

AEROMEDICAL CONSIDERATIONS OF CEREBRAL CAVERNOUS MALFORMATION

CASE REPORT, BY JOHN E. MOORE, MD, MPH & CHRISTOPHER A. ORSELLO, MD, MPH

History

AT OVER 15 years' military service and 3,000 hours as a U.S. Navy aircrewman, an asymptomatic 33-year-old male with two elder siblings, one diagnosed with cerebral arteriovenous malformation (AVM) and cerebral cavernous malformation (CCM) and the other diagnosed with AVM, underwent MRI due to concern for familial CCM.

His MRI revealed three left-sided supratentorial CCMs, the largest of which measured 1.5 centimeters, and punctuate microhemorrhages throughout the cerebral hemisphere. He continued to remain asymptomatic with normal neurological exams, and prior to this finding was considered fully physically qualified for his duties.

Aeromedical Concerns

The primary aeromedical risks associated with the diagnosis of CCM are those of sudden or subtle incapacitation; 20-30 percent of those with CCM will be symptomatic at some time in their lives, with the peak incidence of symptoms occurring during the third to fifth decade of life.² The most common presenting symptom is that of seizure (58%), followed by focal neurological deficits and acute hemorrhage. After initial diagnosis, 4.3% of patients will have seizures at some time during their lives.⁵ Of those presenting with seizure, 30% will have tonic-clonic episodes or focal episodes that generalize. The presence of a CCM carries a 2.4% per person-year risk of seizure, with the median age of first seizure at 42 years.^{5,6} Lesions that are supratentorial most commonly present as seizures, while those that are in the brainstem most frequently present with focal neurological deficits.⁵ Other common neurological symptoms include sensory changes, vertigo, and diplopia.^{3,5}

Rates of cerebral hemorrhage range from 2.4-10.6%, although all published rates are in question since the risk of hemorrhage increases with the number of lesions, and de-novo formation of new lesions occurs at a rate of 0.4 lesions/patient/year.³ The clinical presentation of CCM-related hemorrhages ranges from mild to fatal.⁸ Many hemorrhages are, in fact, asymptomatic. In a study of 40 cases of the familial form of CCM, LaBauge and colleagues found that two-thirds of hemorrhages were asymptomatic and discovered only on routine MRI.⁴ The most important risk factors for a clinically significant hemorrhage are history of a previous hemorrhage, deep

Cerebral cavernous malformations (CCMs) offer a unique and important challenge to the aviation medical examiner. Their presence increases risk for sudden incapacitation during flight, with primary concern for seizures, cerebral hemorrhage, and other neurologic sequelae. CCMs are not uncommon, representing up to 15% of all cerebral vascular malformations and have an estimated prevalence of 1 in 200-600.¹ While this case describes CCM in a military airman, trends such as increased use of imaging and broader understanding of familial and of sporadic CCM, increase the likelihood that this disease will be seen more frequently in civil aviation.

location in the brain, number of lesions, and familial form of the disease. Hemorrhage rates for those with familial CCM have been found to be up to 4.3 - 13% per patient-year, however these numbers include asymptomatic hemorrhages.⁵ Lesion size has not consistently been shown to predict bleed frequency, but symptomatic lesions tend to be larger than those that are asymptomatic.^{2,3,7} Re-bleeding is common, with rates published between 5-60%, and a median time to second hemorrhage of 8 months. Published studies vary widely in regards to re-bleed rates, but a common trend is that higher re-bleed rates are seen in those patients with more severe initial hemorrhages and in females.^{8,9} Some studies have shown a gradual decrease in re-bleed rate after 2-3 years, while others have shown continued elevated risk.^{3,10}

Surgical resection has consistently been shown to produce excellent results when lesions are symptomatic and supratentorial. Most published series demonstrate significant reduction or cessation of symptoms with low associated morbidity and very low mortality. Multiple series evaluating the resection of lesions located in deeper structures and the brainstem have also consistently demonstrated favorable long-term outcomes but with more associated morbidity than resections of more superficial lesions. Tarnaris and colleagues evaluated published reports of brainstem CCM treatment and compared conservative management (observation) to surgical resection and found a statistically significant difference in outcomes favoring surgery.³ Several guidelines have been published and most recommend following asymptomatic lesions with MRI every 1-2 years and surgical resection for symptomatic lesions in areas shown to have favorable outcomes. In patients who have multiple lesions or a history suggestive of the familial form of CCM, genetic testing for confirmed chromosomal mutations is recommended for the patient and family members. Those who are at high risk because of genetic mutation should be followed annually by MRI.^{3,7}

