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RESEARCH ARTICLE

Seizure Incidence Rates in Children and Adults With Familial Cerebral Cavernous Malformations

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Abstract

Background and Objectives

Seizure incidence rates related to familial cerebral cavernous malformation (FCCM) are not well described, especially for children. To measure the seizure incidence rate, examine seizure predictors, and characterize epilepsy severity, we studied a cohort of children and adults with FCCM enrolled in the Brain Vascular Malformation Consortium (BVMC).

Methods

Seizure data were collected from participants with FCCM in the BVMC at enrollment and during follow-up. We estimated seizure probability by age and tested whether cerebral cavernous malformation (CCM) counts or genotype were associated with earlier seizure onset.

Results

The study cohort included 479 FCCM cases. Median age at enrollment was 42.5 years (interquartile range 22.5–55.0) and 19% were children (<18 years old). Median large CCM count was 3 (interquartile range 1–5). Among 393 with genotyping, mutations were as follows: *CCM1* (Common Hispanic Mutation) (88%), another *CCM1* mutation (5%), *CCM2* mutations (5%), and *CCM3* mutations (2%). Prior to or during the study, 202 (42%) had a seizure. The cumulative incidence of a childhood seizure was 20.3% (95% confidence interval [CI] 17.0–23.4) and by age 80 years was 60.4% (95% CI 54.2–65.7). More total CCMs (hazard ratio [HR] 1.24 per SD unit increase, 95% CI 1.1–1.4) or more large CCMs (HR 1.5 per SD unit increase, 95% CI 1.2–1.9) than expected for age and sex increased seizure risk. A *CCM3* mutation also increased risk compared to other mutations (HR 3.11, 95% CI 1.15–8.45). Individuals with a seizure prior to enrollment had increased hospitalization rates during follow-up (incidence rate ratio 10.9, 95% CI 2.41–49.32) compared to patients without a seizure history.

Discussion

Individuals with FCCM have a high seizure incidence and those with more CCMs or *CCM3* genotype are at greater risk. Seizures increase health care utilization in FCCM.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

BVMC = Brain Vascular Malformation Consortium; **CI** = confidence interval; **CCM** = cerebral cavernous malformation; **FCCM** = familial cerebral cavernous malformation; **HR** = hazard ratio; **IQR** = interquartile range; **IRR** = incidence rate ratio; **PH** = proportional hazard; **SWI** = susceptibility-weighted imaging.

Cerebral cavernous malformations (CCMs) are low-flow clusters of abnormally dilated capillaries that can manifest as a sporadic solitary lesion in the CNS. Seizures are a commonly reported presenting symptom of CCMs as a result of hemosiderin deposition into adjacent brain tissue or as an acute symptom of a larger intracerebral hemorrhage.[1,2] In a prospective, population-based study of adults in Scotland with a first diagnosis of a brain arteriovenous malformation or CCM, the 5-year risk of a first seizure at or after diagnosis of CCM was estimated at 4%–6%.[3]

Individuals with familial CCM (FCCM), an autosomal dominant condition caused by mutations in the *CCM1*, *CCM2*, or *CCM3* genes, typically develop multiple CCMs that progressively increase in number over a lifetime.[4,5] Families with the same mutation may show a wide range of severity in number of CCMs and corresponding clinical symptoms.[6]

In 2 studies that pooled individuals with FCCM together with nonfamilial cases, estimates of the incidence rate of a first seizure were 1.5% and 2.4% per person-year.[7,8] Seizures related to a CCM often begin in childhood,[9,10] but seizure incidence rates in children with either sporadic or familial forms of CCM are not well described. In familial cases, a greater numbers of CCMs or genetic variations may influence the likelihood of a seizure or earlier seizure onset. We aimed to measure the seizure incidence rate, examine seizure predictors, and characterize epilepsy severity in a cohort of children and adults with FCCM.

