CASE REPORT

Discovery of familial cerebral cavernous malformation in a Saudi population

Shahpar Nahrir,¹ Majed H Al-Hameed,¹ Omar A Al-Sinaidi,¹ Wafa Al Shakweer²

¹Department of Neurology,
NNI, Riyadh, Saudi Arabia
²Department of Pathology,
King Fahad Medical City,
Riyadh, Saudi Arabia

Correspondence to
Dr Shahpar Nahrir,
s_nahrir@yahoo.com

SUMMARY

Familial cerebral cavernous malformation is a rare entity. It has been described commonly among the Hispanic population and sparsely among the Italian, French, Swedish and Chinese populations. We discovered two families with this condition among the Saudi population for the first time. Both the index patients had a seizure as a prominent manifestation of their underlying structural lesion. One of them had recurrent attacks of bleeding in the cavernoma leading to a focal neurological deficit. The siblings and the parents of both the patients were screened using CT of the brain imaging. Two members within each family were found to have symptomatic cavernoma. A molecular genetics study revealed heterozygous KRIT1/CCM1 for a frameshift mutation in one of the patients. No detectable mutation was found in the other patient. These cases illustrate the existence of this condition beyond the commonly known geographical area of higher prevalence. Moreover, KRIT1/CCM1 might be the possible target gene that is mutated in this region.

BACKGROUND

Cerebral cavernous malformation (CCM) is a rare congenital vascular anomaly that has most probably infected the human brain for many centuries.¹ Nevertheless, only recently have scientists discovered its existence. It is now known to cause substantial morbidity ranging from simple partial seizure to intractable epilepsy, focal neurological deficit, recurrent cerebral haemorrhage, raised intracranial pressure (ICP) and even death. Its true prevalence remains unknown. However, one large autopsy series stated it to be between 0.1–0.5% of the general population.² Approximately 20% of cases are autosomal dominantly inherited, termed as familial CCM (FCCM).³ So far, three genetic mutations have been described as being associated with 78% of FCCM.⁴ Our literature search revealed the presence of FCCM in certain populations only. It is the Hispanic origin where the highest number of FCCMs have been reported relative to other racial origins. These people harbour mostly KRIT1/CCM1 mutation. Fewer cases have been reported from Chinese, Italian, French, Indian and German families. It is vital to report such an entity in other populations, as this will create an awareness and render initiative action among others to search for more cases. This will eventually reduce the morbidity associated with its presence and confer appropriate genetic counselling to our knowledge.

CASE PRESENTATION

We describe the clinical scenario of two Saudi patients with the ultimate diagnosis of FCCM, each with a different course of illness:

Case 1: A 19-year-old medical student had reported a 4 year history of development of a sudden onset throbbing headache, which was unresponsive to regular analgesics. After 14 days of an unremitting headache, he developed a new onset unsteadiness and repeated vomiting. He was then found to have signs of raised ICP from an unknown cause. External ventricular drainage was inserted. Later, it was revealed that he had space occupying lesion (SOL) in the right occipital lobe. He underwent craniotomy and resection of this mass. He recovered without any residual deficit and was prescribed prophylactic antiepileptic drug (AED). However, 2 years later, he started to experience nocturnal seizure. Then one day he developed sudden onset of left-sided weakness and on the same evening, he sustained status epilepticus. Repeat brain imaging showed the presence of a new SOL associated with haemorrhage. He later underwent surgical resection. Since then, he is hemiplegic and has infrequent seizures. Seizure semiology was described as a sudden aura of abnormal sensation over the left arm and leg, followed by loss of awareness, head turning to one side, tonic posturing of the limbs and clonic movements. Family history was significant as out of 10 siblings he had one elder brother with a similar brain lesion and intractable epilepsy. His parents were exsanguine in marriage.

