and provides a family-centered perspective. However, survey results were constrained by a reliance on the accuracy of retrospective caregiver recollections and their interpretation of survey questions. It can also be challenging to definitively classify seizures (e.g., secondary versus primary generalized seizures) based on semiology. Prospective, longitudinal trials enabling dynamic analysis of electroclinical phenotypes and response to specific epilepsy therapies would allow a more comprehensive approach. Other limitations of the current study include the inability to analyze combinations of ASMs used in polytherapy and the lack of information about ASM dosing. The results of the treatment efficacy analysis are also likely to be most applicable for treatment of the more common seizure types (e.g., generalized tonic-clonic and focal seizures) seen in CFCS; treatment of infantile epileptic spasms syndrome and other less common presentations of epilepsy requires other specialized treatment approaches (Kenney-Jung et al., 2022). Additionally, although the majority of study participants with epilepsy were from North America or Europe (93%), national and regional differences in prescribing patterns must be borne in mind in any multinational study. While guidelines for standard of care treatment of epilepsy are broadly similar worldwide, availability and affordability can play a role in determining which medications are used (Pironi et al., 2022). The small sample also precluded comprehensive assessment of therapeutic response based on genotype.

Conclusion

This study is the largest to date to describe therapeutic and adverse effects of ASMs in CFCS. Comparison of the tolerability and caregiver-reported efficacy of ASMs suggests a relatively positive treatment response for sodium-channel-blocking agents. These findings can inform the development of clinical and neurological care guidelines for CFCS. Future prospective trials of ASM response as well as disease-modifying therapies would contribute to development of better methods to attain and maintain seizure control in CFCS, reduce epilepsy burden, and improve quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was supported by funding from CFC International and the National Institutes of Health's National Center for Advancing Translational Sciences, grant UL1TR002494. E.I.P. was also supported by the National Institutes of Health's National Center for Advancing Translational Sciences KL2TR002492 and the National Institutes of Health's National Institute for Neurological Disorders and Stroke K23NS123258. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. M.Z. received funding from the German Ministry of Education and Research (BMBF), project titles GeNeRARe (FKZ 01GM1902A) and NSEuroNet (FKZ 01GM1921A). All authors would like to express appreciation for the families that participated in this research and for CFC International and CFC-Syndrom e.V. for facilitating recruitment.

Data Availability Statement:

The data that support the findings of this study are available on request from the corresponding author.

