



Case Report

A Unique Case Report of Cerebral Amyloid Angiopathy with Literature Review

Nedaa Skeik,¹ Brandon R. Porten,² Josser E. Delgado Almandoz,³ Kyle M. Uittenbogaard,⁴ and William McDonald,⁵ Minneapolis, Minnesota

Cerebral amyloid angiopathy (CAA) is a cerebrovascular disease in which β -amyloid peptides are deposited in leptomeningeal, cortical, and subcortical arteries, arterioles, and capillaries. Most individuals with CAA are asymptomatic. However, patients with CAA can present with cognitive impairment and other neurologic deficits caused by vascular wall amyloid deposition leading to hemorrhage. We present a unique case of CAA in a middle-aged woman with a history of cerebral cortex microhemorrhages and cortical edema. Imaging and pathology findings suggested CAA as the main etiology of this presentation. This is a very rare case of CAA coexisting with aneurysmal subarachnoid hemorrhage. Finally, we present a full discussion on the pathogenesis, clinical features, diagnosis, and treatment of CAA.

CASE REPORT

A 59-year-old Caucasian woman with a history of migraine headaches, glaucoma, and 30-year cigarette use first presented with acute onset, severe, generalized headache, neck pain, and nausea without emesis. Vital signs revealed blood pressure (BP) of 181/100 mm Hg, heart rate 70 beats/min, and temperature 36.6°C. Physical examination revealed a somnolent, difficult to arouse, adult woman speaking in mumbled simple phrases. She had normal muscle strength, normal symmetrical deep tendon reflexes, and intact sensation to light touch in the trunk and extremities. Pertinent laboratory findings revealed white blood cell (WBC) count of 9700/mm³, hemoglobin 12.6 g/dL, hematocrit 38.6%, platelet count

290,000/mm³, international normalized ratio 1.1, activated partial thromboplastin time 27 sec, glucose 153 mg/dL, sodium 133 mmol/L, potassium 3.4 mmol/L, and creatinine 0.73 mg/dL.

Initial axial computed tomography (CT) head imaging revealed extensive acute subarachnoid hemorrhage (SAH) along the basal cisterns, extending significantly into the right cerebral sulci and right greater than left Sylvian fissure regions, with mildly enlarged lateral and third ventricles suggestive of mild early hydrocephalus. Head CT angiogram revealed a 7 × 5 mm ruptured right middle cerebral artery (MCA) bifurcation aneurysm and a nonruptured 6 × 5 mm pericallosal artery aneurysm (Fig. 1A and B) with interval increases in SAH and ventricular size, consistent with worsening hydrocephalus. With intravenous (IV) nicardipine administered at 2.5–15 mg/hr, BP improved to 137/74 mm Hg. A right frontal ventriculostomy, with opening intracranial pressure (ICP) of 14 mm Hg, was placed and set to drain at 20 cm above the external auditory meatus. She was started on IV labetalol 10 mg as needed, IV levetiracetam 1000 mg every 12 hr, pravastatin 40 mg per nasogastric tube, and continued on IV nicardipine 2.5–15 mg/hr. With the patient stabilized, transarterial endovascular coil embolization of the ruptured right MCA aneurysm was successful without complication (Fig. 1C).

The next day, continuous video electroencephalogram (EEG) demonstrated generalized slowing without epileptiform discharges or subclinical seizure. Transcranial Doppler ultrasound (TCD) revealed findings consistent with right MCA vasospasm with mean M1 segment velocity of 111 cm/sec.

¹Vascular Medicine, Minneapolis Heart Institute, Abbott Northwestern Hospital, Minneapolis, MN.

²Minneapolis Heart Research Foundation, Minneapolis, MN.

³Interventional Neuroradiology, Neuroscience Institute, Abbott Northwestern Hospital, Minneapolis, MN.

⁴Neurosurgery, Abbott Northwestern Hospital, Minneapolis, MN.

⁵Pathology, Abbott Northwestern Hospital, Minneapolis, MN.

