

## Varying clinical presentations of familial cerebral cavernous malformations (CCMs) and spinal cord cavernous malformations (SCCMs)

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We present a family afflicted by both extensive cerebral cavernous malformations (CCMs) and spinal cord cavernous malformations (SCCMs). These may be inherited in an autosomal dominant pattern or occur sporadically. The presentation varies and may include a multitude of clinical symptoms separated in time and space. Cavernous malformations should be considered in the differential diagnosis of such entities as stroke, headache, multiple sclerosis, and new-onset seizures after an intraparenchymal hemorrhage.

### Case report

*Patient 1:* A 76-year-old, right-handed Caucasian female presented acutely with increasing left-leg weakness and new right-leg weakness in March 2009. She reported bowel and bladder incontinence over a few months. Her computed tomography (CT) brain without contrast (120KV, ST: 1.0mm) revealed a left basal ganglia hemorrhage, initially thought to be secondary to hypertension (Fig. 1). Blood pressure in the outlying facility was 150/65 mm Hg. Her history was significant for diabetes and a stroke in the 1970s (of unclear etiology) that had resulted in left hemiplegia (arm > leg). On admission, she had been taking aspirin 81mg and clopidogrel daily.

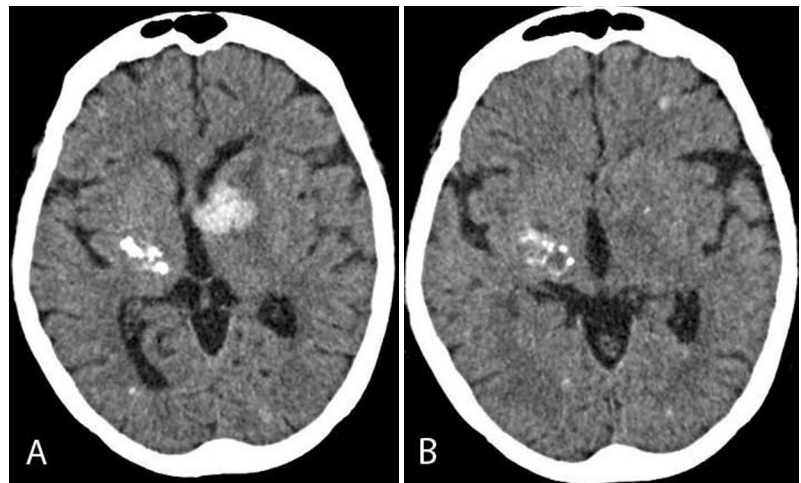


Figure 1. Axial brain CT (120KV, ST: 1.0mm). Scattered areas of hyperintensity are seen throughout the both hemispheres and throughout the centrum semiovale, particularly on the left. A large area of hyperintensity represents a hemorrhage with some mass effect in the left basal ganglia and caudate (A). Note calcifications in the corpus callosum and the right thalamus (B).

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Given that her left basal ganglia hemorrhage could not explain the new bilateral leg weakness, and that it was suspicious for multiple smaller areas of hemorrhage and calcifications, a noncontrast MRI of the brain (Fig. 2) and cervical spine (Fig. 3) were performed using a 3.0T magnet.

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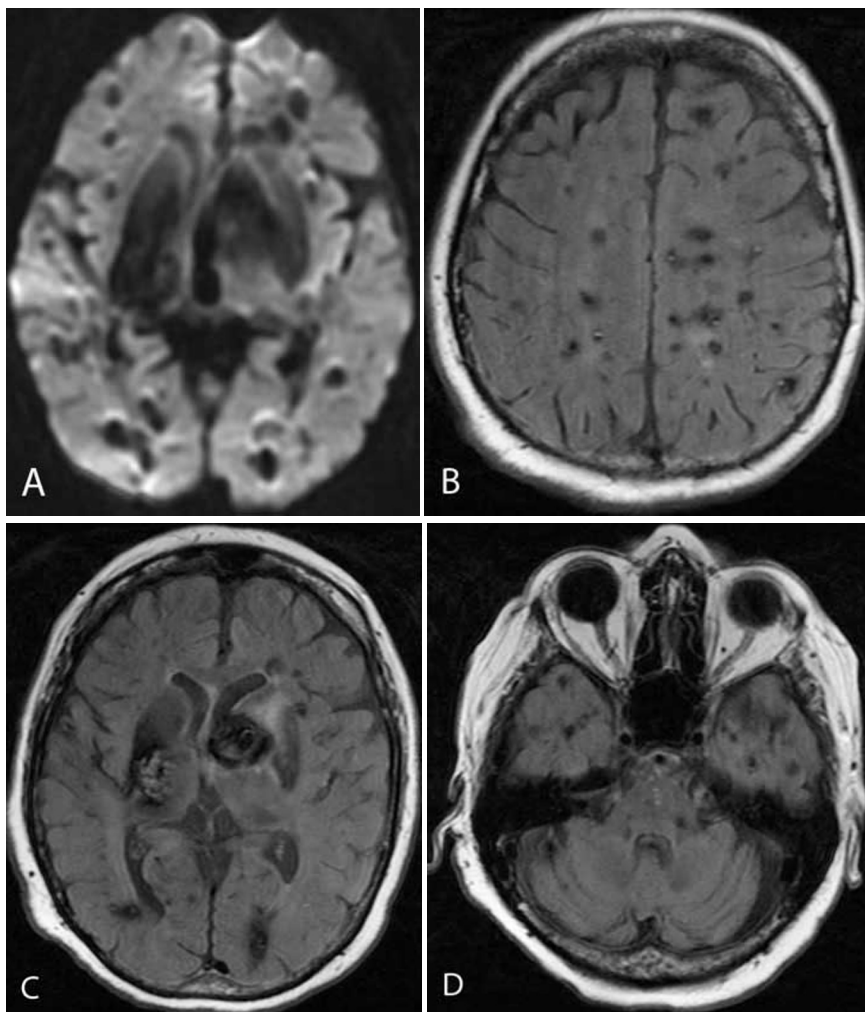