Continued on page 11

Role of the AME

The presence of CCM in airmen requires thoughtful consideration and directed evaluation by the aviation medical examiner, particularly due to the potential for incapacitation. Like other cerebral vascular malformations addressed in the *Guide for Aviation Medical Examiners*, cavernous malformations require the AME's deferral to the FAA Aerospace Medical Certification Division (AMCD) for consideration of a special issuance. Submission requirements include all pertinent medical records, current neurologic specialist evaluation and report, the names, dosages, and side-effects of medication, when applicable.¹¹

Outcome

Based on the MRI results, the airman's flight surgeon consulted the U.S. Navy aviation neurology specialist who recommended the airman be suspended from flight duties. A U.S. Navy aeromedical waiver, the equivalent of an FAA special issuance, was requested but denied, citing concern for elevated risk of seizure and hemorrhage. The airman appealed this decision, and the result is pending.

References

1. Al-shahi Salmon R, Murray GD. The next step in understanding the prognosis of cerebral cavernous malformations. *Neurol* 2012;78:614-15.
2. El-Koussy M, Stepper F, Spreng A, et al. Incidence, clinical presentation and imaging findings of cavernous malformations of the CNS. *Swiss Med Wkly* 2011; 141:w13172.
3. El Ahmedieh TY, Aoun SG, Bendok BR, Batjer HH. Management of brainstem cavernous malformations. *Cerebrovascular Dis & Stroke* 2012; 14: 237-51.
4. Labauge P, Brunereau L, Levy C, et al. The natural history of familial cerebral cavernomas: A retrospective MRI study of 40 patients. *Neuroradiol* 2000; 42: 327-32.
5. Gross BA, Lin N, Du R, Day AL. The natural history of intracranial cavernous malformations. *Neurosurg Focus* 2011; 30 (6):E24.
6. D' Angelo VA, De Bonis C, Amoroso R, et al. Supratentorial cerebral cavernous malformations: Clinical, surgical, and genetic involvement. *Neurosurg Focus* 2006; 21(1):1-7.
7. Raychaudhuri R, Huntington H, Awad IA. Intracranial cavernous angioma: A practical review of clinical and biological aspects. *Surgical Neurol* 2005; 63: 319-28.
8. Dalya RT, Ghobrial G, Awad I, et al. Management of incidental cavernous malformations: A review. *Neurosurg Focus* 2011; 31(6):E5.
9. Al-Shahi Salmam R, Hall JM, Horne MA, et al. Untreated clinical course of cerebral cavernous malformations: A prospective, population-based cohort study. *Lancet Neurol* 2012; 11(3): 217-24.
10. Krisht KM, Whitehead KJ, Niazi T, Couldwell WT. The pathogenetic features of cerebral cavernous malformations: A comprehensive review with therapeutic implications. *Neurosurg Focus* 2012(3):1-6.
11. Federal Aviation Administration. *Guide for Aviation Medical Examiners*. Retrieved on 10/28/2012 from www.faa.gov/about/office_org/headquarters_offices/avs/offices/aam/ame/guide/

ETIOLOGY

Cerebral cavernous malformations (CCM) are one of three types of cerebrovascular malformations that are estimated to affect more than 3 million Americans. CCMs represent up to 15% of cerebral vascular malformation and have an estimated prevalence of 1 in 200-600.¹ The incidence of CCM is rising, with most experts attributing this to increased use of MRI. CCMs can be sporadic or familial. Sporadic lesions are most often single, while those associated with the familial form are commonly multiple. The inheritance of the familial form is autosomal dominant with variable penetrance. Half of familial lesions are found in Hispanics of Mexican origin. The major risks associated with CCMs are seizure, focal neurological deficits, and hemorrhage, with seizure being the most common presenting symptom, with a median age of presentation of 42 years.^{5,6} Prospective familial studies report annual hemorrhage rates of 4.3%–13% per patient-year and an annual risk for recurrent hemorrhage that declines from 18% in the first year after hemorrhage to 3% by 5-10 years after hemorrhage.^{1,5} Other symptoms may include headache, vertigo, diplopia, and sensory deficits. Treatment is largely dependent on symptoms, lesion location, and whether there is suspicion for the familial form of the disease. Surgical intervention has been highly successful for symptomatic supratentorial lesions.³ Asymptomatic lesions should be followed radiologically with MRI every 1-2 years. For those patients who are suspected to have a familial form, the addition of genetic analysis should be recommended for the individual and family members.³

About the Authors

John E. Moore, MD, MPH, CDR, MC, USN and Christopher A. Orsello, MD, MPH, CDR, MC, USN were residents in aerospace medicine when they wrote this case report at the Civil Aerospace Medical Institute. Both are board-certified family medicine physicians and currently command the medical departments of aircraft carriers USS Nimitz and USS Vinson, respectively.