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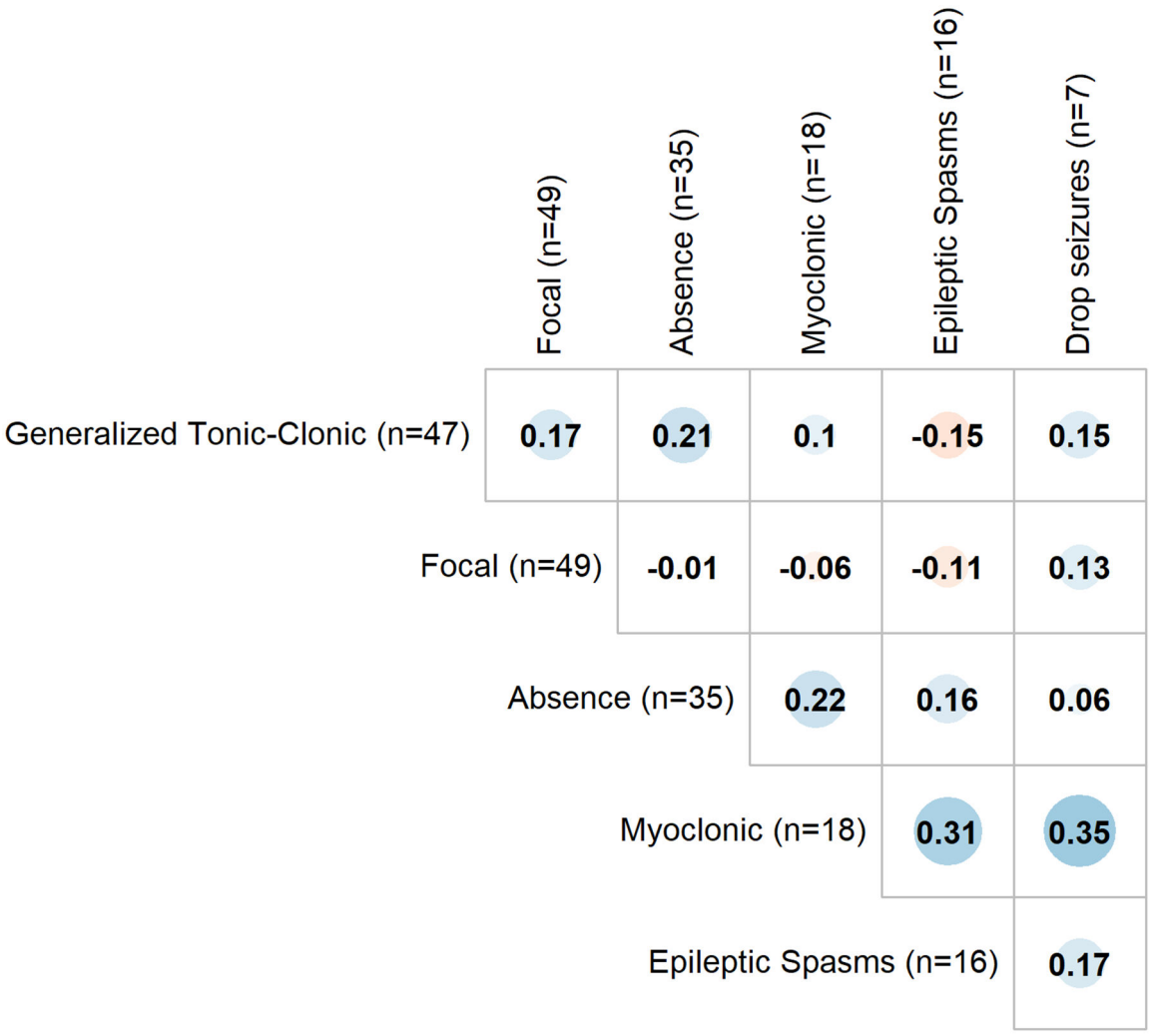

Figure 1.
Frequency and co-occurrence of seizure types over the lifetime in study participants with cardiofaciocutaneous syndrome

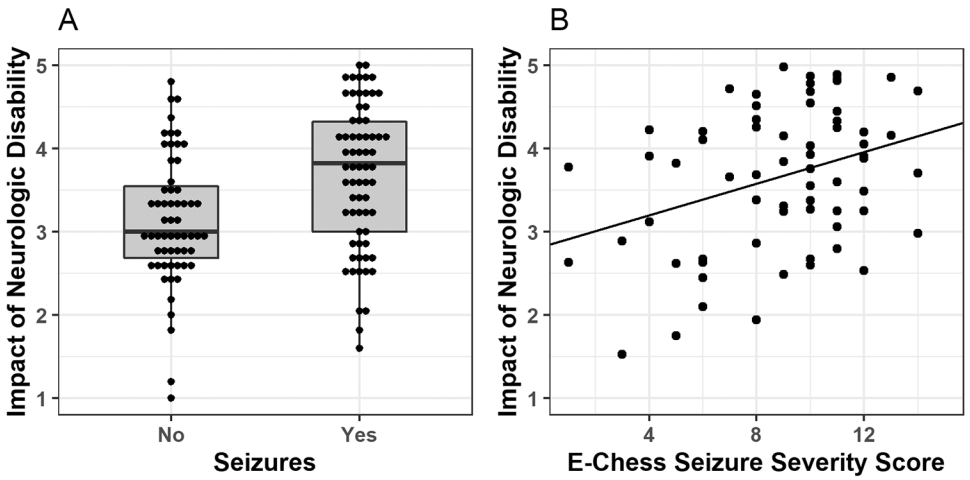

Figure 2.

Impact of neurologic disability on daily life activities in cardiofaciocutaneous syndrome based on presence and severity of epilepsy. (A). The neurological disability burden of CFCS was higher among patients with seizures as compared to those without seizures. (B). Among individuals with epilepsy, higher seizure severity scores were associated with a higher impact of neurological disability.

Table 1.