Figure 2. (A) MRI brain DWI: striking appearance compared to brain CT with numerous hypointense “holes” seen throughout the cortical and subcortical regions of both hemispheres. (B-D) T2 FLAIR brain MRI: Innumerable hypointense lesions in the right and left cerebral hemispheres (B). Left basal ganglia lesion is measured 2.3 cm in diameter associated with hemorrhage (C). Extensive load of brain stem and cerebellar lesions (D).



Figure 3. Cervical MRI sagittal view without contrast STIR (Short T1 Inversion Recovery) sequence. Heterogeneous cord lesions, the largest at the C3-4 level, are associated with a surrounding rim of decreased signal.

MRI of the brain revealed innumerable lesions of decreased signal intensity on T1- and T2-weighted images, with magnetic susceptibility artifacts. The lesions were present throughout both the right and left cerebral hemispheres, and in the brainstem and cerebellum, with the largest (in the left basal ganglia, measuring 2.3 cm in diameter) associated with hemorrhage. The cervical MRI was significant for multiple lesions within the cervical spinal cord; the largest was at the C3-4 level, measuring 1.4 cm in cranio-caudal dimension, and was thought to have bled within the last 3 months. The brain and cord lesions were consistent with CCMs and SCCMs.

*Patient 2:* Over the period of a few days in August 2006, a 47-year-old son of patient 1 progressed from weakness of both lower extremities to complete paraplegia and loss of bowel and bladder control, with little sensation in both legs. A year earlier, he had experienced transient symptoms of right-sided facial droop and dysarthria but had never undergone brain MRI imaging. Although the previous thoracolumbar MRI imaging from 2006 was remarkable for vertebral body hemangiomas, no obvious lesions in the lumbar or lower thoracic cord were identified. Evaluations that included lumbar puncture, tests for HTLV-1, HIV myelopathy, subacute combine degeneration, and neuromyelitis optica were negative. Presently, he displays no cranial-nerve dysfunction or upper-extremity neurological complaints.

A subsequent brain MRI on a 3.0 T magnet (Fig. 4) done in 2010 with a gradient-echo images (GRE) sequence revealed multiple, bilateral, supratentorial as well as infratentorial lesions, with signal intensities consistent with CCMs. Our suspicion is that the spinal cord symptoms are related to this pathology; however, the imaging done previously was not sensitive enough to reveal the etiology.

*Patient 3:* In June 2010, a 45-year-old brother of patient 2 presented with transient right-arm and hand weakness, and numbness with dysarthria for one day. He subsequently developed staring episodes thought to represent seizure activity, headaches, and behavioral changes including inappropriate behavior in public places, disinhibition, and anger outbursts. Brain MRI on a 3.0 T

