Familial cerebral cavernous malformation in a Filipino family

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Abstract

Cerebral cavernous malformation (CCM) is a type of vascular malformations characterized by the absence of intervening brain parenchyma. Cerebral cavernous malformations are of two forms, sporadic and familial. About 0.4-0.8% of the population are affected as assessed based on Magnetic Resonance Imaging (MRI) findings and postmortem findings. Three genetic mutations have been identified: CCM1, CCM2, CCM3, with an incidence of 40%, 40% and 20%, respectively.

This study presents five members diagnosed with Familial CCM in a Filipino family. A 25-year-old male, from a low socio-economic background, was admitted due to a progressive generalized headache of 2 years' duration, during which multiple brain lesions were observed on MRI. All members of the family became symptomatic before 30 years of age, and four out of the five members underwent surgery. However, molecular genetic testing was not performed as the patient could not afford it. The testing was not covered by the country's insurance system, and it would have been an out-of-pocket expense.

In patients diagnosed with cerebral cavernous malformations, a thorough clinical and family history is warranted accompanied by MRI-GRE (Magnetic Resonance Imaging - Gradient Echo) and MRI T2 help establish final diagnosis. Confirmation with molecular genetic testing should be offered to all members of the family for proper neurological and genetic care.

Key words: cavernous malformation, familial cerebral cavernous malformation, cavernoma

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Cerebrovascular malformations are developmental abnormalities that affect the blood vessels supplying the brain. They include venous malformations, arteriovenous malformations, cavernous malformations, and telangiectasis.[1] The feature that distinguishes them from other types of vascular malformations is the absence of intervening brain parenchyma.[2] Cerebral cavernous malformations are of two forms, sporadic and familial. About 0.4-0.8% of the population are affected as assessed based on MRI findings and postmortem findings.[2,3] Three genetic mutations have

been associated with Familial Cerebral Cavernous Malformation: CCM1, CCM2, CCM3.CCM1, CCM2 and CCM3 denote three distinct genetic variants linked to Cerebral Cavernous Malformation (CCM). These mutations are accountable for the onset of CCM and are situated in three separate genes. The prevalence of these mutations differs among the population, with each mutation associated with particular forms of CCM. The CCM1 mutation, associated with the KRIT1 gene, is the most prevalent, accounting for around 40% of CCM cases. It transpires in the KRIT1 (Krev interaction trapped 1) gene. The CCM2 mutation, associated with the MGC4607 gene, accounts for an additional 40% of CCM instances. The CCM3 mutation, associated with the PDCD10 gene, is the rarest variant, accounting for around 20% of CCM cases. The three mutations are integral to the genetic foundation of CCM and are crucial for its diagnosis. Genetic testing can ascertain the presence of specific mutations in affected people, perhaps guiding treatment approaches and familial counseling.[4]

The familial form of the disease is inherited in an autosomal dominant pattern. It is involved in up to 30% of all cases and is present mostly in Hispanic Americans of Mexico than in other ethnic groups.[5] Patients with multiple lesions constitute 12-20% in sporadic form and more than 50% in the familial form of CCMs.[2] Patients with CCMs may present with seizures, hemorrhage, focal deficits or nonspecific headaches.[6,7] In MRI studies, they appear as mixed signal intensity core with a hypo-intense hemosiderin rim giving the pathognomonic MRI finding of "popcorn-like" masses.[1,8] These lesions are rarely appreciated on angiography and are considered angiographically occult.[9] Few cases have been reported from other racial origins. It is vital to report such case to render awareness, reduce morbidity and perform genetic counseling to diagnosed cases.

Methods

The data were collected from available medical records, patient interview and histopathologic registry. Four out of the five members of this family were operated on. However, only one has been admitted and operated on in this institution. Histopathologic examination of the specimen has been recorded for this case. No molecular genetic testing has been done for all four members diagnosed through histopathologic examinations.

The Cases

Five members of the family were identified with cavernous malformation based on MRI findings. Family pedigree is presented in Figure 1.

