Cerebrovasc Dis 2008;26:206–208
DOI: [10.1159/000145329](https://doi.org/10.1159/000145329)

Familial Cerebral Cavernous Malformation: Features of Clinical Manifestation, Pathology and Imaging in a Chinese Family

Ling-Yi Chi^b, Shu-Hua Wang^a, Xue-Wu Liu^a, Li-Jun Su^a,
Xiu-He Zhao^a, Wei Wu^a, Sheng-Jun Wang^a, Shu-Zheng Wang^a,
Lili Cao^a, Rui-Dong Chen^a, Jing Gao^a, Xiao-Hua Wang^a

Departments of ^aNeurology and ^bNeurosurgery, Qilu Hospital,
Medical School of Shandong University, Jinan, China

Introduction

Cerebral cavernous malformation (CCM) is a common and frequently encountered disease which constitutes about 10–20% of central nervous system vascular malformations [1]. From large series studies involving postmortem examinations or MRI of patients, the prevalence of CCM in the general population has been estimated at 0.1–0.5% [2]. Two forms of CCM have been described, i.e. a sporadic and a familial type. Familial CCM (FCCM) has mainly been described in the Hispanic-American population [3]. However, FCCM in a Chinese family has rarely been reported. We here describe a typical FCCM patient of a Chinese (Han) family including a detailed family survey, clinical analysis, pathology and imaging.

Case Report

The proband, at age 59, had right limb weakness and alalia for 3 days before hospital admission. Two abnormal mauve clumps (size about 3 × 2 cm) located within the skin were found at the lateral malleolus of the right foot and the epicondyle of the left hand (fig. 1a, b). The right nasolabial groove was shallow. The patient had hypermyotonia in the right limb, with a muscle power of grade 4 and decreased pain sense in the right half of the body. The Babinski sign and Chaddock sign were positive on the right. Brain CT showed a mixed high-density focus in the left basal ganglia (fig. 2a). The lesion showed mixed T₁ and T₂ signal intensity in the central core with a peripheral rim of decreased signal intensity (fig. 2b–d). With gradient-recalled echo (GRE), multiple almost round foci of abnormal signal intensity in the brain parenchyma (bilateral cerebrum, cerebellum and brainstem) were sharp at the border; the lesions showed mixed signal intensity at the center and decreased signal intensity at the peripheral rim. The patient was diagnosed as having FCCM. Seventeen days after medical treatment, resection of the hemangioma of the left basal ganglia was performed though linear accelerator radiosurgery would have been an alternative treatment [4]. The tumor tissue

was examined pathologically (fig. 1c, d). The cavernous angioma was composed of endothelial-linked sinusoidal spaces not separated by significant amounts of neural tissue. Hemorrhagic residua were common. Clots were seen at different stages of evolution within the lesion. The basal membrane of the sinus became thick and soft. Parts of it were layered.

Nine of 18 people in the family (11 male and 7 female) were conclusively diagnosed as having FCCM. Six male and 3 female family members were between 8 and 77 years old (mean age 35.5 years) and all had multiple foci (highest number: 36 foci, size 0.2–5.5 cm). The symptoms were repeated headache and dizziness (3 patients), hemiparesis (3 patients), hemianesthesia (3 patients), refusal to drink and dysphagia (1 patient), seizure (1 patient), hemispasm (1 patient), skin angioma (4 patients) and asymptomatic manifestation (4 patients). Eight subjects had no foci on the MRI scan.

Discussion

The report describes a typical case of FCCM in a Chinese (Han) family. Fifty percent (9/18) of the family members also had FCCM based on MRI. All patients had multiple foci. The youngest patient was 8 years old. However, the patients diagnosed only by MRI had no clinical symptoms. Besides, consistent with Labauge et al. [5], we found that the younger the patient was, the smaller the number and volume of the foci.

CT is not the first choice for the diagnosis of FCCM because microangioma was not discovered at all in this family. With MRI, the foci of the cavernous angioma showed specific mixed signal intensity with a peripheral rim of decreased signal intensity related to the deposition of hemosiderin. However, GRE was more sensitive for multiple foci than spin echo. Indeed, multiple foci were discovered with GRE in 2 affected patients but no foci using MRI. So, we think that GRE (MRI with 3.0 T) might be the best method for FCCM diagnosis. Four patients complicated with skin cavernous angioma were ascertained as having FCCM (coincidence rate 100%). Thus, skin cavernous angioma is a significant diagnostic evidence for FCCM patients.

The pathologic structure of FCCM is the same as for sporadic CCM. The pathogenesis of FCCM, according to Laberge-le Cousteulx et al. [1], is related to the structural and functional change of the CCM1 gene and the coding product KRIT1 protein and the interaction with CCM1 and CCM2 coding proteins in cells [6]. The virulence gene for FCCM in Chinese (Han) families needs to be further studied.

L.-Y. Chi and S.-H. Wang contributed equally to this work.

Fig. 1. Skin CCM and the features of FCCM pathology. **a** Lateral malleolus of the right foot. **b** Epicondyle of the left hand. **c** HE, magnification $\times 50$. **d** Double fixation (glutaraldehyde, OsO_4) and double stain (uranyl acetate-lead citrate), angioma under electron microscope.

Fig. 2. The features of brain imaging of FCCM. **a** CCM on CT. **b, c** CCM on MRI. **d** CCM on gradient-recalled echo.

References

- 1 Laberge-le Couteux S, Jung HH, Labauge P, Houtteville JP, Lescoat C, Cecillon M, Marechal E, Joutel A, Bach JF, Tournier-Lasserre E: Truncating mutations in CCM1, encoding KRIT1, cause hereditary cavernous angiomas. *Nat Genet* 1999;23:189–193.
- 2 Otten P, Pizzolato GP, Rilliet B, Berney J: 131 cases of cavernous angioma (cavernomas) of the CNS, discovered by retrospective analysis of 24,535 autopsies (in French). *Neurochirurgie* 1989;35:82–83, 128–131.
- 3 Kattapong VJ, Hart BL, Davis LE: Familial cerebral cavernous angiomas: clinical and radiologic studies. *Neurology* 1995;45:492–497.
- 4 Hsu PW, Chang CN, Tseng CK, Wei KC, Wang CC, Chuang CC, Huang YC: Treatment of epileptogenic cavernomas: surgery versus radiosurgery. *Cerebrovasc Dis* 2007;24:116–121.
- 5 Labauge P, Laberge S, Brunereau L, Levy C, Tournier-Lasserre E: Hereditary cerebral cavernous angiomas: clinical and genetic features in 57 French families. *Lancet* 1998;352:1892–1897.
- 6 Zawistowski JS, Stalheim L, Uhlik MT, Abell AN, Ancrile BB, Johnson GL, Marchuk DA: CCM1 and CCM2 protein interactions in cell signaling: implications for cerebral cavernous malformations pathogenesis. *Hum Mol Genet* 2005;14:2521–2525.

Xue-Wu Liu
Department of Neurology, Qilu Hospital
Medical School of Shandong University
Jinan 250012 (China)
Tel. +86 531 8838 3332, Fax +86 531 8692 7544
E-Mail snlxw1966@yahoo.com.cn