Cohort demographics and seizure characteristics among 74 individuals with CFCS with a history of epilepsy

Variable	Overall N = 74
Sex	
N	74
Female	38 (51%)
Male	36 (49%)
Affected gene	
N	74
BRAF	50 (68%)
MAP2K1	22 (30%)
MAP2K2	2 (3%)
Living status at time of survey	
N	74
Alive	68 (92%)
Deceased	6 (8%)
Age at seizure onset (years)	
N	71
Median (Q1, Q3)	3.8 (1.0-8.0)
Range	0.1-21.0
Number of seizure types (lifetime)	
N	74
1 Seizure Type	27 (36%)
2 Seizure Types	17 (23%)
≥ 3 Seizure Types	30 (41%)
Longest duration of seizures (minutes)	
N	73
< 5	21 (28%)
5-30	20 (27%)
30-60	7 (9%)
> 60	26 (35%)
Number of seizure-related hospitalizations	
N	74
≤ 1	30 (41%)
2 to 5	27 (37%)
6 to 9	6 (8%)
≥ 10	10 (14%)
Seizure frequency in past year *	
N	74

Variable	Overall N = 74
Less than weekly	40 (54%)
Weekly	19 (26%)
Daily	8 (11%)
More than daily	7 (9%)

* For deceased participants, seizure frequency refers to the year preceding death

Table 2.

Epilepsy treatment approaches among 74 patients with CFCS-associated seizures

	Overall N = 74
ASMs most commonly used at seizure onset	
Levetiracetam	20 (27%)
Oxcarbazepine	10 (14%)
Phenobarbital	6 (8%)
Valproate	5 (7%)
Carbamazepine	4 (5%)
Topiramate	4 (5%)
ASMs most commonly used at time of survey	
Levetiracetam	25 (34%)
Valproate	18 (24%)
Oxcarbazepine	15 (20%)
Lamotrigine	13 (18%)
Clonazepam	12 (16%)
Clobazam	11 (15%)
Number of ASMS currently used	
0	12 (16%)
1	17 (23%)
2+	45 (61%)
Number of ASMs used over the lifetime	
0	6 (8%)
1-2	25 (34%)
3-4	18 (24%)
5+	25 (34%)
Neurosurgical intervention	
Temporal lobe epilepsy surgery	2 (3%)
Vagus nerve stimulation (VNS)	6 (8%)
Dietary intervention	
Ketogenic Diet	13 (18%)

Table 3.

Treatment response to ASMs among patients with CFCS. Results are provided for each medication episode reported by caregivers among the full cohort (n=74) as well as in the sub-cohorts with variants in the two most common CFCS genes (*BRAF* and *MAP2K1*). Higher efficacy scores indicate better seizure control and less frequent discontinuation of medication due to adverse effects.

Drug	*N used in efficacy score Total*	Seizure control efficacy score Total	% good response Total	% poor response Total	*N used in efficacy score BRAF*	Seizure control efficacy score *BRAF*	% good response *BRAF*	% poor response *BRAF*	*N used in efficacy score MAP2K1*	Seizure control efficacy score *MAP2K1*	% good response *MAP2K1*	% poor response *MAP2K1*
Oxcarbazepine	21	3.67	76	19	12	3.67	67	25	9	3.67	89	11
*Diazepam	10	3.40	50	30	8	3.38	50	25				
*Clonazepam	15	3.13	40	20	10	3.00	40	30	5	3.40	40	0
Zonisamide	9	3.00	33	44	8	2.75	25	50				
Lacosamide	12	2.92	50	42	8	3.12	50	50				
Levetiracetam	39	2.90	36	33	25	3.12	44	32	14	2.50	21	36
Topiramate	19	2.74	32	42	15	2.80	40	40				
Lamotrigine	21	2.71	43	52	11	2.55	36	64	10	2.90	50	40
Clobazam	16	2.69	25	38	13	2.85	25	50				
Valproate	28	2.57	32	43	19	2.58	33	50	9	2.56	33	33
Phenobarbital	13	2.46	31	31	10	2.30	30	30				

Putative Mechanism of Action
Sodium Channel Blocker
GABAergic
Pyrrolidine Derivatives
More than one/other

*Typically used as rescue medication