Correspondence to: Nedaa Skeik, MD, Abbott Northwestern Hospital, Minneapolis Heart Institute Vascular Medicine, 800 East 28th Street, Suite H 2000, Minneapolis, MN 55407, USA; E-mail: nedaa.skeik@allina.com

Ann Vasc Surg 2014; ■: 1–6

<http://dx.doi.org/10.1016/j.avsg.2013.12.001>

© 2014 Elsevier Inc. All rights reserved.

Manuscript received: September 10, 2013; manuscript accepted: December 2, 2013; published online: ■ ■ ■

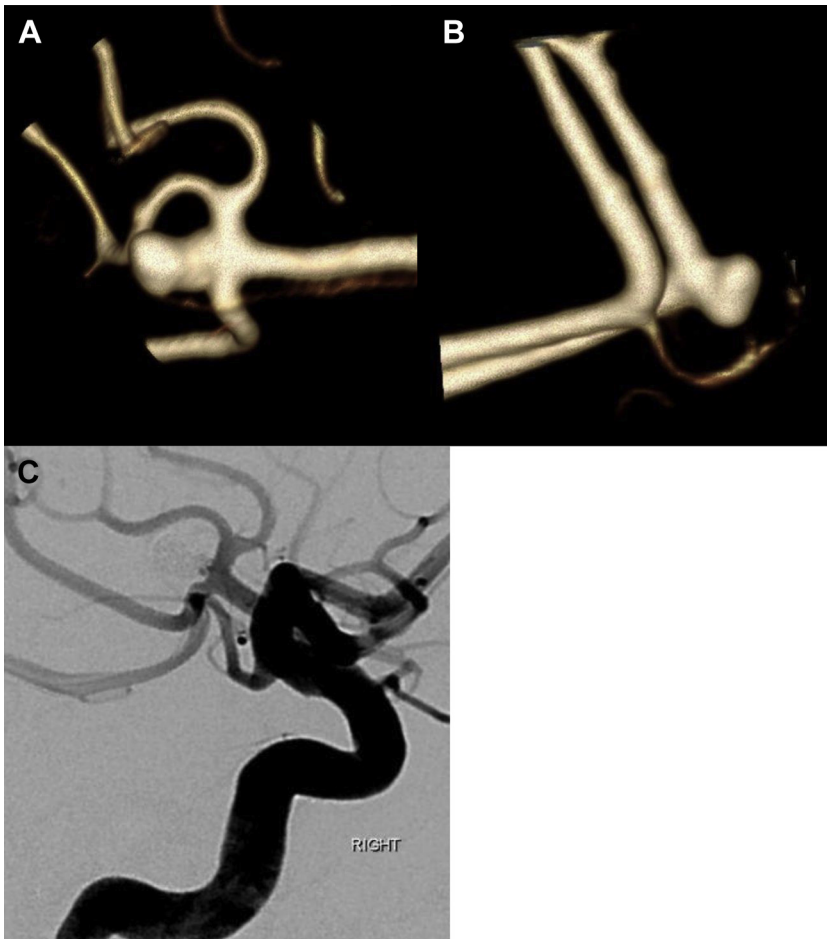


Fig. 1. (A) Three-dimensional reconstruction of a head CT angiogram demonstrates a 7-mm right middle cerebral artery aneurysm, likely the etiology of the subarachnoid hemorrhage. (B) Three-dimensional reconstruction of a head CT angiogram demonstrates an incidental 6-

mm left pericallosal artery aneurysm. (C) Right internal carotid artery angiogram demonstrates near-complete obliteration of the ruptured right middle cerebral artery aneurysm after coil embolization. CT, computed tomography.

Over the following 3 weeks, her level of consciousness and neurologic examination continued to improve with physical examination revealing increased left upper extremity strength. Repeat continuous video EEG revealed increased left hemisphere brain activity with rare left frontal sharp transients. Repeat TCD was unremarkable, with no more evidence of arterial vasospasm. The ventriculostomy drain was clamped and removed 2 weeks after presentation.

Six weeks after initial presentation, she underwent successful elective endovascular treatment of the nonruptured pericallosal artery aneurysm with a Pipeline device (Fig. 2). Her neurologic and clinical status remained stable, and she was discharged the next day to a rehabilitation facility on aspirin 325 mg and clopidogrel 75 mg orally every other day, because she had demonstrated a hyperresponse to standard clopidogrel dosing.

