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Will There Be a Seizure? Predicting Seizures in Children (and Adults) with Familial Cerebral Cavernous Malformations

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Cerebral cavernous malformations (CCM) occur in the brain or spinal cord as low flow collections of sinusoidal channels lined with endothelium without tight junctions. The vessels forming these channels lack an elastic/muscular layer and blood in various stages of thrombosis and organization fills these channels. They have a dynamic biology with progressive growth and repeated hemorrhages and can present with headache, seizures or focal neurological signs related to the location and extent of hemorrhage.[1]

What do we know about seizures and CCM?

Most CCMs (48%) are diagnosed incidentally on MRI scans done for non-seizure indications[2] but seizures are the second most common symptom in patients with CCM, accounting for >25% cases.[2] The frequency of an incidental CCM in a patient with newly diagnosed epilepsy is .4-.9%. Since the incidence of epilepsy in the general population is .5-1.0%, it is likely that all patients who are found to have a CCM during the evaluation of epilepsy likely have CCM related epilepsy (CRE). CCM inheritance is either familial (20%) or sporadic (80%). Familial forms are inherited in an autosomal dominant fashion with variable penetrance and varying clinical manifestations within the same family. A loss of function mutation in either the CCM1 (KRIT1), CCM2 (malcalverin) or CCM3(PDC10) gene is causative.[1] Familial cases are likely to have multiple CCMs. The rate of new CCM formation is reported at .5-2.7% per patient year in CCM3 patients.[3,4] Established risk factors for CRE include supratentorial location (vs infratentorial), cortical involvement (vs subcortical) and archicortical or mesiotemporal (vs exclusively neocortical) localization. Controversial risk factors include lobar (other than mesiotemporal) localization, number, and size of the CCM.[2]

Most natural history studies on CCM are based on retrospective surgical series; focused chiefly on the feared outcome of hemorrhage.[4-7] The only natural history study that focused on seizures as an outcome; reports only on adults and quotes a 5 year seizure risk of 6% when patients present with bleeds vs 4% when the patients present incidentally.[8] A recent consensus recommendations paper[4] commissioned by the Angioma Alliance of UK does not address specific questions related to prevalence of seizures/epilepsy in pediatric patients (prevalence in this paper is quoted for >16 years).

With the above knowledge how would I counsel a mother with CRE about the risk of seizures in her 10-year-old child presenting to my clinic for evaluation of "spells"?

Two years ago, my best guess for the risk of seizures would have been shaky at best. Risk factors to consider might include identification of one or more CCMs on MRI, location, size, results of genetic work up. Let us assume that we did find a single CCM in the right temporal region that is 14 mm by 16 mm by 20 mm in size, has no evidence of hemorrhage-then what? Is there any better way to counsel this family about actual risks for a seizure?

The recent study by Fox et al answers some these questions.[9] Aim of the paper was to measure the seizure incidence rate, examine the seizure predictors and characterize epilepsy severity in a familial CCM cohort. Authors recruited patients who were enrolled in the brain vascular malformation consortium (BVMC). The BVMC is a multidisciplinary, inter institution group of investigators and is a part of the Rare Disease Clinical Research Network (RDCRN). Being a part of the RDCRN allows BVMC to partner with patient support organizations to allow for greater patient recruitment and collect data in a standardized fashion across institutional and geographic silos.[10]

This longitudinal; retrospective and prospective study design enrolled 479 familial CCM cases (93 children) at four sites over 9 years. Median age at enrollment was 42.5 years (IQR 22.1-55.0) and median age at last follow up was 45 years (IQR 25.6-57.8). Median follow up was 2 years (IQR 0-5.7).

What is unique about this study and how does it differ from other natural history studies in predicting a certain outcome?

In natural history studies on hemorrhage, authors who assumed that CCMs were present since birth noted annual hemorrhage rates of .3-2.3% per patient year while studies that defined

observation period as that from initial presentation and diagnosis to last follow up came up with hemorrhage rates of .5-10% per patient year.[1] Fox et al have calculated probability of having a seizure between birth and various ages using a Weibull proportional hazards (PH) method in addition to calculating an incidence rate by looking at date of seizure as the date for seizure onset. PH method models were also used to determine whether CCM genotype, number of lesions, size of lesions affected age at onset for seizures. Large lesion was defined as any lesion >5 mm in maximum diameter. Only familial CCM cases were studied.

The study found a cumulative incidence of childhood seizure at 20.3%. For the patients with a history of seizures prior to enrollment, the risk of hospitalization for seizures during follow up was higher (IRR 10.9, 95% CI 2.4-49.3). Additionally, the rate of any hospital visit due to seizures was 9.5 per 100 patient years (95% CI 5.02-16.3).

A higher lesion count than expected for age and sex increased risk for an earlier first seizure (HR 1.24 per SD unit increase, 95% CI 1.08-1.43 P =.002). A larger effect size was noted for higher-than-expected large lesion counts (HR 1.51, 95% CI 1.22-1.88 P < .001). CCM3 mutation positive patients were at thrice the risk of patients with CCM1 mutations for seizures (HR 3.24, 95% CI 1.19-8.83). For those patients reporting seizures at enrollment, 10% reported 50 or more seizures per year (median frequency = 1 seizure/year). Of those treated with antiseizure medication, 12.5% reported poor control. This number is certainly less that the 25-30% quoted in the literature for medical intractability and is likely a reflection of the type of data collected in this cohort.

Does this paper help me with answers to my clinical vignette?

All in all, for the 10-year-old patient I describe, this paper gives me a lot of material for a discussion that is based on something better than my best guess. If we don't end up with a CCM3 mutation and considering that the patient has a solitary lesion which is larger than 5 mm Table 2 in this manuscript provides a probability for seizures of 1.2% at age 10 and 1.7% by age 15 years. Additionally, if seizures develop; I might predict median seizure frequency of 1 per year and the risk of any hospital visit related to a seizure as .09 per year.

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