Methods

Study Population and Design

The study was a retrospective and prospective longitudinal cohort study of children and adults with FCCM enrolled in the Brain Vascular Malformation Consortium (BVMC)[4] from June 2010 to August 2019. Individuals were identified and recruited at 4 enrolling sites in the United States (the University of California San Francisco, the Barrow Neurologic Institute, the University of New Mexico, and the Angioma Alliance, a patient advocacy group).

Eligibility

The first 5-year cycle of the BVMC study enrolled and genotyped patients with FCCM with the founder Q455X (Common Hispanic Mutation) in the *KRIT1/CCM1* gene (*CCM1-CHM*).[11-13] The second 5-year cycle expanded to include patients with FCCM who had a *CCM1*, *CCM2*, or *CCM3* mutation or who met 2 of the 3 following FCCM criteria: (1) clinical diagnosis of CCM, (2) multiple cavernous malformations on MRI, or (3) family history of CCM. All participants with FCCM enrolled in the BVMC were included in analyses.

Standard Protocol Approvals, Registrations, and Patient Consents

Local institutional review boards at all 4 enrolling sites approved the study. Written informed consent for the research was obtained from all participants or guardians of participants.

Data Collection

FCCM genotyping, brain MRI, and a clinical assessment with an in-person interview using standardized case report forms were performed at enrollment as previously described.[11,12] Briefly, a study neuroradiologist reviewed brain MRIs to determine the total number of CCMs as well as the size, location, and number of large CCMs (defined as ≥5 mm in maximum diameter). Lesion counting was based on axial susceptibility-weighted imaging (SWI) with 1.5 mm reconstructed images (available in 64%) or 3 mm axial T2 gradient echo sequences. Lesion measurement was based on fast spin echo T2-weighted sequences to avoid blooming artifacts that occur on gradient echo imaging.[11-13] Because of the large number of CCMs in most individuals in this cohort, it was not feasible to record the location of the numerous lesions smaller than 5 mm.

Patients were contacted annually for follow-up. At enrollment and at each study follow-up, clinical data were collected and abstracted onto standardized case report forms. Seizures were ascertained by patient or guardian report and review of medical charts. If a seizure was identified, seizure frequency in the past year, duration and type of a typical seizure, and a patient assessment of seizure control by antiseizure medications (yes/no) were collected. Emergency visits and overnight hospitalizations for any indication in the prior year were recorded.

Children were defined as <18 years old. A childhood seizure was one that occurred prior to age 18 years.

Statistical Analysis

We used summary statistics to describe the cohort demographics and clinical characteristics. For patients with a history of seizures prior to enrollment, we noted the number who provided additional information about seizures and calculated the rate of overnight hospitalizations due to seizures during study follow-up using Poisson regression. We also calculated the rate of any hospital visits (including emergency visits and overnight hospitalization) due to seizures. We used Poisson regression to calculate the incidence rate ratio (IRR) to compare hospitalization rates between patients with seizures

prior to enrollment to those without. We used Weibull proportional hazards (PH) models to estimate the probability of having a seizure between birth and various ages and the annual incidence rate; in addition, Weibull PH models were used to determine whether CCM genotype and both total and large lesion count on imaging at enrollment were individually associated with an earlier onset of first seizure adjusting for age at enrollment and sex. For the total and large lesion predictors, the values used were the residuals of log-transformed lesion counts regressed on age and sex; more plainly stated, these values can be viewed as disease severity scores (with a mean of 0 and SD of 1) where patients with more lesions than expected for their age and sex will have values greater than zero. We used the date of symptom onset reported by patient/guardian or noted in the medical record as the seizure onset to calculate incidence rate. Because the precise timing of an individual's first seizure was missing in some cases, the models used accommodated interval-censored data. We report hazard ratios (HRs) and 95% confidence intervals (CIs) for predictors of earlier seizure. Data analysis was performed on Stata 15.1 (StataCorp 2017).

Data Availability

Data are available upon reasonable request through the BVMC.