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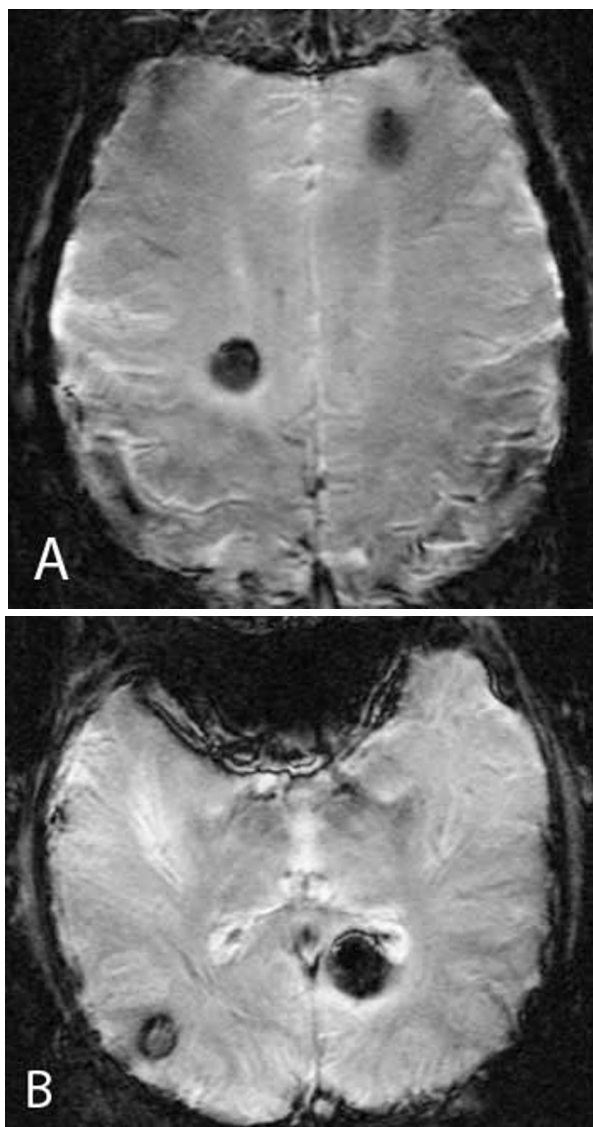


Figure 4. GRE images demonstrate multiple low-signal-intensity lesions along the subcortical medial right anterior frontal lobe, as well as the left anterior frontal lobe (A), right parieto-occipital lobe, and left paramedian parietal lobe (B).

magnet (Fig. 5) revealed multiple cortical and subcortical areas of blood products bilaterally involving the supratentorial cerebral hemispheres. One large lesion in particular affecting the cingulum was thought to contribute to the behavioral issues.

*Patient 4:* The 33-year-old daughter of patient 2 presented with chronic headaches and a nonfocal neurological exam in June 2011. Given her family history, she underwent brain MRI (3.0T). GRE sequences revealed multiple areas demonstrating susceptibility artifact in the left putamen, left thalamus, left temporal lobe, and left cerebellar hemisphere. Similar lesions were also seen in the anterior corpus callosum and the right peritrigonal white matter (Fig. 6).

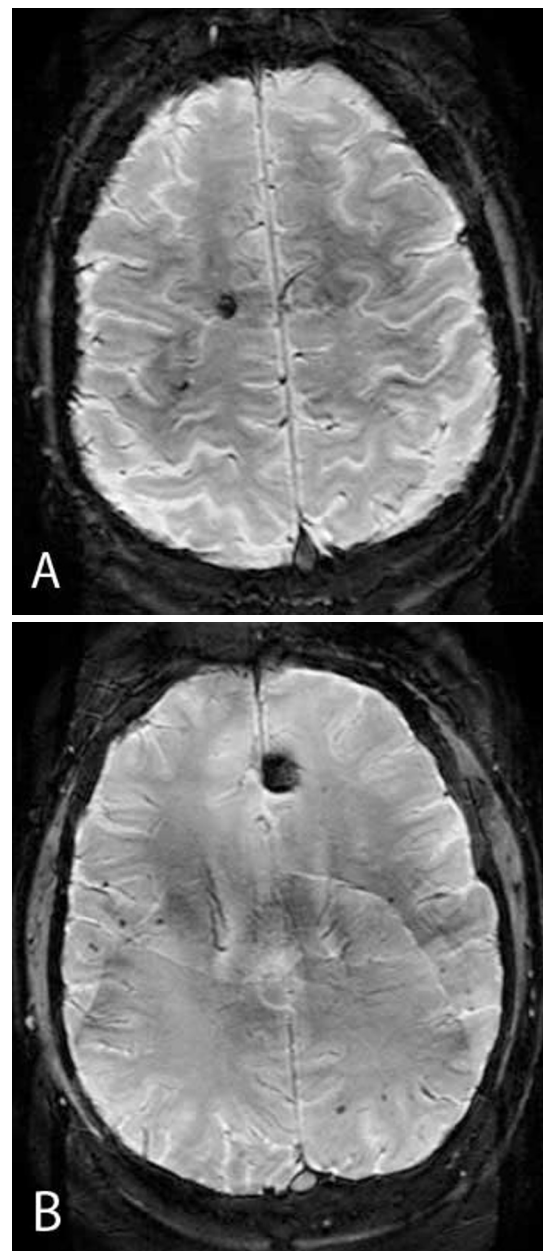


Figure 5. Axial brain MRI GRE images demonstrate multiple low-signal-intensity lesions seen along the left cingulum (A) and right medial superior frontal lobe (B), indicating blood products and consistent with cavernous malformations.