Case 2: A 32-year-old married woman and mother of four children was known to be epileptic for 8 years. Her first seizure occurred during her second pregnancy. She described two different types of seizures. One type was where she experienced an aura of numbness over the left arm and leg followed by tonic posturing of the limbs and later clonic movements of the body. Postictally, she felt weak on her left side for a day or two. She had three such attacks. Her other spells were characterised by a sudden turning of the body to one side, followed by moaning and groaning sounds and vigorous abdominal and pelvic thrusting without loss of consciousness. She experiences this type of spell as frequently as once in every week. Her family history is significant as, out of eight siblings, she and her younger brother are known to have seizure disorder with multiple brain lesions and are both diagnosed with FCCM. All her siblings and her parents have undergone brain imaging studies to screen for the lesions. She also

CrossMark

To cite: Nahrir S, Al-Hameed MH, Al-Sinaidi OA, et al. *BMJ Case Rep*
Published online: [please
include Day Month Year]
doi:10.1136/bcr-2013-009417

claims that her maternal aunt and a first degree cousin have similar conditions.

INVESTIGATIONS

Case 1

MRI of the brain: Figure 1 (A,B)—(gradient-echo; GRE/T2*)—showing the presence of multiple areas of hypointense lesions in the GRE/T2* sequence indicative of haemosiderin deposition and also evidence of postoperative changes.

MR venography: Figure 2 showing intact major venous sinuses.

MR angiography of circle of Willis: Figure 3 showing no evidence of any vascular abnormality.

EEG: Figure 4—ictal—low-voltage fast activities over the right parietotemporal area evolving to spread to F4 then had generalised seizure activity.

Figure 1 (A and B) MRI (GRE/T2*) showing the presence of multiple areas of hypointense lesions in GRE/T2* sequence indicative of haemosiderin deposition and also evidence of postoperative changes.

Figure 2 MR venogram showing intact major venous sinuses.

Histopathology slide: Figure 5—H&E stain shows numerous dilated blood vessels of variable wall thickness.

Molecular genetic study: This patient is heterozygous in the KRIT1 gene for a frameshift mutation defined as C.1249_1252delAAAC and predicted to result in premature protein termination (p.Lyse417HisfsStop19). Sequencing of the KRIT1 gene exon 9 in biological relatives.

Case 2

MRI of the brain: Figure 6(A–C)—(T1 with contrast and GRE/T2*)—showing multiple infratentorial and supratentorial mixed signal intensity lesions harbouring haemosiderin and a subacute blood degradation product as well as calcification. These lesions

Figure 3 MR angiogram of the circle of Willis—demonstrating no identifiable vascular malformation.

Figure 4 EEG showing evolution of low-frequency medium amplitude asynchronous sharp waves from right frontocentral leads propagating to a more generalised synchronous rhythm.

are noted to affect the basis pontis on the right side, the frontal lobes bilaterally, and the largest lesion located in the left frontal lobe affecting the cortex and the frontal operculum.

EEG: Interictal—sharp waves as well as phase-reversing at F3 and F7 along with frequent paroxysmal lateralised epileptiform discharges like activity which would appear in pseudoperiodic fashion without evolving and propagating into a seizure discharge.

Molecular genetic study: Negative for KRIT1/CCM1, CCM2 and PDCD10/CCM3 gene sequencing.

DIFFERENTIAL DIAGNOSIS

The constellation of recurrent seizure, focal neurological deficit and presence of multiple SOLs on the brain of a young patient reflects varied aetiology. Arteriovenous malformation (AVM) is certain to be the top differential diagnosis. Multiple haemorrhagic metastases, multiple calcified metastasis, cerebral amyloid angiopathy, central nervous system vasculitis and mycotic aneurysm are just some of the other conditions that one may ponder about in such a situation. Cerebral AVM may often mimic