Four months later, she presented with progressive generalized headache that started over the previous 2

months with worsening memory loss, decreased cognitive functioning, mild left-sided weakness, paresthesia, and imbalance. Brain magnetic resonance images revealed marked left temporo-occipital edema (Fig. 3A), numerous enhancing leptomeningeal lesions (Fig. 3B) associated with susceptibility artifact involving both cerebral hemispheres (Fig. 3C). CTs of the chest, abdomen, and pelvis ruled out other pathologies, such as metastatic disease or primary malignancy. Transesophageal echocardiogram revealed normal ventricular function, no valve vegetation, and mild aortic atherosclerosis. Lumbar puncture revealed no clear etiology (cells counted 100, WBC count $8/\text{mm}^3$, red blood cell count $1/\text{mm}^3$, neutrophils 2%, lymphocytes 75%, monocytes 23%, total protein 54.8 mg/dL, and albumin 33 mg/dL with negative bacterial, viral, and fungal cultures).

Clopidogrel therapy was held, and left occipital brain biopsy of leptomeningeal and nodular enhancing areas revealed leptomeninges with mild chronic inflammation,

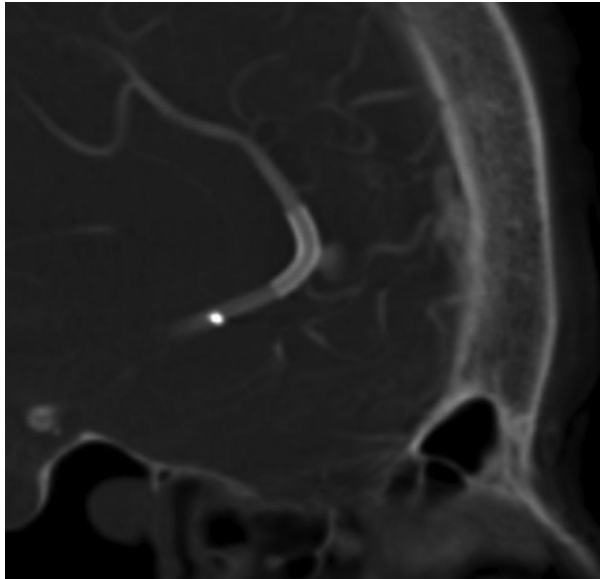


Fig. 2. Sagittal reconstruction of a Dyna-CT angiogram demonstrates the Pipeline device across the neck of the left pericallosal artery aneurysm. CT, computed tomography.

microhemorrhage, and scattered macrophages containing hemosiderin (Fig. 4A). Immunohistochemical (IHC) stain for β -amyloid showed leptomeningeal arterioles with β -amyloid deposition, consistent with cerebral amyloid angiopathy (CAA) (Fig. 4B). IHCs for CD3, CD20, CD79a, and CD68 confirmed the impression of mixed T- and B-cell infiltrates with macrophages within the leptomeninges, with no evidence of a lymphoproliferative disorder. Although mild astrogliosis of the underlying neocortex was confirmed with IHC staining for glial fibrillary acidic protein, no brain parenchymal deposition of β -amyloid was noted. There was no evidence for malignancy, vasculitis, or identifiable organisms. Further work-up revealed weakly positive antinuclear antibodies (1:40, homogenous), slightly elevated erythrocyte sedimentation rate of 44 mm/hr and C-reactive protein of 1.0 mg/dL. Anti-neutrophil cytoplasmic antibodies were negative. Clopidogrel therapy was not reinstated because of the diagnosis of CAA. Our patient underwent physical and occupational therapy along with symptomatic and supportive measures, when her level of consciousness and neurologic function was noted to improve. After discharge to a rehabilitation facility, our patient eventually was able to return home. At the 1-year follow-up visit, she was noted to have improved cognitive function and general strength. Catheter-based cerebral angiogram during this visit demonstrated stable findings. We plan to obtain a magnetic resonance angiogram of the head at a 2-year follow-up visit.

