Familial cerebral cavernous malformation

Familial cerebral cavernous malformations, which account for at least 20% of all cases, can be passed from parent to child. Individuals with familial CCMs typically have multiple lesions. Familial CCMs are passed through families in an autosomal dominant manner, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Each child of an individual with familial CCM has a 50% chance of inheriting the mutation.

It is an autosomal-dominant disease with incomplete penetrance. The pathogenic genes of FCCM have been mapped into three loci: CCM1/KRIT1, CCM2/MGC4607, and CCM3/PDCD10.

see https://www.ncbi.nlm.nih.gov/books/NBK1293/.

Although the clinical course is unpredictable, symptoms typically present during adult life and include headaches, focal neurological deficits, seizures, and potentially fatal stroke. In addition to neural lesions, extraneural cavernous malformations have been described in familial disease in several tissues, in particular the skin [1)].

In recent years there has been an increasing amount of publications linking FCCMs with other pathology, predominantly with extracranial and intracranial mesenchymal anomalies.

When faced with an unusual clinical feature in a patient with a Mendelian disorder, the clinician may entertain the possibilities of either the feature representing a novel manifestation of that disorder or the co-existence of a different inherited condition. Here we describe an individual with a submandibular oncocytoma, pulmonary bullae and renal cysts as well as multiple cerebral cavernous malformations and haemangiomas. Genetic investigations revealed constitutional mutations in FLCN, associated with Birt-Hogg-Dubé syndrome (BHD) and CCM2, associated with familial cerebral cavernous malformation. Intracranial vascular pathologies (but not cerebral cavernous malformation) have recently been described in a number of individuals with BHD (Kapoor et al. in Fam Cancer 14:595-597, 10.1007/s10689-015-9807-y , 2015) but it is not yet clear whether they represent a genuine part of that conditions' phenotypic spectrum. We suggest that in such instances of potentially novel clinical features, more extensive genetic testing to consider co-existing conditions should be considered where available. The increased use of next generation sequencing applications in diagnostic settings is likely to lead more cases such as this being revealed [2)].

A study described an unusual association between 2 independent hereditary diseases of confirmed genetic origin-a combination that has not been described previously [3)].

Rosário Marques et al. documented a novel mutation on KRIT1 gene, and the second to be reported in a Portuguese family. This mutation consists in a two nucleotide insertion (c.947_948insAC) within the exon 10, resulting in premature protein termination (p.Leu317Argfs*2). These findings will hopefully contribute to a better clinical, imaging and genetic characterisation of this disease, particularly while trying to identify the factors that influence its treatment and prognosis [4)].

Yang et al., investigated the genetic mutation in a Chinese family with FCCM.

The proband is a 29-year-old female presenting with a 1-month history of headache. Brain magnetic resonance imaging (MRI) revealed multiple intracranial lesions, the largest one showing a popcorn-like appearance. After a 4-year conservative observation, there was no significant clinical or radiological progression. Family investigation found five of her relatives had multiple CCM lesions. DNA sequencing analysis in the proband disclosed a novel heterozygous deletion mutation (c.1919delT; p.Phe640SerfsX21) in exon 17 of the CCM1/KRIT1 gene. This mutation leads to a frameshift and is predicted to cause a premature termination codon to generate a truncated Krev interaction trapped-1 (Krit1) protein of 659 amino acids. The mutation segregated with the disease in the family. C The current study identified a novel CCM1/KRIT1 heterozygous deletion mutation (c.1919delT) associated with FCCM. The findings expand the CCM gene mutation profiles in the Chinese population, which will be beneficial for genetic counseling [5)].

A proband was hospitalized for sudden unconsciousness and underwent surgical treatment. The section of lesions showed classical cavernous-dilated vessels without intervening brain parenchyma, and hemosiderin-laden macrophages were accumulated in the surrounding tissue. In addition, magnetic resonance imaging (MRI) showed severe multiple cerebral cavernous malformation (CCM) lesions in cerebrum, brainstem, and cerebellum in other affected subjects. Especially, for the proband's mother, hundreds of lesions were presented, and a few lesions were found in the expanded lateral ventricle (Evans' index =0.33). Moreover, she showed the similar symptoms of hydrocephalus, including headache, dizziness, and diplopia. It was extremely rare in previous reports. To date, the genetic alterations leading to FCCM in Chinese population remain largely unknown. We investigated genetic defects of this family. Sequence analyses disclosed a novel heterozygous insertion mutation (c.1896_1897insT; p.Pro633SerfsTer22) in KRIT1/CCM1. Moreover, our real-time PCR results revealed that the mRNA level of KRIT1/CCM1 were significantly decreased in FCCM subjects (CCM family =0.42 ± 0.20 vs. healthy control =1.01 ± 0.16, P = 0.004). It indicated that this mutation could cause KRIT1/CCM1 functional mRNA deficiency. It may be closely related with the pathogenesis of FCCM. Our findings provided a new gene mutation profile which will be of great significance in early diagnosis and appropriate clinical surveillance of FCCM patients [6)].