cavernous malformation by their radiological appearances and clinical presentation. This fact becomes more confusing when as many as 30% of patients with CCM have coupled other malformations, AVM being the most notorious of all. However, the distinctive histological feature of CCMs is that they do not pose any neural tissue in between the clusters of dilated capillaries. Cavernomas commonly do not exhibit contrast enhancement in MRI studies in contrast to AVM. Moreover, cavernomas alone are angiographically occult. AVM can also have repeated bleeding akin to cavernoma. In addition, they are not usually so numerous in number in one's brain and normally tend to be of a larger size. Multiple haemorrhagic/calcified metastases is a condition that one would consider looking at the CT of the brain. However, the long-standing history of seizure or focal neurological deficit makes this differential less likely. Cerebral vasculitis can give rise to multiple haemorrhagic lesions within the brain, but they usually have a more dramatic course, a more profound neurological deficit due to infarction, and they may also have associated systemic manifestations. Cerebral mycotic aneurysm rarely mimics the radiological feature of CCM. Nevertheless, our patient did not possess any associated cardiac problem (ie, right to left shunt) and neither was there any history of drug abuse, as commonly seen in mycotic aneurysm patients. Most importantly, a familial history of similar disease is unexplainable in these conditions.

TREATMENT

As our patients are symptomatic, they were offered the best available treatment options.

For the first patient, owing to recurrent bleeding and a history of raised ICP, he underwent resection of the lesions on several occasions. Currently, he still possesses multiple cavernomas. However, as his seizures are rather controlled with AED and are not causing any new focal neurological deficit, it was decided to maintain him on medical therapy alone. He is under close surveillance for any new symptoms or intractability of his seizures.

The second patient had her seizures evaluated at our epilepsy monitoring unit (EMU). Also, during her 7-day stay at EMU, she

Figure 5 Histopathology slide H&E stain shows numerous dilated blood vessels of variable wall thickness.

Figure 6 (A–C) MRI of the brain of case 2 (T1 with contrast and GRE/T2*) showing multiple infratentorial and supratentorial mixed signal intensity lesions harbouring haemosiderin and subacute blood degradation product as well as calcification. These lesions are noted to affect the basis pontis on the right side, the frontal lobes bilaterally, and the largest lesion located in the left frontal lobe affecting the cortex and the frontal operculum.

did not have any generalised tonic clonic seizure, but she had several spells of abnormal posturing and altered behaviour. A thorough evaluation revealed these events to be non-epileptiform in nature. So it was believed that she has psychogenic non-epileptiform seizure in addition to true symptomatic seizure. Her lesion was detected to be in the near vicinity of the language area. As her true seizures are not intractable, weighing the risk to benefit, it was decided to withhold the surgical option.

OUTCOME AND FOLLOW-UP

Our patients are in close follow-up at our centre. Both are leading a normal life.

Seizure frequency is controlled with a careful selection of anti-epileptic medications. Genetic counselling has been offered to both the families. The family members of the patient in case 1 have been advised to undertake sequencing of the KRIT1 gene. The family members of the patient in case 2 may bear a mutation that was probably not tested and can in future be identified through genomic sequencing study in a research laboratory.

DISCUSSION

FCCM (OMIM #116860)⁵ is a rare but indisputably perilous condition. CCMs are clusters of abnormal capillaries and venules, which periodically bleed, giving a mulberry appearance in bare eyes and a popcorn-like appearance in radiological images.^{6–7} Structurally, they are thin walled caverns that have a single layered endothelium, without any supporting smooth muscle and elastin.⁸ These endotheliums have disrupted tight junctions between endothelial cells and astrocyte foot processes. They commonly have sparse laminin and collagen IV within their endothelial cells and are associated with a hypertrophic surrounding basal lamina and do not have intervening neural tissue.^{9–10} These characteristics make them very liable to leakage, leading to haemorrhage. The blood flow through these cavities is very sluggish and can thus result in thrombus formation. Clinical characteristics depend on the location and the integrity of the wall of the malformation. Seizures are the commonest manifestation. They also have a recurrent neurological deficit due to repeated bleeding and even raised ICP. A considerable number of cases remain asymptomatic (25–50%). As many as hundreds of cavernomas could be detected in a person depending on the age of the patient and the quality and

modality of the brain image used.¹¹ The usual age of presentation is around the second decade of life, but case reports of multiple CCMs detected in infants have also been reported.¹² The study by Gunel *et al*¹³ reported that 9% of individuals were symptomatic before the age of 10 years, 62–72% between the ages 10 and 40 years, and 19% after the age of 40 years. Lesions are best identified on MRI using GRE, or susceptibility-weighted imaging.⁷ These techniques may identify hundreds of lesions in a given patient. They are venous malformations and are thus angiographically occult. The cavernomas have been reported to occur most commonly in the cerebrum, as well as in the spine, retina and skin. They can be sporadic or familial. The former is the most common form of occurrence. However, the familial form is distinct by its property of being more numerous and having a higher propensity to complicate.