DISCUSSION

CAA is a cerebrovascular disorder characterized by β -amyloid deposition in the media and adventitia

of leptomeningeal, cortical, and subcortical arteries, arterioles, and capillaries.^{1–5} Amyloid deposition leads to smooth muscle cell destruction,³ vascular wall thickening^{1,3,6} and weakening,^{2,3} microaneurysm formation,^{2,3,6,7} and fibrinoid necrosis^{2,3,5–7} changes that can cause hemorrhage.^{1,2,5}

Most cases of CAA are sporadic,^{5,6} but it can also be hereditary.^{1,2,6} Amyloid- β (A4) precursor protein gene mutations increase β -amyloid peptide toxicity toward vessel wall components and also decrease the susceptibility of these peptides to proteolysis and clearance from the central nervous system.¹ Furthermore, carriers of the apolipoprotein E (APOE) epsilon 2 (ϵ 2) or epsilon 4 (ϵ 4) alleles tend to have earlier onset CAA and are at greater risk for CAA-related hemorrhage and hemorrhage recurrence than carriers of only the common APOE epsilon 3 (ϵ 3) allele.^{1,6} Evidence suggests that APOE ϵ 4 increases β -amyloid deposition whereas APOE ϵ 2 causes vessels with amyloid deposits to undergo wall changes.¹

The prevalence and severity of CAA increases with age,^{1,2,5,6,8,9} but it rarely affects individuals <60 years of age.¹ Patients with CAA are mostly asymptomatic;^{1,2} thus, CAA remains an underrecognized cause of cerebrovascular disease.² However, CAA can be associated with cerebral hemorrhage^{1–3,5–10} and cognitive impairment.⁸

CAA is most commonly manifested as spontaneous lobar hemorrhage,^{1,2,5} often extending into the subarachnoid space,^{1,2,5,6} with a predilection for the temporal and occipital lobes.⁸ Patients with CAA-related hemorrhage may present with headache,^{1,2,5} nausea and vomiting,^{1,2,5} hemiparesis or hemiplegia,¹ paresthesias,¹ decreased consciousness,^{1,2,5,6} seizure,^{1,2,5,6} or other transient neurologic symptoms.⁶ Recurrent hemorrhage is common.⁵ Cerebral cortex microhemorrhages with perivascular inflammation are also relatively common with CAA.^{1,5,9} Microhemorrhages are often asymptomatic,⁵ but CAA-related perivascular inflammation can cause acute or subacute cognitive decline^{1,2} with seizures and headache.¹ Advanced CAA is associated with cognitive impairment and dementia.^{1,2}

The Boston criteria were developed to standardize the clinical diagnosis of CAA and to help differentiate associated hemorrhage from other possible etiologies. There are 4 diagnostic categories of CAA: definite, probable with supporting pathology, probable, and possible (Table I).^{2,6,11}

No existing treatment prevents or reverses β -amyloid deposition² and thus, no specific therapy is currently available to treat CAA.⁵ CAA-associated hemorrhages are treated similar to other causes of

