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ORIGINAL ARTICLE

Inherited cavernous malformations of the central nervous system: clinical and genetic features in 19 Swiss families

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Abstract Cavernous malformations (CCMs) are benign, well-circumscribed, and mulberry-like vascular malformations that may be found in the central nervous system in up to 0.5% of the population. Cavernous malformations can be sporadic or inherited. The common symptoms are epilepsy, hemorrhages, focal neurological deficits, and headaches. However, CCMs are often asymptomatic. The familiar form is associated with three gene loci, namely 7q21-q22 (CCM1), 7p13-p15 (CCM2), and 3q25.2-q27 (CCM3) and is inherited as an autosomal dominant trait with incomplete penetrance. The CCM genes are identified as Krit 1 (CCM1), MGC4607 (CCM2), and PDCD10 (CCM3). Here, we present the clinical and genetic features of CCMs in 19 Swiss families. Furthermore, surgical aspects in such families are also discussed.

Keywords Cavernous malformations · Genetics · CCM1 · CCM2 · Surgical outcome

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Introduction

Cavernous malformations (CCMs) of the central nervous system are well-circumscribed, lobulated, mulberry-like, and often encapsulated structures that can vary greatly in size [25]. They are found in about 0.5% of the population and represent approximately 10–20% of cerebral vascular lesions [22]. Microscopically, CCMs consist of enlarged thin-walled blood vessels without intervening neural tissue. Clinically, they may remain asymptomatic, but often manifest with epileptic seizures, gross hemorrhages, focal neurological deficits, and/or headache [7, 24, 26].

Cavernous malformations may be sporadic or inherited in an autosomal dominant fashion with a high penetrance [9, 11]. While sporadic CCMs are often solitary, the familial form is usually associated with multiple lesions [26]. In genetic studies, three genetic loci have been defined [5]: CCM1 on chromosome 7q21-q22 (MIM 116860) accounting for 40% of all familial cases [6, 9, 11, 18], CCM2 on 7p13-p15 (MIM 603284) accounting for 13–20% [17, 29], and CCM3 on 3q25.2-q27 (MIM 603285) for 40% [2].

In this study, we present the clinical and genetic features of 19 Swiss families with inherited CCMs.

Patients and methods

The families were ascertained by a national search procedure performed at eight Swiss regional and university hospitals. Criteria for inclusion in this study were neuroradiologically diagnosed and/ or histopathologically proven CCMs of the CNS in at least two family members. By this search, 19 families of Swiss origin with inherited CCMs were obtained from five hospitals (Aarau, Basle, Berne, Lausanne, and Zurich). In the affected individuals, both clinical and genetic data were analyzed. If symptomatic parent–offspring pairs were available, we also measured anticipation by intergenerational comparison of mean age at symptom onset. Genetic analyses for CCM1 and CCM2 have been performed by the use of methods previously described [10, 17, 28, 29]. Due to logistic and financial reasons, we focussed on the index patients for genetic analysis. Type and outcome of surgical procedures were also presented. This study was approved by the Committee for the Protection of Human Subjects at the Dartmouth College, New Hampshire, USA.

Results

Demographic data

The 19 families comprised a total of 56 affected individuals. In these families, between two and four generations were affected. Thirty-three (59%) individuals were females and 23 males. The number of affected individuals per family ranged from 2 to 6.

Clinicopathological features

Of the 56 affected individuals, 12 (21%) were asymptomatic. These individuals have been identified in the scope of family screening. In the 44 symptomatic individuals, the most frequent manifestations encountered were epilepsy (16 or 36%), followed by focal neurological deficits (14 or 32%), hemorrhage (8 or 18%), and headache (6 or 14%). The mean age at symptom onset was 27.9 years (range, 1 to 79 years). Individuals with epilepsy became first symptomatic (mean age at onset 19.7 years), followed by headache (29.2 years), focal neurological deficits (29.3 years), and hemorrhages (40.6 years). Ten affected symptomatic individuals had an offspring with clinical symptoms. Of these parent–offspring pairs, the mean age at first clinical manifestation was 37.8 years in the first and 20.4 years in the second generation. Of the 56 affected individuals, 32 (57%) harbored multiple CCMs (range 2 to 78 lesions), whereas, 24 (43%) had a single lesion. Of the 19 index individuals, 12 (63%) harbored multiple lesions and seven had single ones.

