Title: Fetal familial cerebral cavernous malformation with a novel mutation

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Abstract

Objectives: To identify the fetal familial cerebral cavernous malformation and a novel mutation

Methods: A 37-year-old pregnant woman performed brain magnetic resonance imaging (MRI) and fetal MRI. Whole Exome Sequencing (WES) and Sanger sequencing were performed to determine genotype.

Results: The mother's brain MRI demonstrated numerous cerebral cavernous malformations (CCMs) involving the brain stem, cerebral hemispheres, and cerebellum. Fetal MRI showed a CCM located in the left frontal lobe in SWI. The neuroimaging characteristics of the mother and the fetus suggested that their CCMs may be familial. Genetic analysis revealed a novel mutation in KRIT1 (c.1A>G, p.0?), also called CCM1, in both the mother and the baby.

Discussion: This severe mutation of the initial codon in the **KRIT1** gene leads to a phenotype that tends to be early and severe. To our knowledge, this is the first-ever reported case of fetal familial CCM and this novel mutation. Brain MRI has excellent sensitivity and specificity, providing the best option for detecting CCM, even in utero, primarily when SWI is used.

Introduction

Cerebral cavernous malformations (CCMs) are intracranial low-flow hemorrhagic vascular lesions composed of endothelium-lined cavities. They affect 0.16% to 0.8% of the population, and 63% are clinically silent.[1] CCMs can be sporadic or familial. Three protein-encoding genes (CCM1, CCM2, and CCM3) cause familial-type inheritance in an autosomal dominant fashion with variable penetrance.[2] Here, we describe a case of a pregnant woman and her fetus with familial CCM1 (MIM 116860) caused by a novel mutation.

Case Presentation

A 37-year-old pregnant woman presented with hand numbness for two weeks. Her brain magnetic resonance imaging (MRI) demonstrated numerous CCMs involving the brain stem, cerebral hemispheres, and cerebellum (Panel A, B: Susceptibility weighted imaging, SWI). Physical examination revealed no abnormalities. At 31 weeks of gestation, routine fetal ultrasonography showed a hyperechoic lesion around the left lateral ventricle; fetal MRI confirmed a CCM located in the left frontal lobe (Panel C: T2-weighted imaging, Panel D: SWI).

The MRI characteristics of mother and fetus suggested their CCMs may be familial. Whole Exome Sequencing (WES) revealed a heterozygous pathogenic mutation in the **KRIT1** gene (NM_194456.1:c.1A>G, p.0?) (Panel F), also called CCM1, in the fetus. Sanger sequencing confirmed that her mother carries the same mutation. To our knowledge, this is the first-ever reported case of fetal familial CCM and this novel mutation.

After steroid administration to promote fetal lung maturation, the mother delivered an asymptomatic daughter at 32 weeks of gestation with an Apgar score of 10 by cesarean section without complications. Eleven days after birth, the baby's brain MRI confirmed the CCM (Panel E: SWI).

Discussion

This report highlights the importance of considering fetal CCMs in pregnant women with multiple CCMs. Prompt diagnosis and close follow-up are vital because this novel mutation of the initial codon may cause CCMs to grow faster than other mutations.

Loss-of-function mutations in CCM genes cause CCM lesions. Loss of CCM proteins affects CCM and striatin-interacting phosphatase and kinase (STRIPAK) complexes, thus disrupting the endothelial barrier. During CCM lesion formation, pathologic events include increased oxidative stress, exocytosis, inflammation and angiogenesis, and decreased autophagy.[3] Blocking these events with targeted inhibitors has shown to be effective in animal models.[4] Statins have been shown to prevent CCM formation and decrease permeability in animal models through RhoA kinase inhibition. However, simvastatin fails to decrease CCM permeability among patients who received the drug for three months in a small randomized controlled clinical trial (NCT01764451).[5] Additionally, a pathogenic microbiome is permissive for CCM lesion development, which is linked to lipopolysaccharide generated by Gram-negative bacteria.6 The association between fetal CCM and microbiome in uterus needs further investigations.

In this report, DNA sequence analysis of the mother and the fetus revealed an A to G replacement at the first position in the coding region of the CCM1 gene. This severe mutation of the initial codon affects mRNA translation, leading to the production of nonfunctional protein and a phenotype that tends to be early and severe.

Owing to its intrinsic risks, familial forms often have multiple intracranial CCMs that grow in size and number over time. Brain MRI has excellent sensitivity and specificity, providing the best option for detecting CCMs with variable size, even in utero, primarily when susceptibility-weighted pulse sequences are used that are sensitive to deoxyhemoglobin and hemosiderin.

The current management options for CCMs include surgical resection and

radiotherapy, depending on symptom severity and location. Surgical resection is considered in solitary asymptomatic CCM in non-eloquent area, or in brainstem CCM with a second symptomatic bleed to prevent future hemorrhage, while it is not suitable for CCM located in eloquent, deep areas, or brainstem or with multiple lesions. Radiotherapy may be considered in solitary CCMs with previous symptomatic hemorrhage and is not recommended for asymptomatic CCMs or familial CCM because of concern about de novo CCM genesis.[7]

Owing to the strategic location, neurosurgical treatment was not an option for the mother. The baby was very young and asymptomatic. Thus, surgery was not the preferred option; close observation and follow-up are the management of choice at present. The mother complained that she had a slight unilateral drop of her mouth during follow-up and did not take any medicine. The eight-month-old baby presented no neurological abnormality at the last follow-up.

In conclusion, this report presents a case of familial CCMs on MRI in the mother and the fetus and identified a novel heterozygous **KRIT1** mutation. This finding expands the CCM gene mutation profile, impacting genetic counseling and clinical management.

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Figure. The mother and the fetal brain MRI

The mother's axial susceptibility-weighted imaging (SWI) (A, B) shows multiple hypointensities in the brain stem, cerebral hemispheres, and cerebellum.

The fetal axial T2-weighted imaging demonstrates an irregular hypointensity in the left frontal lobe (C), which is more evident on SWI (D).

A follow-up brain MRI at 11 days after the birth of the baby reveals the irregular hypointensity in the left frontal lobe on SWI (E).

Whole Exome Sequencing (WES) of the baby demonstrated a novel loss of function (LOF) mutation in the KRIT1 gene on chromosome 7. The same mutation was found in her mother, confirmed by sanger sequencing (F).