Natural History

The 5-year annual and cumulative symptomatic hemorrhagic risk in our pediatric FCCM cohort equals the overall risk described in children and adults with all types of CCM. Imaging features at first brain MRI may help to predict potential symptomatic hemorrhage at 5-year follow-up [7)].

Case series

The authors assessed the influence of medication intake on first or recurrent intracerebral hemorrhage (ICH) using univariate and multivariate logistic regression adjusted for age and sex. The

longitudinal cumulative 5-year risk of hemorrhage was calculated by applying Kaplan-Meier and Cox regression analyses adjusted for age and sex.

Results: Two hundred five patients with FCCMs were included in the study. Multivariate Cox regression analysis revealed ICH as a predictor for recurrent hemorrhage during the 5-year FU. The authors also noted a tendency toward a decreased association with ICH during FU in patients on statin medication (HR 0.22, 95% CI 0.03-1.68, p = 0.143), although the relationship was not statistically significant. No bleeding events were observed in patients on antithrombotic therapy. Kaplan-Meier analysis and log-rank test showed a tendency toward a low risk of ICH during FU in patients on antithrombotic therapy (p = 0.085), as well as those on statin therapy (p = 0.193). The cumulative 5-year risk of bleeding was 22.82% (95% CI 17.33%-29.38%) for the entire cohort, 31.41% (95% CI 23.26%-40.83%) for patients with a history of ICH, 26.54% (95% CI 11.13%-49.7%) for individuals on beta-blocker medication, 6.25% (95% CI 0.33%-32.29%) for patients on statin medication, and 0% (95% CI 0%-30.13%) for patients on antithrombotic medication.

ICH at diagnosis was identified as a risk factor for recurrent hemorrhage. Although the relationships were not statistically significant, statin and antithrombotic medication tended to be associated with decreased bleeding events [8].

Fifty-seven familial CCM type-1 patients were included in this institutional review board-approved study. Baseline SWI (n = 57) and follow-up SWI (n = 17) were performed on a 3T Siemens MR scanner with lesions counted manually by the study neuroradiologist. We modified an algorithm for detecting radiation-induced microbleeds on SWI images in brain tumor patients, using a training set of 22 manually delineated CCM microbleeds from two random scans. Manual and automated counts were compared using linear regression with robust standard errors, intra-class correlation (ICC), and paired t tests. A validation analysis comparing the automated counting algorithm and a consensus read from two neuroradiologists was used to calculate sensitivity, the proportion of microbleeds correctly identified by the automated algorithm. RESULTS: Automated and manual microbleed counts were in strong agreement in both baseline (ICC = 0.95, p < 0.001) and longitudinal (ICC = 0.88, p < 0.001) analyses, with no significant difference between average counts (baseline p = 0.11, longitudinal p = 0.29). In the validation analysis, the algorithm correctly identified 662 of 1325 microbleeds (sensitivity=50%), again with strong agreement between approaches (ICC = 0.77, p < 0.001). CONCLUSION: The automated algorithm is a consistent method for counting microbleeds in familial CCM patients that can facilitate lesion quantification and tracking [9].

The authors retrospectively reviewed abdominal CT scans in 38 patients with fCCM, 38 unaffected age- and sex-matched control subjects, and 13 patients with sporadic, nonfamilial cerebral cavernous malformation (CCM). The size, number, and laterality of calcifications and the morphologic characteristics of the adrenal gland were recorded. Brain lesion count was recorded from brain magnetic resonance (MR) imaging in patients with fCCM. The prevalence of adrenal calcifications in patients with fCCM was compared with that in unaffected control subjects and those with sporadic CCM by using the Fisher exact test. Additional analyses were performed to determine whether age and brain lesion count were associated with adrenal findings in patients with fCCM. Results Small focal calcifications (SFCs) (≤5 mm) were seen in one or both adrenal glands in 19 of the 38 patients with fCCM (50%), compared with 0 of the 38 unaffected control subjects (P < .001) and 0 of the 13 subjects with sporadic CCM (P = .001). Adrenal calcifications in patients with fCCM were more frequently left sided, with 17 of 19 patients having more SFCs in the left adrenal gland than the right

adrenal gland and 50 of the 61 observed SFCs (82%) found in the left adrenal gland. No subjects had SFCs on the right side only. In patients with fCCM, the presence of SFCs showed a positive correlation with age (P < .001) and number of brain lesions (P < .001). Conclusion Adrenal calcifications identified on CT scans are common in patients with fCCM and may be a clinically silent manifestation of disease [10].