Genetic features

Of 37 individuals, genetic analysis has not been performed due to financial and logistic reasons. However, genetic analysis could be performed in 19 individuals representing all 19 families. Of these, in nine individuals (47%), a mutation in CCM1 has been found. The observed CCM1 mutations comprised frameshifts in four individuals (44%), nonsense mutations in three (33%), changes in the invariant splice junctions and missense mutations in each one (11% each). Six individuals (32%) had a CCM2 mutation consisting of two frameshift and one nonsense mutation. In the remaining individuals, we did not screen for CCM3.

Surgical treatment

None of the 12 asymptomatic individuals have been operated for their CCMs. Of the 44 symptomatic cases, 24 (55%) were surgically treated. Of these, 14 were operated on for their medically refractory epilepsy, five for a hemorrhage, and five for focal neurological deficits. The mean age at surgery was 29.4 years. All procedures performed included lesionectomy and in cases with epilepsy, additional resection of the surrounding hemosiderin rim. There was no perioperative mortality, and the perioperative morbidity was 4% (1/24). Two patients with epilepsy refused an operation. Of the 14 patients surgically treated for epilepsy, 11 (78%) became seizure-free postoperatively and only three had rare seizures (one to two seizures per year) following surgery. Of the 11 seizure-free patients, antiepileptic drugs could be tappered off in three patients.

Discussion

Familial CCMs of the central nervous system have first been described 80 years ago. In 1928, Hugo Friedrich Kufs reported on a family in which he assumed a common pathological basis in two members [15] (Fig. 1). He reported on an 81-year-old man in whom multiple cerebral and hepatic cavernomas have been found in an autopsy. His daughter presented with an “apoplexia pontis” with a right-sided hemiparesis and hemihypesthesia at the age of 17 years. Although CCMs have not been pathologically confirmed in the daughter, Kufs has to be given the credit for the first description of this entity. By the use of magnetic resonance imaging, further families have increasingly reported. Thus, since the first description, almost 1,000 families have been reported all over the world [5, 16,

Fig. 1 Picture of Hugo Friedrich Kufs who first described the inherited form of cavernous malformations in 1928.

26]. Despite this large number of families reported, the prevalence of the inherited form of CCM is still not known yet. In early "semiepidemiological" studies in hispanics, a prevalence of inherited CCM of up to 50% has been suggested [22]. The high prevalence of CCMs in this ethnic group, however, is due to a "founder mutation" in the CCM1 gene that caused a sample bias [12, 13]. In later studies, this high prevalence could not be confirmed for other ethnic populations. Large epidemiologically based national studies in France and other studies have shown a lower but still undetermined prevalence for inherited CCMs [16, 27]. Here, we report 19 families found in Switzerland (with a population of 7.5 million) indicating a very low prevalence. However, our study comprises several methodological biases. Firstly, we did not perform screening by MRI in family members of individuals with CCMs as other studies have been previously performed [16]. Secondly, individuals who were not referred to one of the involved hospitals were not object to our study. Thirdly, we were not able to detect families with asymptomatic individuals only. Thus, to determine an accurate prevalence, further epidemiological studies have to be established.