Results

The study cohort consisted of 479 individuals with FCCM who were a median age of 42.5 years (interquartile range [IQR] 22.1–55.0 years) at the time of enrollment, including 93 children (19% of the cohort). Table 1 provides demographics and clinical characteristics of the study population at the time of enrollment. There was no difference in large or total CCM counts between those with and without SWI (p = 0.38 and p = 0.32, respectively).

Table 1 Demographics and Characteristics of 479 Individuals With Familial Cerebral Cavernous Malformation Enrolled in the Brain Vascular Malformation Consortium

Characteristics	Values
Enrollment site	
Angioma Alliance	46 (10)
Barrow Neurologic Institute	39 (8)
University of California San Francisco	68 (14)
University of New Mexico	326 (68)
Age at enrollment, y	42.5 (22.1–55.0)
Age at last follow-up, y	45.0 (25.6–57.8)
Female	292 (61)
Hispanic ethnicity	363/463 (78)
Caucasian	438/452 (97)
Seizure prior to enrollment	188 (39)
Seizure prior to last follow-up	202 (42)
CCM mutation	
CCM1*, *CHM	347 (72)
***CCM1*, other mutation**	21 (4)
CCM2	19 (4)
CCM3	6 (1)
Unknown	86 (18)
Total lesion count at enrollment	14 (5–47)
Large lesion count at enrollment	3 (1–5)

Abbreviation: CCM = cerebral cavernous malformation.
Values are median (interquartile range), n (%), or n/total (%).

Seizure Incidence

At enrollment, 188 individuals reported a prior seizure. During prospective follow-up (median 2.0 years, IQR 0–5.7 years), an additional 14 individuals reported a new seizure, for a total of 202 (42%) who had a seizure at any time before or during the study. Time at risk for seizure was 16,930 years across the 479 individuals in the cohort. The cumulative incidence of a childhood seizure was 20.3% (95% CI 17.0–23.4). A 19-year-old individual with no prior seizures had a 1.17% chance of having a seizure within the next year (95% CI 1.00–1.35). The risk of a first seizure slowly decreases as patients get older. At age 80, the estimated cumulative incidence is 60.4% (95% CI 54.2%–63.3%). Table 2 provides estimates of cumulative incidence across a range of ages.

Among patients with a history of seizure prior to enrollment, the rate of overnight hospitalizations due to seizures during follow-up was 4.02 per 100 patient-years (95% CI 2.19–7.39); the rate of any hospital visit due to seizures was 9.05 per 100 patient-years (95% CI 5.02–16.3). Patients with a history of seizure prior to enrollment were more likely to be hospitalized for seizures during follow-up (IRR 10.9, 95% CI 2.41–49.32, p = 0.002) and had a greater rate of hospital visits (IRR 9.81, 95% CI 2.99–32.18, $p < 0.001$) compared to patients without a history of seizures prior to enrollment. There were 13 deaths during the study. There were no known deaths attributed to sudden unexpected death in epilepsy. Cause of death was missing or unknown in 3, but only one of these had a history of seizure.

Among study participants with a history of seizures at enrollment, 140 provided additional data about their seizure frequency, duration, and seizure management with antiseizure medications in the prior year. The median frequency was 1 seizure (IQR 1–4) per year, but 10% reported 50 or more seizures. Among 72 participants who provided their typical seizure duration, 25% reported seizures of 5 minutes and 10% reported a typical seizure duration of at least 30 minutes. Most were treated with an antiseizure medication (75%; n = 104). Of those treated with an antiseizure medication, 12.5% reported that seizures were poorly controlled.