1)
de Vos IJ, Vreeburg M, Koek GH, van Steensel MA. Review of familial cerebral cavernous malformations and report of seven additional families. Am J Med Genet A. 2017 Feb;173(2):338-351. doi: 10.1002/ajmg.a.38028. Epub 2016 Oct 28. Review. PubMed PMID: 27792856.
2)
Whitworth J, Stausbøl-Grøn B, Skytte AB. Genetically diagnosed Birt-Hogg-Dubé syndrome and familial cerebral cavernous malformations in the same individual: a case report. Fam Cancer. 2017 Jan;16(1):139-142. doi: 10.1007/s10689-016-9928-y. PubMed PMID: 27722904; PubMed Central PMCID: PMC5243871.
3)
Belousova OB, Okishev DN, Ignatova TM, Balashova MS, Boulygina ES. Hereditary Multiple Cerebral Cavernous Malformations Associated with Wilson Disease and Multiple Lipomatosis. World Neurosurg. 2017 Sep;105:1034.e1-1034.e6. doi: 10.1016/j.wneu.2017.06.002. Epub 2017 Jun 8. PubMed PMID: 28602929.
4)
Rosário Marques I, Antunes F, Ferreira N, Grunho M. Familial cerebral cavernous malformation: Report of a novel KRIT1 mutation in a Portuguese family. Seizure. 2017 Nov 10;53:72-74. doi: 10.1016/j.seizure.2017.10.020. [Epub ahead of print] PubMed PMID: 29145060.
5)
Yang C, Wu B, Zhong H, Li Y, Zheng X, Xu Y. A novel CCM1/KRIT1 heterozygous deletion mutation (c.1919delT) in a Chinese family with familial cerebral cavernous malformation. Clin Neurol Neurosurg. 2017 Nov 20;164:44-46. doi: 10.1016/j.clineuro.2017.11.005. [Epub ahead of print] PubMed PMID: 29169046.
6)
Wang H, Pan Y, Zhang Z, Li X, Xu Z, Suo Y, Li W, Wang Y. A Novel KRIT1/CCM1 Gene Insertion Mutation Associated with Cerebral Cavernous Malformations in a Chinese Family. J Mol Neurosci. 2017 Feb;61(2):221-226. doi: 10.1007/s12031-017-0881-5. Epub 2017 Feb 3. PubMed PMID: 28160210.
7)
Geraldo AF, Alves CAPF, Luis A, Tortora D, Guimarães J, Abreu D, Reimão S, Pavanello M, de Marco P, Scala M, Capra V, Vaz R, Rossi A, Schwartz ES, Mankad K, Severino M. Natural history of familial cerebral cavernous malformation syndrome in children: a multicenter cohort study. Neuroradiology. 2022 Oct 6. doi: 10.1007/s00234-022-03056-y. Epub ahead of print. PMID: 36198887.
8)
Santos AN, Rauschenbach L, Saban D, Chen B, Lenkeit A, Gull HH, Rieß C, Deuschl C, Schmidt B, Jabbarli R, Wrede KH, Zhu Y, Frank B, Sure U, Dammann P. Medication intake and hemorrhage risk in patients with familial cerebral cavernous malformations. J Neurosurg. 2022 Feb 25:1-7. doi: 10.3171/2022.1.JNS212724. Epub ahead of print. PMID: 35213840.
9)
Zou X, Hart BL, Mabray M, Bartlett MR, Bian W, Nelson J, Morrison LA, McCulloch CE, Hess CP, Lupo JM, Kim H. Automated algorithm for counting microbleeds in patients with familial cerebral cavernous malformations. Neuroradiology. 2017 Jul;59(7):685-690. doi: 10.1007/s00234-017-1845-8. Epub 2017 May 22. PubMed PMID: 28534135; PubMed Central PMCID: PMC5501247.
10)
Strickland CD, Eberhardt SC, Bartlett MR, Nelson J, Kim H, Morrison LA, Hart BL. Familial Cerebral Cavernous Malformations Are Associated with Adrenal Calcifications on CT Scans: An Imaging

Biomarker for a Hereditary Cerebrovascular Condition. Radiology. 2017 Aug;284(2):443-450. doi: 10.1148/radiol.2017161127. Epub 2017 Mar 20. PubMed PMID: 28318403; PubMed Central PMCID: PMC5519414.