Clinicopathological features

Clinically, inherited CCMs do not differ from the sporadic form. Both in sporadic and inherited CCMs 20% to 50% of patients with CCMs remain asymptomatic [3, 19, 26]. Between 41% and 59% of symptomatic cavernomas are associated with recurrent epileptic seizures, which are drug resistant in about 40% of cases [3, 4]. The estimated risk for seizure development was estimated at 1.51% per patient and year, or 2.48% per lesion and year in patients with multiple lesions [7]. CCMs may also cause major hemorrhages in 9% to 70% with a reported annual risk between 1% to 4%, while being associated with a higher risk of hemorrhage after an initial hemorrhagic event and in localizations involving deep structures or the brain stem [3, 23, 27].

Other clinical manifestations are focal neurologic deficits and headache [7, 20, 21]. Similar clinical data have been reported for familial CCMs. In a literature review of 109 families with 379 individuals with inherited CCMs, 91 (24%) were asymptomatic and 288 (76%) presented with symptoms comprising epileptic seizures (in 43%), followed by major hemorrhages (in 28%), chronic headache (in 23%), or focal neurological deficits (in 15%) [26]. In our series, clinical features were in line with these previous studies.

Here, we also analyzed the clinical data for the phenomenon of anticipation. The term "anticipation" refers to a progressively earlier age of symptom onset and/or increase in severity of an inherited disease in successive generations. In a previous study, we have shown that the mean age at first clinical manifestation decreased across generations from 32.7 years in the first generation to 18.0 years in the second generation then to 7.7 years in the third generation [26]. In this study, ten parent–offspring pairs could be analyzed for anticipation. These intergenerational pairs showed a decreased mean age at symptom onset in the offspring (20.4 years) compared to the parents (37.8 years). While expansion of unstable trinucleotide repeat has been found as the cause for anticipation in various neurological diseases, the cause for this phenomenon in CCMs is still not known [26].

In our series, 57% of the affected individuals harbored multiple CCMs, and 43% had single malformations. This corresponds to previous studies reporting multiple lesions in up to 69% of familial cases [26]. These numbers support previous findings that carriers of multiple CCMs are more often associated with the familial form of this disease, but a solitary lesion does not exclude inheritance [26]. This awareness of this finding is important for genetic counseling.

Genetic aspects and counseling

Genetic analysis identified three CCM loci: CCM1 on chromosome 7q21-q22 accounting for 40% of all familial cases, CCM2 on 7p13-p15 accounting for 13–20%, and CCM3 on 3q25.2-q27 for up to 40% [5, 29].

The gene CCM1 encodes for a 736 amino acids protein called the "Krev Interaction Trapped 1" (Krit 1) protein. Krit1 contains three ankyrin repeats, a FERM (Band 4.1, ezrin, radixin, and moesin) domain and a NPXY (Asn-Pro-X-Tyr) motif. Molecular studies show that the NPXY motif seem to modulate a strong interaction with the integrin cytoplasmic domain-associated protein 1 (icap1), suggesting that this protein might be involved in bidirectional signaling between the integrin and the cytoskeleton in CCM1 pathogenesis [31]. In addition, Krit1 has been shown to be a microtubule-associated protein that may help determine endothelial cell shape and function in response to cell–cell and cell–matrix interactions by guiding cytoskeletal structure

[14]. The CCM2 gene found at locus 7p13-p15 encodes for the "Malcavernin" protein [8, 17]. "Malcavernin" is a similar protein as the Krit 1 binding partner ICAP1, a protein with a phosphotyrosin binding domain [32]. Recently, the PDCD10 (Programmed Cell Death 10) gene also called TFAR15 has been identified as the CCM3 gene [2]. Although the product and function of PDCD10 is still not known, it is thought to interact with angiogenesis.

In our series, genetic analysis could be performed in 19 individuals. The mutations found were mainly in the CCM1 gene (in nine individuals) and less commonly in CCM2 (in six individuals). Type of mutations were reported in detail elsewhere [10, 28, 30]. In four individuals, neither in CCM1 nor in CCM2 mutations have been found indicating a mutation in CCM3. Recently, some studies have suggested that an additional gene (CCM4) might be involved since there were some affected in whom no mutations could be detected in the three known CCM genes.