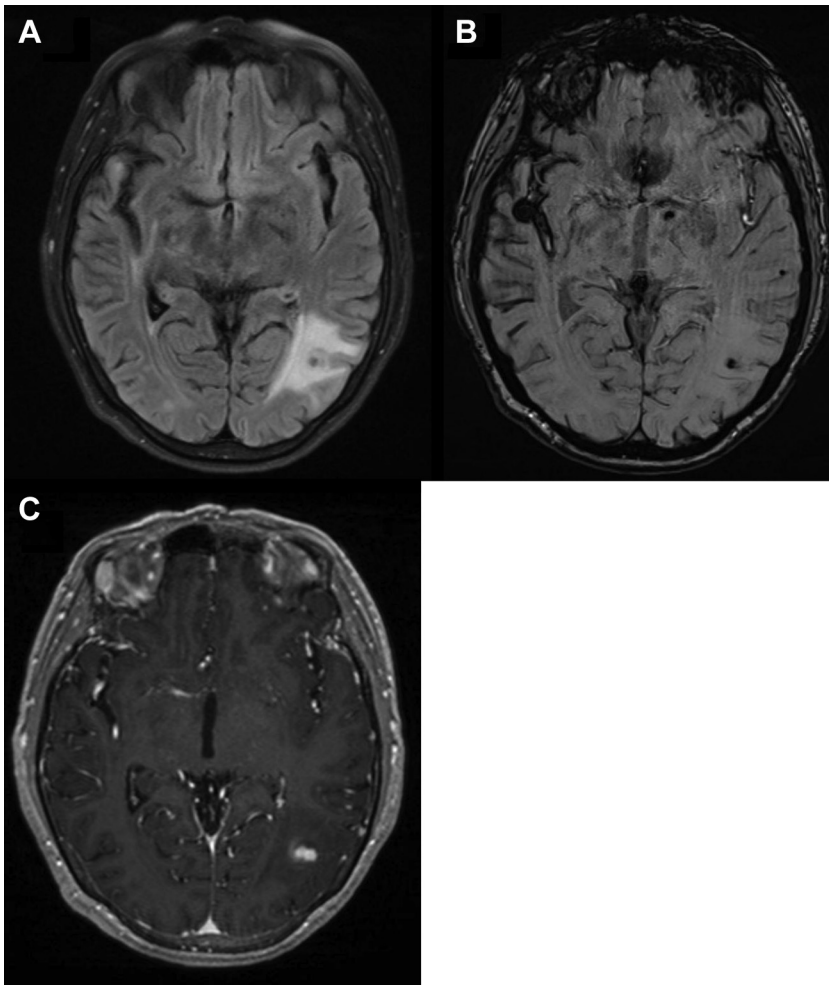


Fig. 3. (A) Axial brain MRI FLAIR image demonstrates marked signal hyperintensity in the left temporo-occipital region consistent with edema. (B) Axial susceptibility weighted brain MRI image demonstrates numerous foci of susceptibility artifact in the left cerebral hemisphere, including a focus in the region of the enhancing lesion in the left temporo-occipital region. A large focus of susceptibility in the right Sylvian fissure

corresponds to the coiled right MCA aneurysm. (C) Axial post-contrast brain MRI image demonstrates an avidly enhancing leptomeningeal lesion in the left temporo-occipital region. A large focus of susceptibility in the right Sylvian fissure corresponds to the coiled right MCA aneurysm. FLAIR, fluid-attenuated inversion recovery; MCA, middle cerebral artery; MRI, magnetic resonance imaging.

cerebral hemorrhage. After stabilization, the main goals are to maintain airway and cardiovascular function and to prevent rebleeding, vasospasm, seizure, and hydrocephalus.¹³ Consensus guidelines recommend anticoagulant and antiplatelet therapies to be discontinued until the source of hemorrhage has been repaired.^{1,6,12,13} Vascular wall changes associated with amyloid deposition increase the risk for cerebral hemorrhage and microhemorrhages in patients with and without history of cerebral hemorrhage.^{1,5,9} Thus, anticoagulant and antiplatelet therapies should be avoided unless clear indications are present.¹ Because of the high rate of hemorrhage and microhemorrhage recurrence,

clopidogrel was not restarted in our patient because there is no other clear indication.

Our patient presented with clinical, imaging, and pathologic findings consistent with CAA, a rare condition in middle-age patients, which accounts for only 2–10% of all intracerebral hemorrhages.^{2,5} There was no clinical, imaging, or pathologic finding to support a diagnosis other than CAA. Approximately 80% of SAH cases are caused by ruptured intracranial arterial aneurysms.¹⁴ Trauma,¹⁵ arteriovenous malformation,^{1,15} central nervous system vasculitis,^{1,15} anticoagulants and bleeding disorders,¹ infective endocarditis,¹ connective tissue diseases,^{12,14,15} and fibromuscular dysplasia¹⁴ are