Case 1

A 25-year-old male, right-handed, was admitted for the first time due to progressive generalized headache of 2 years duration. The headache was then associated with numbness on the right arm, leg and trunk. MRI T1 sequence (Figure 2) showed shortening while T2 sequence showed prolongation of signal resulting in a "popcorn ball" like configuration with multiple intra-axial nodular foci of varying sizes scattered in the cerebral hemispheres, pons and left cerebral hemisphere. He then underwent surgery and was discharged 7 days postoperatively with noted relief from the headache but still with numbness on the right trunk, arm and leg. Genetic testing has not been done due to financial constraints.

Case 2

A 58-year-old female presented with seizures and was diagnosed with cavernoma through MRI at 19 years old. She underwent surgery abroad which revealed cavernoma.

Case 3

A 55-year-old female presented with seizures of unknown semiology. She was diagnosed radiographically with cavernoma at 20 years old. She refused surgery and is on medications for seizure control.

Case 4

A 27-year-old male, Professional Nurse, presented with severe headache and dizziness, was diagnosed radiographically with Cavernoma at 16 years old; underwent surgery in 2007 which showed Cavernoma. Postoperative MRI showed no recurrence.

Case 5

The proband's grandmother is already deceased. She presented with headache and dizziness at the age of 70. She underwent surgery which showed Cavernoma.

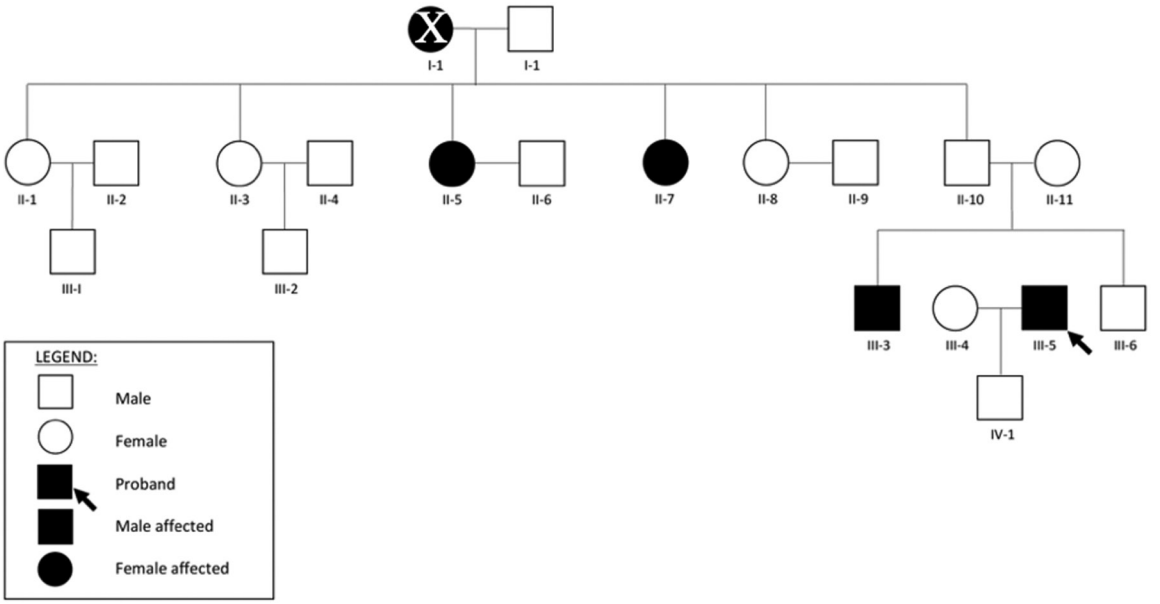

Figure 1. Family pedigree showing five members spanning three generations diagnosed with cerebral cavernous meningioma.

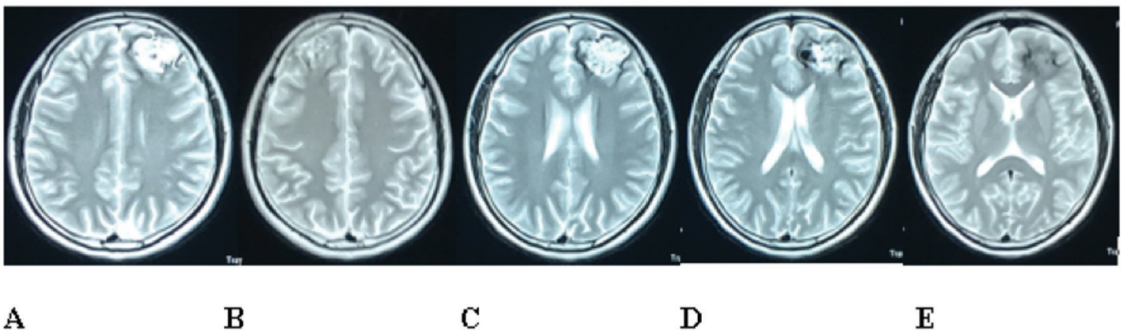

Figure 2. (A-E) MRI (GRE/T2*) showing the presence of multiple areas of hypointense with hyperintense lesions in GRE/T2* sequence indicative of hemosiderin deposition.

Outcome and Follow Up

Not all family members performed periodic MRI examinations for economic reasons. The patient is now seizure-free. All of them are now leading a normal life.

Discussion

Cerebral cavernous malformations are clusters of abnormal capillaries and venules, which periodically bleed with a mulberry appearance grossly and a "popcorn-like" lesion radiographically.[10] Cerebral cavernous malformations are of two forms, sporadic and familial. The familial form of the disease is inherited in an autosomal dominant pattern. It is involved in up to 30% of all cases and is present mostly in Hispanic Americans of Mexico than in other ethnic groups.[5] Three genetic mutations have been associated with Familial Cerebral Cavernous Malformation: CCM1, CCM2, CCM3.[4] CCM1 is located at chromosome locus 7q11-q22 and was the first gene identified in association with the familial form of CCM.[11] CCM1 mutation is involved in 40% of familial CCMs and nearly half will have neurological symptoms before the age of 25 years.[7,12] CCM2 is localized at 7p15-13 and are involved in

up to 40% of familial CCMs. CCM3, localized at 3q25.2-q27, encodes programmed cell death protein 10 (PDCD10).[13] It is the most recently discovered gene involved in familial CCM and are less common than CCM1 or CCM but are most likely to present with hemorrhage and early symptom onset before 15 years of age.[14]

A study among Hispanic Americans showed that 9% of individuals diagnosed with CCM were symptomatic before the age of 10 years, 62-72% between the ages 10-40 years and 19% after the age of 40 years.[15] In this current study, the earliest family member diagnosed was at 16 years and all were symptomatic before 30 years of age. The prevalence of CCM1, CCM2 and CCM3 in families is 40%, 20%, and 40% respectively.[11]

In a study on the natural history of familial cavernous malformations, a total of 59 members from 6 families were studied and results showed the dynamic state of CMMs as seen in changes in the number, size and imaging characteristics of the lesions.[1]

In recent literature, it is advised that incidentally discovered, asymptomatic or no increase in size CCMs should be observed and followed by periodic MR imaging while symptomatic lesions responsible for seizure, progressive neurological deficit, first clinically significant hemorrhage in non-eloquent areas and a second hemorrhage in eloquent areas should be considered for surgical removal.[16,17]

Conclusion

Several conclusions from this case report have been made:

1. Diagnosis of Familial Cerebral Cavernous Malformation requires a detailed patient history, family history, high-quality MRI utilizing gradient-refocused imaging, histopathologic examinations.

2. Diagnosis is confirmed by molecular genetic testing.

3. Repeat periodic MRI for symptomatic cases are recommended for follow-up monitoring. MRI should be offered to family members at risk.

Limitations

Although genetic testing was advised for the patient, however, due to financial constraints, the patient was unable to afford it. Instead, authors focused on highlighting the symptoms, physical findings, and alternative diagnostic methods, including imaging, laboratory results, and clinical observation, which led to the working diagnosis.

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