Surgical outcome

Since CCMs are often symptomatic, a surgical treatment becomes mandatory. There is a large variety of studies reporting excellent surgical outcome following removal of CCMs [1, 3, 7, 21]. Thus, in a large series of 72 patients, there was no mortality, and the immediate perioperative morbidity rate was 29.2% (21/72), while the rate of long-term morbidity was 5.5% (4/72). Similarly, in our series of familial CCMs, there was also no mortality, and the long-term morbidity was 4%. Surgery has particularly proven to be an effective treatment in CCMs manifesting with epilepsy. Patients become seizure-free in about 70% to 80% [1, 3]. In our patients, 11 of 14 (78%) became seizure-free. This excellent result gets endorsed by the fact that antiepileptic drugs could be tapered off after surgery in three patients. None of our patients have been operated on for multiple CCMs. Analogously to sporadic cases in patients with multiple CCMs, the question is under debate whether more than the symptomatic malformation should be removed. So far, there are no guidelines, and often, the neurosurgeon's philosophy is decisive. Another important issue is the management of asymptomatic affected individuals. Here, the annual risk of hemorrhages or seizures has to be weighed in contrast to the risk of an operation. Though, there are no strict guidelines in either of these cases, the indication for surgery should be given rather cautiously.

Conclusion

Although accurate prevalence data are still not available, the familial occurrence of CCMs seems to be underestimated. Therefore, each individual with CCMs has to be thoroughly interviewed for a positive family history. However, the identification of other affected family members might be facilitated in the future by the use of increasingly available genetic testing. Current genetic studies focuses on the search for additional genes causing CCMs. While CCMs may remain asymptomatic, they are often symptomatic and an operation may become mandatory.

In the management of this entity, some questions still have to be answered. Thus, it is still debatable whether asymptomatic individuals with familial CCMs should also be surgically treated. Furthermore, the methodological drawbacks of our study mentioned above might be reduced by establishing a center for this disorder in Switzerland.

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Comments

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This is an interesting study detailing the presumed prevalence of inherited cerebral cavernous malformation in Switzerland.

The female/male ratio instead of the expected 1:1 is 3:2; the ratio between multiple/single lesions is approximately 3:2.

Due to financial and logistic reasons, only 19 (34%) individuals out of the 56 affected individuals underwent genetic testing; nine individuals (47%) had mutations in the CCM1 gene, six individuals (31.5%) had mutations in CCM2, and 21% (four individuals) have neither CCM1 nor CCM2 mutations. The authors suggest that these four individuals (21%) might have mutation in CCM3.

This again is somewhat at odds with the reported prevalence of the genetic abnormalities in the published literature that suggests that CCM1 (on chromosome 7q21-q22) accounts for 40% of all familial cases, CCM2 (on 7p13-p15) accounts for 13–20%, and CCM3 (on 3q25.2-q27) accounts for 40%.

Symptoms presentation is typical, and surgical results are quite good with 4% morbidity and 78% of patients with intractable epilepsy rendered seizures-free by the surgery.

The authors nicely touch upon the importance of genetic counseling and careful neurosurgical management approach.

Oguzkan Sürücü, Zurich, Switzerland

In this publication, Graeni et al. have retrospectively reviewed clinical and genetic data of patients with familial cerebral cavernous malformations collected from five, mainly universitary hospitals in Switzerland. Genetic features from 19 of 56 affected individuals have been published already elsewhere and are not presented in detail here. The focus is on clinicopathological data which is summarized adequately. Surgical indications, therapy and good outcome, e.g. for epilepsy, matches with previous studies. As stated in the conclusion this study is not representative for accurate prevalence data for Switzerland. But it points out that comprehensive management of patients with familial cerebral cavernomas requires an interdisciplinary approach from neurological, neurosurgical and genetically aspects in centres with broad experience in the treatment of this disease. This is of major interest for these patients who are often confused by ambiguous statements from medical staff, press or internet.