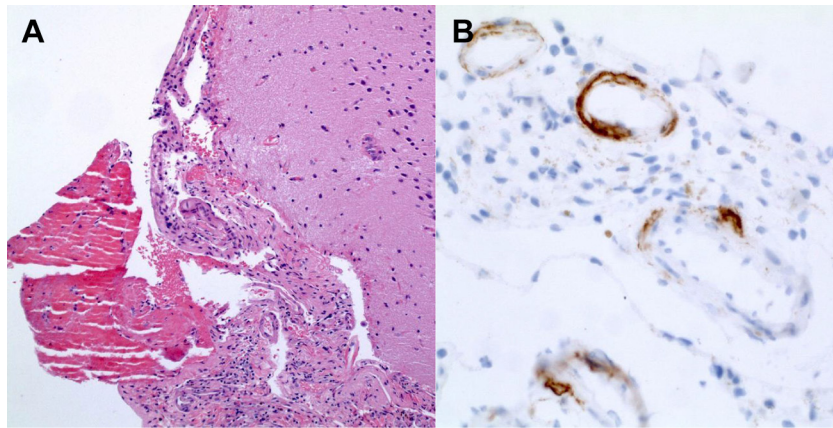


Fig. 4. (A) Leptomeninges with hemorrhage and reactive changes (hematoxylin and eosin stain, original magnification at $\times 100$). (B) Leptomeningeal arterioles with IHC staining for β -amyloid (original magnification at $\times 400$). IHC, immunohistochemical.

Table I. Boston criteria for the diagnosis for CAA-associated hemorrhage^{2,6,11}

Diagnostic category	Classic Boston criteria
Definite CAA	Full postmortem examination demonstrating: <ul style="list-style-type: none"> ■ Lobar, cortical, or subcortical hemorrhage ■ Severe CAA with vasculopathy ■ Absence of an alternate diagnostic lesion
Probable CAA with supporting pathology	Clinical data and pathologic tissue demonstrating: <ul style="list-style-type: none"> ■ Lobar, cortical, or subcortical hemorrhage ■ Some degree of CAA present in tissue specimen ■ Absence of an alternate diagnostic lesion
Probable CAA	Clinical data and MRI or CT demonstrating: <ul style="list-style-type: none"> ■ Multiple hemorrhages restricted to lobar, cortical, or subcortical regions or single lobar, cortical, or subcortical hemorrhage and focal or disseminated superficial siderosis ■ Age ≥ 55 years ■ Absence of other cause of hemorrhage
Possible CAA	Clinical data and MRI or CT demonstrating: <ul style="list-style-type: none"> ■ Single lobar, cortical, or subcortical hemorrhage or focal or disseminated superficial siderosis ■ Age ≥ 55 years ■ Absence of other cause of hemorrhage

other known etiologies. Cerebral microaneurysm formation with β -amyloid deposition has been described previously.^{3,4,7,10,16,17} However, to our knowledge, our case is the first to report SAH from a ruptured intracranial macroaneurysm in the presence of coexisting CAA. The pericallosal and MCA aneurysms can very well be a separate diagnosis in a middle-age smoking female. Although there is no evidence from the current literature, we cannot exclude a possible correlation between CAA and cerebral macroaneurysms. We believe further research is required to answer this question.

Four months after the initial presentation, our patient returned with progressive generalized

headache, worsening memory loss, decreased cognitive function, mild left-sided weakness, paresthesia, and imbalance. MRI images revealed areas of scattered nodular enhancement in the frontal lobe, left parietal lobe, and left temporal lobe, with cortical edema in the left parietal lobe. Differential diagnoses included hypertensive vasculopathy, cerebral vasculitis, fibromuscular dysplasia, septic or atrial myxoma emboli, leptomeningeal carcinomatosis, and an inflammatory or infectious meningeal process. Brain biopsy findings were consistent with CAA, which is a rare etiology to explain these findings. A small subset of patients with CAA develop an inflammatory response termed "A β -related

angiitis'' (ABRA)¹⁸; although fully formed vasculitis was not observed in the brain biopsy, mild lymphohistiocytic infiltrates were present and may help explain evolving imaging abnormalities in this case. Based on the fact that these symptoms have progressed 4 months later and based on the MRI images and the brain biopsy findings, we believe these symptoms were related to CAA. Furthermore, CAA is associated with cerebral cortex microhemorrhages and perivascular inflammation, which can cause focal neurologic effects, seizure, and headache.