Five months later, she began to have intermittent blurred vision with flashes of light in both eyes during a headache. Brain CT (Fig. 7) confirmed blood products, and a follow-up brain MRI confirmed recent hemorrhage from a cavernous malformation. A neurosurgery consultation recommended conservative management.

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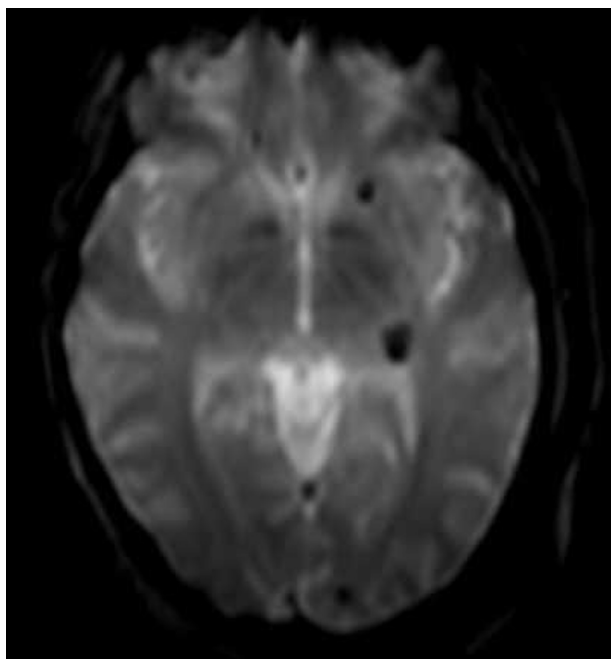


Figure 6. Axial brain MRI GRE sequence showing a large area of susceptibility artifact in the posterior lateral left thalamus, consistent with blood products.

### Discussion

Pathologically, CCMs are congenital vascular anomalies that consist of thin-walled, lobulated vascular channels without intervening neural tissue. They are responsible for roughly 9% of CNS vascular malformations (1, 2). Cavernous malformations of the spinal cord (SCCMs) are thought to account for 5-12% of all spinal vascular tumors (3). In the general population, the prevalence of CCMs is considered to be around 0.5%, and familial CCMs account for 10 to 15% of the cases (4). There appears to be racial disparity in the familial forms, with a Hispanic preponderance (5). The prevalence of familial CCM with spinal-cord lesions is unclear but thought to be rare.

CCMs are thought to be inherited in an autosomal dominant pattern with variable penetrance (6). Familial forms are associated with loss of function mutations in the genes encoding the following proteins: KRIT1 (KREV Interaction Trapped 1 protein; aka CCM1), malcavernin (aka CCM2), or PDCD10 (programmed cell death 10; aka CCM3). Familial studies indicate that the KRIT1 mutation appears to be the most common (7). Italian, Swiss, French, Hispanic, and Chinese cohorts have shown primarily KRIT1 mutations (8-12); a German family displayed a novel large deletion encompassing the CCM3 gene (13), and families from Spain and Portugal were shown to have mutations of the CCM2 gene (14).

While prior reports of familial forms of CCMs tend to have multiple lesions, the lesion load in our family seems to be substantially greater, especially in patient 1. Genetic studies have not been performed on this family. A genetic

study would be helpful in evaluating whether a more aggressive mutation exists within this family.

The presentation of a patient with CCM depends on the location of the lesions as illustrated in our patients. Smaller lesions may be asymptomatic. Supratentorial lesions are commonly associated with seizures, and smaller recurrent bleeds may cause a gradually progressive focal neurological



Figure 7. Axial brain CT (120KV, ST: 5.0mm): an 8x4mm area of increased density in the left retrolenticular portion of the internal capsule, consistent with blood products.

deficit. Annual bleeding rates have been estimated to range between 0.7% and 6.5% (15), with infratentorial lesions having a higher risk for rebleeding than supratentorial CCMs. MRI GRE sequences are thought to be the modality of choice for diagnosis. The lesions have a characteristic “popcorn” appearance on MRI T2 FLAIR imaging. The “popcorn” describes heterogeneous centers with blood products of various ages and a rim of hypointense hemosiderin (16).

Some authors recommend yearly MRI studies to follow lesion load with GRE sequences, which improve identification of hemorrhage (17). No consensus exists for treatment, but general guidelines include a consideration of surgical resection if hemorrhages cause severe neurological signs and symptoms and are superficial enough to access. Deeper lesions present the potential for greater morbidity and mortality. In some cases, radiosurgery is an option.

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