The natural history of familial form was studied by Zabramski *et al*¹⁴ in six families with 59 members, where they demonstrated its dynamic nature by showing changes in size, number and imaging characteristics of the cavernomas over a period of time. The familial form carries an autosomal dominant mode of inheritance. So far, the genetic mutation responsible for FCCM is found in 78% of the familial form. The target gene is known to encode proteins, KRIT1 (aka CCM1), CCM2 (aka Osmosensing Scaffold for MEKK3-OSM, Malcavernin or MGC4607), or Programmed cell death 10 (PDCD10, aka CCM3).³ The remaining 22% of familial forms are caused by an unknown mutation. The identified mutations are germ line in nature and are held on structurally distinct intracellular proteins that lack catalytic domain. Studies have proven that a two-hit mechanism is involved in CCM pathogenesis.³ Experiments have demonstrated that KRIT1 and CCM2 protein have a crucial role in antiangiogenesis through the inhibition of endothelial proliferation, apoptosis, migration, lumen formation and sprouting angiogenesis in endothelial cells in humans.¹⁵ Gene mutations in all types of FCCM are likely to be due to haploinsufficiency. A two-hit hypothesis seems to explicate the growth of localised lesions through the loss of a second allele. Accurate interpretations of the results of such a genetic study are imperative. A positive result signifies the detection of a gene mutation that is predicted to cause CCM. In contrast, a negative result does not rule out CCM as there may be an undetectable mutation in the gene(s) tested or there may be other causative genes that were not tested. Therefore, in a negative study, diagnosis should be made on the basis of clinical

findings and family history. An uncertain result implies detection of a gene alteration, but it is not certain whether it is a benign genetic variant or pathogenic (to cause CCM). Hence, good understanding of the genetic test result serves as vital information pertaining to genetic counselling and needful management. Most of the familial cases were described in a Hispanic American population. These Hispanic Americans are descendants of settlers who migrated to northern New Mexico and south-western USA and the northern Mexico state of Chihuahua and Sonora. Some sparse reports of the existence of FCCMs in Italian, German, French and Indian families can be found. The first gene identified is KRIT1.^{16 17} It accounts for the maximum number of FCCMs in the world. A majority of Hispanic people have been found to have a mutation in the CCM1 locus (KRIT1 protein) in chromosome.¹⁸ However, researchers have detected Caucasian families to have a different pattern of genetic mutation. They have 40% CCM1, 20% CCM2 and another 40% have CCM3 gene mutations.¹¹ Recent studies have concluded that there is incomplete clinical and neuroimaging penetrance in families with a KRIT1 mutation.¹⁹ These Saudi patients expand the geographical map of occurrences of FCCM.

Learning points

- Familial cerebral cavernous malformation (FCCM) may be prevalent in any racial group.
- Genetic mutation in one Saudi family with FCCM was found to be KRIT1/CCM1.
- Screen all family members of the patient with cavernous malformation.
- Keep a high index of suspicion to proceed for genetic study and family screening.