When viewed retrospectively, our patient initially presented with severe headache, nausea, decreased consciousness, and CT evidence of lobar SAH. Although these manifestations could represent CAA, this diagnosis was not entertained then because these symptoms and findings were thought to be secondary to rupture of the right MCA aneurysm, a more common etiology of SAH. No tissue specimen was collected during the initial hospitalization, and thus, the diagnosis of probable CAA with supporting pathology could not have been made either. The diagnosis of CAA would not have changed medical management, at least during the initial hospitalization, because managing the SAH, stabilizing airway and cardiovascular function, and preventing rebleeding, vasospasm, seizure, and hydrocephalus would have remained treatment priorities.

Our article represents a rare case of concurrent CAA with pericallosal aneurysm and intracranial hemorrhage in a middle-age female. We suggest that CAA should be considered as a possible etiology for cortical microhemorrhages with associated contrast enhancement and perivascular inflammation.

REFERENCES

- Greenberg S. Cerebral amyloid angiopathy. In: Basow DS ed. UpToDate. Waltham, MA: UpToDate, 2013.
- Chao C, Kotsenas A, Broderick D. Cerebral amyloid angiopathy: CT and MR imaging findings. *Radiographics* 2006;26:1517–31.
- Natté R, Vinters H, Maat-Schieman M, et al. Microvasculopathy is associated with the number of cerebrovascular lesions in hereditary cerebral hemorrhage with amyloidosis, Dutch type. *Stroke* 1998;29:1588–94.
- Masuda J, Tanaka K, Ueda K, et al. Autopsy study of incidence and distribution of cerebral amyloid angiopathy in Hisayama, Japan. *Stroke* 1988;19:205–10.
- Thanvi B, Robinson T. Sporadic cerebral amyloid angiopathy—an important cause of cerebral haemorrhage in older people. *Age Ageing* 2006;35:565–71.
- Mehndiratta P, Manjila S, Ostergard M, et al. Cerebral amyloid angiopathy—associated intracerebral hemorrhage: pathology and management. *Neurosurg Focus* 2012;32:E7.
- Maeda A, Yamada M, Itoh Y, et al. Computer-assisted three-dimensional image analysis of cerebral amyloid angiopathy. *Stroke* 1993;24:1857–64.
- Rosand J, Muzikansky A, Kumar A, et al. Spatial clustering of hemorrhages in probable cerebral amyloid angiopathy. *Ann Neurol* 2005;58:459–62.
- Rordorf G, McDonald C. Spontaneous intracerebral hemorrhage: pathogenesis, clinical features, and diagnosis. In: Basow DS ed. UpToDate. Waltham, MA: UpToDate, 2012.
- Vonsattel J, Myers R, Hedley-White E, et al. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. *Ann Neurol* 1991;30:637–49.
- Linn J, Halpin A, Demaerel P, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology* 2010;74:1346.
- Charidimou A, Gang Q, Werring D. Sporadic cerebral amyloid angiopathy revisited: recent insights into pathophysiology and clinical spectrum. *J Neurol Neurosurg Psychiatry* 2012;83:124–37.
- Singer R, Ogilvy C, Rordorf G. Treatment of aneurysmal subarachnoid hemorrhage. In: Basow DS ed. UpToDate. Waltham, MA: UpToDate, 2011.
- Suarez J, Tarr R, Selman W. Aneurysmal subarachnoid hemorrhage. *N Engl J Med* 2006;354:387–96.
- Singer R, Ogilvy C, Rordorf G. Etiology, clinical manifestations, and diagnosis of aneurysmal subarachnoid hemorrhage. In: Basow DS ed. UpToDate. Waltham, MA: UpToDate, 2012.
- Okazaki H, Reagan T, Campbell R. Clinicopathologic studies of primary cerebral amyloid angiopathy. *Mayo Clin Proc* 1979;54:22–31.
- Mandybur T. Cerebral amyloid angiopathy: the vascular pathology and complications. *J Neuropathol Exp Neurol* 1986;45:79–90.
- Scolding N, Joseph F, Kirby P, et al. Abeta-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. *Brain* 2005;128:500–15.