Table 2 Probability and 95% Confidence Interval (CI) of First Seizure by Age Among Individuals With Familial Cerebral Cavernous Malformation

Age, y	Probability	95% CI
5	0.065	0.046–0.084
10	0.122	0.096–0.147
15	0.174	0.143–0.203
20	0.221	0.188–0.253
25	0.266	0.230–0.300
30	0.307	0.269–0.343
35	0.346	0.305–0.384
40	0.382	0.339–0.422
45	0.416	0.371–0.458
50	0.448	0.400–0.492
55	0.478	0.428–0.523
60	0.506	0.453–0.554
65	0.533	0.478–0.582
70	0.558	0.500–0.608
75	0.581	0.522–0.633
80	0.604	0.542–0.657

Predictors of Seizure

Individuals with higher than expected total lesion counts for their age and sex were at increased risk of an earlier first seizure (HR 1.24 per SD unit increase, 95% CI 1.08–1.43, p = 0.002, Table 3). We observed a larger effect size for higher than expected large lesion counts (HR 1.51, 95% CI 1.22–1.88, $p < 0.001$). Those with a *CCM3* mutation were at increased seizure risk compared to *CCM1-CHM* individuals (HR 3.24, 95% CI 1.19–8.83, p = 0.021), as well as when compared to all other genotypes combined (HR 3.11, 95% CI 1.14–8.45, p = 0.026). Individuals with a seizure were more likely to enroll in the study at a younger age (HR 0.63 per decade older at enrollment, 95% CI 0.57–0.69, p = 0.001).

Table 3 Predictors of Earlier Seizure Among Individuals With Familial Cerebral Cavernous Malformation

Predictor	HR	95% CI	*p* Value
CCM mutation genotype[a]			
***CCM1*, *CHM* (ref)**	—	—	—
***CCM1*, other mutation**	1.43	0.77–2.64	0.257
CCM2	1.58	0.83–3.02	0.164
CCM3	3.25	1.19–8.83	0.021
Residual total lesion count per SD unit[a]	1.24	1.08–1.43	0.002
Residual large lesion count per SD unit[a]	1.51	1.22–1.88	<0.001
Age at enrollment (per decade)	0.63	0.57–0.69	<0.001
Female	0.96	0.72–1.27	0.767

Abbreviations: CCM = cerebral cavernous malformation; CI = confidence interval; HR = hazard ratio.
[a] Predictors were tested individually while adjusting for age and sex.

Discussion

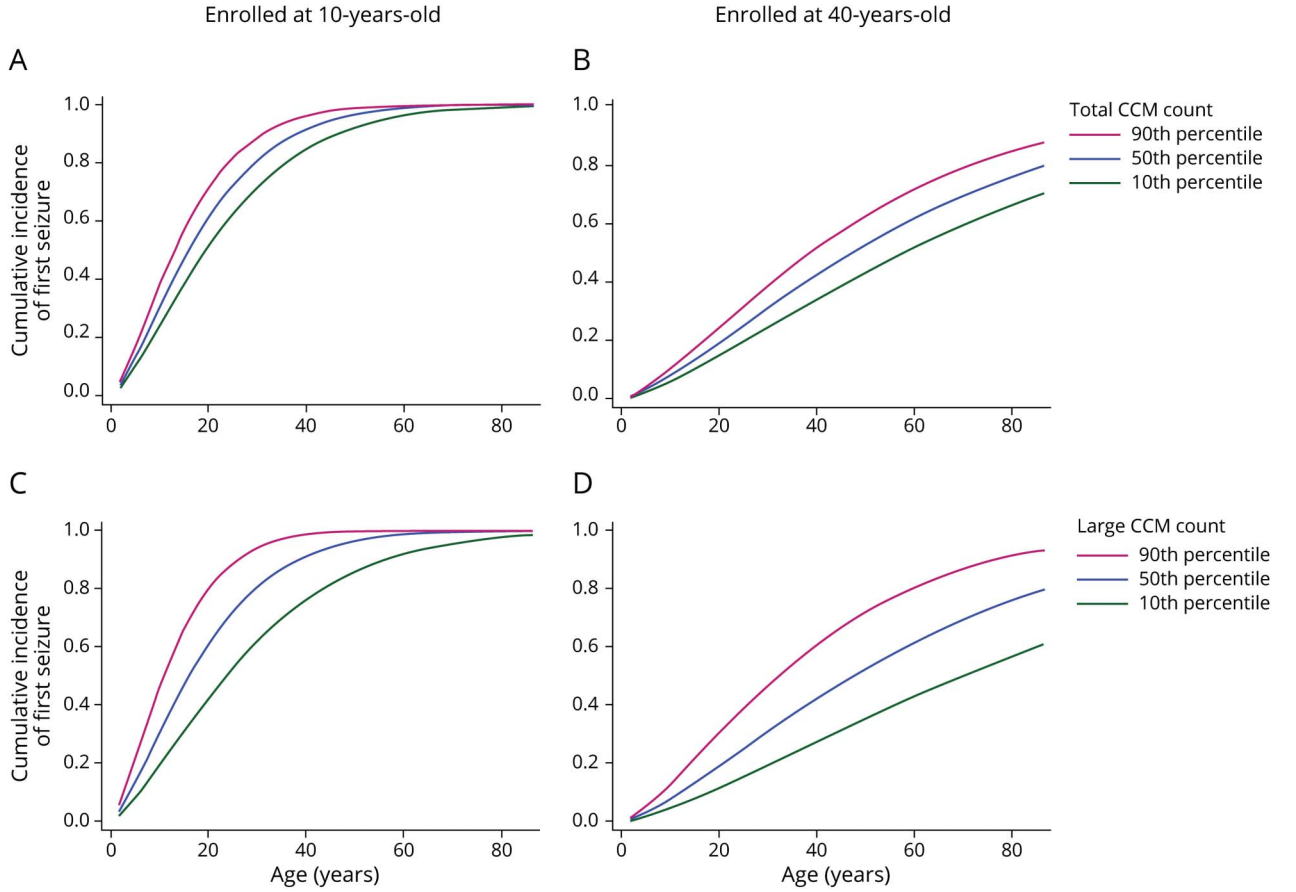
In the largest study of FCCM to date, we demonstrated that children and adults with FCCM have a high incidence rate of seizures. About one-fifth of people with FCCM have a seizure during childhood, and three-fifths have a seizure by age 80. Our analyses focused primarily on a first seizure, but the 5-year risk of epilepsy after a first seizure is adults with a CCM is estimated at 94%,[3] and a single unprovoked seizure in a person with a CCM meets the International League Against Epilepsy practical clinical definition of epilepsy.[14] The attribution of seizure to a specific CCM vs another cause was beyond the scope of our study, but it is likely that many individuals in our cohort meet criteria for probable or definite CCM-related epilepsy.[15]

Epilepsy severity is difficult to interpret without data on the number of antiseizure medication failures or on epilepsy surgery, but the high proportion of our cohort reporting poorly controlled seizures suggests that medically refractory epilepsy may be a significant problem. One quarter of those who provided typical seizure duration reported seizures longer than 5 minutes, meeting the definition of status epilepticus.[16] Frequency of status epilepticus should be interpreted with caution because patients or families may overestimate seizure duration. Only 36% reported a typical seizure duration and those who did not may have had shorter seizures. However, other measures suggest that epilepsy is a significant burden. Study participants with seizures had greater health care utilization, with 11 times greater frequency of a hospital admission or emergency department visits than those who had no seizures before enrolling in the study.

Incidence rate and predictors of earlier seizures may be useful for clinical prognosis. Prior estimates of seizure incidence rates in people with CCM excluded children or did not distinguish individuals with a solitary CCM and those with FCCM, who may have hundreds of intracranial lesions. We found that a greater lesion burden (a greater total number of CCMs or more large CCMs) is associated with earlier seizure onset and higher probability of a seizure over the course of a person's lifetime. A mutation in *CCM3*, which is typically associated with a more severe phenotype, is also associated with earlier seizures. The *CCM3* mutation is characterized by several factors that could lead to earlier seizures, including the presence of numerous CCMs, an increased risk of symptomatic hemorrhage, and the presence of meningiomas.[17]

In the BVMC cohort, individuals who had a history of seizure at the time of study enrollment were younger than individuals

Figure Cerebral Cavernous Malformation (CCM) Lesion Burden Predicts Seizure Risk in Children and Adults With Familial FCCM



A higher total number or a higher count of large CCMs (≥5 mm) is associated with an increased probability of earlier seizure, as illustrated by survival curves modeling the effects of lesion burden and age on seizure probability. (A, B) Effect of total CCM count on seizure cumulative incidence for individuals who have an average number of CCMs expected for their age (50% curve, blue) as well as those at the 10th and 90th percentiles of CCM counts (green and red curves, respectively). (C, D) Seizure cumulative incidence for individuals at the 10th, 50th, and 90th percentiles of large CCM counts expected for age. Individuals who enrolled at younger ages also had earlier seizures, illustrated by survival curves for children enrolled at 10 years of age (A and C) vs adults enrolled at 40 years of age (B and D).

who had no seizures prior to enrollment, suggesting detection bias (Figure; A and C vs B and D). A seizure may result in an earlier identification of FCCM and therefore earlier study enrollment, or may increase an individual's desire to participate in a research study. However, it is likely that a similar detection bias occurs in the clinical setting because new-onset seizures typically lead to imaging and earlier CCM diagnosis. Therefore, providers could reasonably apply our models to provide estimates of seizure likelihood to patients with FCCM in clinical practice.

Our study might not be generalizable to all people with FCCM. Recruitment from a patient advocacy group or tertiary care center could bias towards inclusion of people with more severe disease, earlier seizure onset, and higher seizure frequency. Only a small minority of our cohort (2%) have a mutation in *CCM3* because the BVMC study initially focused enrollment on families with a founder mutation in *CCM1*,[12] and later expanded enrollment to individuals with FCCM related to any CCM mutation.

Our study was limited in some ways. From the small proportion of participants with *CCM3* mutation, we could not determine whether earlier seizure onset in *CCM3* cases was primarily attributable to a greater CCM lesion burden or to other genetic or comorbid conditions. Prior studies suggest mesiotemporal or cortical CCM location is a risk factor for epilepsy.[8,18,19] We did could not determine the association of these CCM locations with epilepsy in our cohort because the locations of numerous tiny CCMs were not recorded. In addition, other factors such as treatment with statin medications, vitamin D, or aspirin may influence seizure presentation related to CCMs and have been suggested as potential therapeutics.[20-22] However, we were unable to appropriately analyze medications as seizure predictors because we did not have reliable information about the timing that medications were started or duration of treatment in relationship to seizure onset in our cohort.

Despite limitations, these data provide important prognostic information and a measure of epilepsy severity, illustrating the degree that seizures affect children and adults with FCCM.

Whereas a single seizure might not always be a dangerous event, seizures are important factors that influence patients' lives. Even a single seizure measurably decreases health-related quality of life in children.[23] People with epilepsy have greater difficulty maintaining a driver's license,[24] attain a lower level of education,[24,25] are more likely to be unemployed,[24,25] and have an increased mortality risk compared to the general population.[26] Our study suggests that patients with FCCM with seizures have more frequent emergency department visits and hospitalizations, contributing to increased health care costs, compared to those without seizures. These data may be particularly important for individuals with FCCM as new treatment strategies become available. Future studies are needed to determine the best practices to reduce the burden of seizures and epilepsy related to FCCM.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Christine Fox, MD, MAS	University of California San Francisco	Designed and conceptualized study, interpreted the data, drafted the manuscript for intellectual content
Jeffrey Nelson, MS	University of California San Francisco	Designed and conceptualized study, analyzed the data, revised the manuscript for intellectual content
Charles E. McCulloch, PhD	University of California San Francisco	Designed and conceptualized study, analyzed the data, revised the manuscript for intellectual content
Shantel Weinsheimer, PhD	University of California San Francisco	Major role in acquisition of data, revised the manuscript for intellectual content
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Helen Kim, PhD	University of California San Francisco	Designed and conceptualized study, major role in acquisition of data, interpreted the data, revised the manuscript for intellectual content

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