Contributors SN came up with the idea of writing up the case report and has written the whole manuscript solely. He was also involved in the management of both the patients. MHA was the attending consultant in the care of these two patients. He proofread the whole manuscript and rendered his suggestions. He reported and selected the EEG. OAA was active in obtaining the detailed family history of the patients and he also helped in retrieving the pathological slide. WAS reported and selected the histopathology slide.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Morrison L, Akers A. Cerebral cavernous malformation, familial, 2003 Feb 24 (updated 2011 May 31). In: Pagon RA, Adam MP, Bird TD, *et al*, eds. GeneReviews [Internet]. Seattle: University of Washington, 1993–2013.
- 2 Otten P, Pizzolato GP, Rilliet B, *et al*. 131 cases of cavernous angioma (cavernomas) of the CNS, discovered by retrospective analysis of 24,535 autopsies. *Neurochirurgie* 1989;35:82–3, 128–131, (Fr).
- 3 Li DY, Whitehead KJ. Evaluating strategies for the treatment of cerebral cavernous malformations. *Stroke* 2010;41(10 Suppl):S92–4.
- 4 Labauge P, Denier C, Bergametti F, *et al*. Genetics of cavernous angiomas. *Lancet Neurol* 2007;6:237–44.
- 5 Database: Omim; Entry: 116860; title: #116860 cerebral cavernous malformations; ccm.
- 6 Tagle P, Huete I, Mendez J, *et al*. Intracranial cavernous angioma: presentation and management. *J Neurosurg* 1986;64:720–3.
- 7 Brunereau L, Labauge P, Tournier-Lasserre E, *et al*. Familial form of intracranial cavernous angioma: MR imaging findings in 51 families. French Society of Neurosurgery. *Radiology* 2000;214:209–16.
- 8 Frischer JM, Pipp I, Stavrou I, *et al*. Cerebral cavernous malformations: congruency of histopathological features with the current clinical definition. *J Neurol Neurosurg Psychiatry* 2008;79:783–8.
- 9 Clatterbuck RE, Eberhart CG, Crain BJ, *et al*. Ultrastructural and immunocytochemical evidence that an incompetent blood-brain barrier is related to the pathophysiology of cavernous malformations. *J Neurol Neurosurg Psychiatry* 2001;71:188–92.
- 10 Cavalcanti DD, Yashar M, Kalani S. Cerebral cavernous malformations: from genes to proteins to disease. *J Neurosurg* 2012;116:122–32.
- 11 Riant F, Bergametti F, Aygnac X, *et al*. Recent insights into cerebral cavernous malformations: the molecular genetics of CCM. *FEBS J* 2010;277:1070–5.
- 12 Verma P, Saleem R, Harijan P, *et al*. Multiple cerebral cavernous haemangiomas in an infant. *J Pediatr Neurosci* 2012;7:200–1.
- 13 Gunel M, Awad IA, Finberg K, *et al*. A founder mutation as a cause of cerebral cavernous malformation in Hispanic Americans. *N Engl J Med* 1996;334:946–51.
- 14 Zabramski JM, Wascher TM, Spetzler RF, *et al*. The natural history of familial cavernous malformations: results of an ongoing study. *J Neurosurg* 1994;80:422–32.
- 15 Wüsthube J, Bartol A, Liebler SS, *et al*. Cerebral cavernous malformation protein CCM1 inhibits sprouting angiogenesis by activating DELTA-NOTCH signaling. *Proc Natl Acad Sci USA* 2010;107:12640–5.
- 16 Sahoo T, Johnson EW, Thomas JW, *et al*. Mutations in the gene encoding KRIT1, a Krev-1/rap1a binding protein, cause cerebral cavernous malformations (CCM1). *Hum Mol Genet* 1999;8:2325–33.
- 17 Polymeropoulos MH, Hurko O, Hsu F, *et al*. Linkage of the locus for cerebral cavernous hemangiomas to human chromosome 7q in four families of Mexican-American descent. *Neurology* 1997;48:752–7.
- 18 Denier C, Labauge P, Brunereau L, *et al*. Clinical features of cerebral cavernous malformations patients with KRIT1 mutations. *Ann Neurol* 2004;55:213–20.
- 19 Battistini S, Rocchi R, Cerase A, *et al*. Clinical, magnetic resonance imaging, and genetic study of 5 Italian families with cerebral cavernous malformation. *Arch Neurol* 2007;64:843–8.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>. BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow