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Familial Cerebral Cavernous Malformation in a Filipino Family

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Abstract

Background of the Study

Cerebral cavernous malformation 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 MRI findings and postmortem findings. Three genetic mutations have been identified: CCM1, CCM2, CCM3, with an incidence of 40%, 40% and 20% respectively.

Clinical Presentation

This author presents 5 members diagnosed with FCCM within a Filipino family. A 25-year-old male who was admitted due to progressive generalized headache of 2 years duration wherein multiple brain lesions on MRI were seen. All members of the family became symptomatic before 30 years of age. 4 out of the 5 members underwent surgery. However, molecular genetic testing was not done.

Conclusion

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

Keywords: cavernous malformation, familial cerebral cavernous malformation, cavernoma Familial Cerebral Cavernous Malformation in a Filipino Family

INTRODUCTION

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.[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.

MATERIALS AND 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 our 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.

CASE PRESENTATION

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

Case 1. A 25-year-old male, right-handed, was admitted for the first time at Neurology Ward 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.

Outcome and Follow Up

Not all family members performed periodic MRI examinations for economic reasons. Our 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. [13] CCM3, localized at 3q25.2-q27, encodes programmed cell death protein 10 (PDCD10). 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 by Gunel et al[15] 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. In this family, earliest diagnosed was 16 years of age and all were symptomatic before 30 years of age. Proportions of families affected with CCM1, CCM2 and CCM3 have been assessed as 40%, 20% and 40% respectively.[11]
In a study by Zabramski et al[1] 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.
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.

CONFLICT OF INTERESTS: None

DISCLOSURE OF FUNDING: None

INSTITUTIONAL REVIEW BOARD: This case report has been checked by our Ethics Review Committee and no ethical issues were found by the board.

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