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BEHAVIOR (H. KIRSHNER, SECTION EDITOR)

Atypical Clinical Manifestations of Cerebral Amyloid Angiopathy

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Abstract

Purpose Cerebral amyloid angiopathy is a vasculopathy caused by β-amyloid deposition in cerebral arterioles and capillaries. It is closely linked to Alzheimer's disease and predisposes elderly patients to intracerebral hemorrhage, transient focal neurological episodes, and cognitive impairment. Because of a predilection for symptomatic hemorrhage, particularly in the frontal lobes, cerebral amyloid angiopathy may also cause a dysexecutive syndrome.

Recent Findings In this case series, we describe presentations of classic clinical dementia syndromes which are not are widely thought to be associated with cerebral amyloid angiopathy, namely logopenic variant primary progressive aphasia ($n = 3$), normal pressure hydrocephalus ($n = 3$), and Lewy body dementia ($n = 2$). In every case, after a clinical diagnosis was established, neuroimaging, brain biopsy, and/or autopsy confirmed the presence of cerebral amyloid angiopathy.

Summary Cerebral amyloid angiopathy has significant clinical implications, and its ability to mimic and/or contribute to other clinical dementia syndromes can complicate its diagnosis. This series of cases broadens the range of clinical scenarios associated with cerebral amyloid angiopathy.

Keywords Cerebral amyloid angiopathy · Alzheimer's disease · Aphasia · Hydrocephalus · Lewy body · Hallucinations

Introduction

Cerebral amyloid angiopathy (CAA) is a small vessel disease of the brain in which the β-amyloid peptide forms rigid, ring-shaped deposits in arterioles, and less commonly in capillaries and small veins in the gray matter of the brain [1]. This is associated with complement activation; connective tissue remodeling; dysfunction and eventual loss of vascular smooth muscle, which leads to altered autoregulation; and ultimately vascular degeneration [2]. While classically associated with hemorrhage, this process also leads to microischemic injury [3, 4]. Cerebral microhemorrhages in a typical pattern are a reliable biomarker for CAA. Iron sensitive MRI sequences (gradient echo T2* and susceptibility weighted imaging) are used to identify microangiopathic changes [5–7]. CAA is classically associated with Alzheimer's disease (AD), intracerebral hemorrhage in the elderly, and transient focal neurological episodes (TFNEs or colloquially, "amyloid spells") [8–10]. Of AD cases, 75–90% also demonstrate some degree of CAA, suggesting that CAA may have a pathogenic role in the progression of cognitive decline in AD [11, 12]. Furthermore, CAA has been shown to contribute independently to cognitive impairment and interact with parenchymal AD pathology [13]. Consistent with the cortical production of β-amyloid, hemorrhages related to CAA are generally lobar [14]. While patient outcomes are often better than their counterparts with intracerebral hemorrhage related to hypertension, there is a high re-hemorrhage rate [15].

TFNEs are associated with cortical superficial siderosis (cSS). A recent study of patients with cSS found that 24.6% of patients with cSS also had a history of TFNEs, as opposed to only 8.1% of patients without cSS [16]. cSS has also been shown to be closely associated with CAA, although trauma, reversible cerebral vasoconstriction syndrome and septic embolism from infective endocarditis can mimic these findings [17, 18]. Because of the association between CAA and TNFEs, patients with TFNEs may be at a higher risk of subsequent hemorrhage. While not entirely understood, the mechanism of TFNEs is likely epileptiform.

Understanding the full breadth of the clinical spectrum of CAA is important to identify and treat appropriate patients. Moreover, it is becoming increasingly recognized that

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multiple neurodegenerative pathologies often coexist and interact, and the presence of CAA in the context of other neurodegenerative pathologies may be an important variable. In this paper, we present a series of patients with classical clinical dementia syndromes which are not typically thought to be associated with CAA—logopenic variant primary progressive aphasia ($n = 3$), normal pressure hydrocephalus (n = 3), and Lewy body dementia ($n = 2$).

Cases

All cases were encountered in the course of clinical care in the Vanderbilt University Medical Center, Department of Neurology. This study was authorized by the Institutional Review Board, IRB # 180287, Observational Study of Cerebral Amyloid Angiopathy and Related disorders (OSCAAR).

Primary Progressive Aphasia

Our first patient presented at age 76 after 2 to 3 years of progressive difficulty with her speech. She had notable deficits in naming and repetition with mild reductions in fluency. When asked to repeat "No ifs, ands or buts," she would say "No ins, bits, buts." Formal neuropsychological testing confirmed a clinical syndrome typical of logopenic variant primary progressive aphasia. Neuroimaging is shown in Fig. 1a, b and demonstrated scattered white matter changes, focal microhemorrhages in the left temporal and parietal lobes, and asymmetric atrophy, particularly in the left parietal and occipital lobes with accompanying *ex vacuo* changes in the left occipital horn of the lateral ventricle. Importantly, the focality of the findings observed on MRI aligns with the expected localization of her clinical symptoms. These highly focal cerebral microhemorrhages may suggest focally severe vasculopathy—this type of focality has occasionally been reported in pathological series of patients with CAA [19]. It may also be due to an unrecognized episode of CAA-related inflammation (CAARI), in which vasculitis results from an autoimmune reaction to vascular β-amyloid deposits [20]. This often causes focally severe microhemorrhagic changes with transient cerebral edema, and emerging literature suggests that some patients may be nearly asymptomatic [21, 22]. A remote episode of CAARI would look similar to the imaging findings depicted. Her symptoms have worsened at a moderate pace over the 2 years following her diagnosis, and she has developed intermittent paranoia, hallucinations, and depression along with worsening of her language and memory deficits. At current follow-up, she is without symptomatic hemorrhage.

Two additional cases were identified that met clinical criteria for primary progressive aphasia and had neuroimaging features of CAA. One had the onset of subjective cognitive symptoms, primarily short-term memory impairment and trouble multitasking, at age 62. At the same time, she noted episodes of left facial numbness lasting 45 min and occurring every few months. Neuropsychological testing revealed difficulty with verbal list learning (CVLT-II) more than with visual memory (CVMT). Follow-up testing 15 months later revealed progressive difficulty with naming, and 3 years from the initial presentation her naming and fluency were substantially impaired. At this evaluation, she had slowed processing speed, the emergence of symptoms of executive dysfunction, and she had begun to require assistance with activities of daily living. Brain MRI showed focal atrophy in the dominant parietal lobe, with white matter hyperintensities and scattered microhemorrhages in a pattern consistent with CAA. Her symptoms have continued to progress, and at age 73 she required assistance with most activities of daily living.

Our final patient with primary progressive aphasia was a retired schoolteacher, who presented at age 67 with 2 years of "trouble finishing sentences," along with short-term memory loss. She noted that the severity of symptoms fluctuated considerably from day-to-day. Initial examinations noted impaired repetition, broken prosody, and decreased short-term recall (recalled one of three items at 5 min). Brain MRI showed extensive white matter disease and asymmetric prominence of the occipital horn of the left lateral ventricle (no GRE-T2* or susceptibility weighted imaging was obtained at this time). Two years later, after mild progression of her symptoms, she presented to the emergency department with the worst headache of her life. She was found to have a cortical subarachnoid hemorrhage overlying the left frontal lobe near the Broca's area. Repeat MRI at this time demonstrated scattered microhemorrhages consistent with CAA (Fig. 1c). Two months after her subarachnoid hemorrhage, she suffered an intraparenchymal hemorrhage in the left anterior temporal lobe. Her language and other cognitive symptoms continued to progress, and she died 15 months later.

Normal Pressure Hydrocephalus

We present three patients with a clinical syndrome and neuroimaging consistent with hydrocephalus, documented normal intracranial pressure, and MRI evidence of CAA. Two had remarkable improvement with ventriculoperitoneal shunting, while one elected not to undertake a surgical intervention.

Our first case was an 86-year-old gentleman with chronic gait imbalance and several falls. Several years prior, he tested within normal ranges on neuropsychological measures, but he had subjective memory impairment which he felt was worsening, as well as falling for a financial scam. He had difficulty lifting his feet and had episodes of leg freezing and gait hesitation requiring him to walk with a cane. A CT myelogram

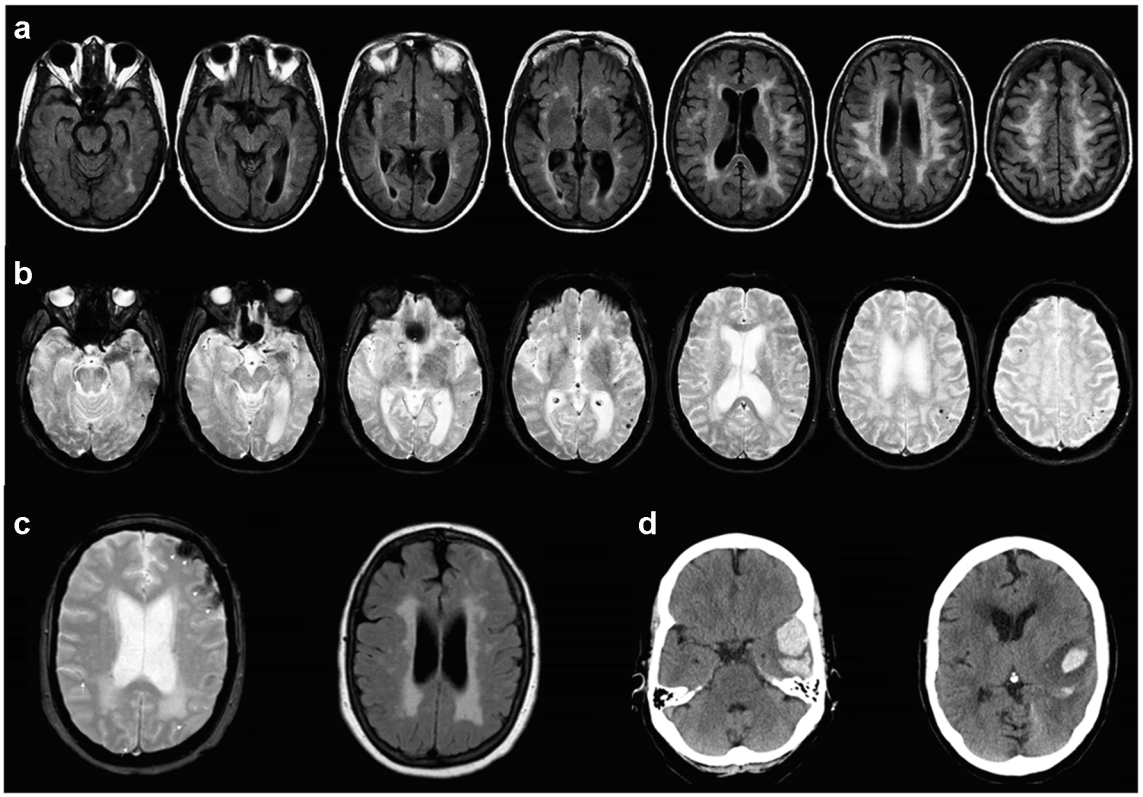

Fig. 1 Primary progressive aphasia and cerebral amyloid angiopathy. **a** FLAIR and **b** GRE-T2* sequences from a patient who clinically had the logopenic variant of primary progressive aphasia. She has scattered white matter hyperintensity and focal atrophy of the left parieto-occipital area accompanied by *ex vacuo* expansion of the occipital horn of the left lateral ventricle. She had one cerebral microhemorrhage in the right frontal lobe, but the majority of microhemorrhages clustered in the left temporoparietal area. **c** GRE-T2* and FLAIR images from another patient with primary progressive aphasia showing acute subarachnoid bleeding (arrowheads) near the Broca's area occurring several years after the onset of aphasia. She also has scattered microhemorrhage (arrows) and white matter changes. **d** The same patient 2 months later suffered an intracerebral hemorrhage of the left anterior temporal lobe

showed an L3–4 lumbar stenosis, which was not felt to be severe enough to account for his symptoms. MRI of the brain (Fig. 2a**)** demonstrated enlarged ventricles characteristic of normal pressure hydrocephalus, and he had improvement of his symptoms with a large volume lumbar puncture. He underwent ventriculoperitoneal shunting at age 86 with a resolution of the hydrocephalus and a substantial improvement in his mobility. Brain biopsy obtained at the time of shunt placement demonstrated CAA without neuritic plaques or neurofibrillary tangles. A CT scan performed at age 90 captured two small acute microhemorrhages and decompression of the ventricular system (Fig. 2b). The clinical improvement after shunting was durable for several years, though his cognitive deficits eventually progressed, and he died of pneumonia while in hospice care at age 91. His family donated his brain for study; innumerable cerebral microhemorrhages were grossly observed and tissue staining revealed severe CAA with minimal plaques or tangles (Fig. 2c, d).

Our second patient presented at age 84 with worsening short-term memory for over 10 years. He had severe white matter disease and hundreds of cerebral microhemorrhages in a pattern we thought suggestive of mixed hypertensive disease and CAA. He had been incontinent of urine for several years and had a 1-year history of impairment of gait with retropulsion and parkinsonism. This latter symptom rendered him essentially wheelchair-bound, and he required continuous care. His mobility improved minimally with dopaminergic therapy. He underwent a large volume lumbar puncture and 12 h later was greatly improved, both cognitively and in terms of mobility. He stated, "I feel like I've crawled out of my own grave." As expected, this improvement was short-lived, but he underwent VP shunting and the improvement returned and was durable for approximately 2 years, though he recently passed away in home hospice care.

One final patient with NPH suffered a small left parietal intracerebral hemorrhage at age 69 and then a small right temporal lobe hemorrhage at age 75. He recovered well from each hemorrhage but had progressive memory and gait impairment throughout this time. At age 77, an MRI was obtained showing ventriculomegaly and cerebral microhemorrhages (Fig. 2e, f). He consequently underwent a large volume lumbar puncture for evaluation of normal pressure hydrocephalus and had no substantial change in mobility, incontinence, or cognitive, either objectively or by the family's subjective

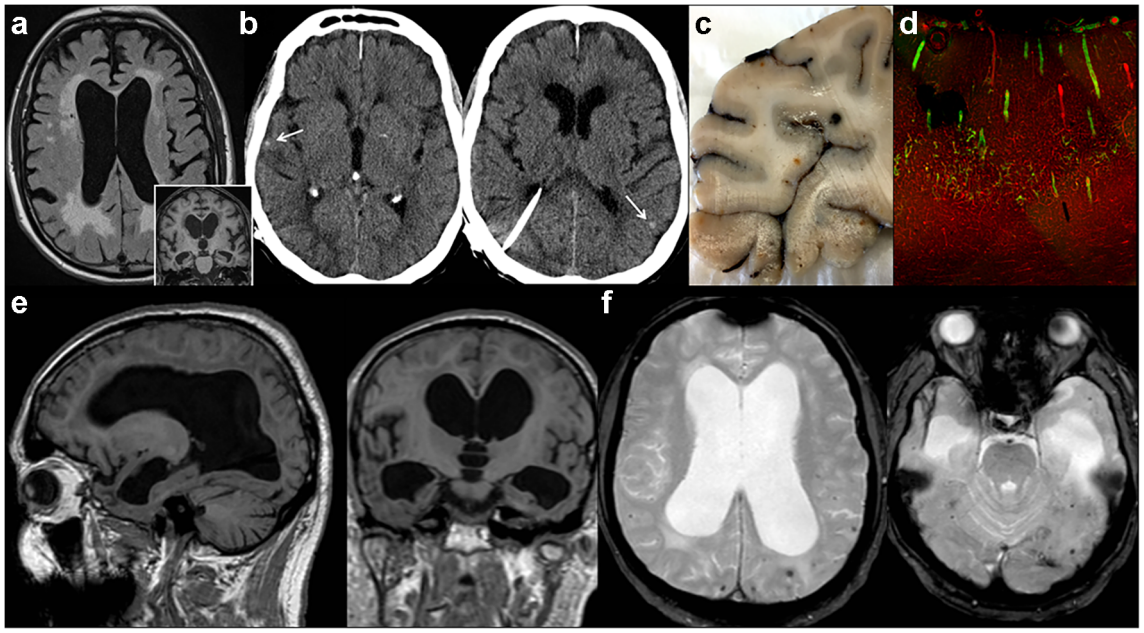

Fig. 2 Normal pressure hydrocephalus and cerebral amyloid angiopathy. **a** MRI from a patient with a clinical syndrome of normal pressure hydrocephalus just prior to ventriculoperitoneal shunting. **b** The CT scan at age 91 showed two tiny acute hemorrhages and ventricular catheter with reduced ventricular size. **c** At post-mortem analysis, he was found to have hundreds of cerebral microhemorrhages of varying age. **d** Microscopy through the full thickness of the occipital cortex (far right) demonstrated β-amyloid deposition (methoxy-XO4, green) in most penetrating arterioles and some capillaries (vascular endothelium stained in red with FITC-lectin) in the cortex sparing the white matter consistent with type 1 CAA. **e** T1-weighted MRI shows ventriculomegaly in another patient with normal pressure hydrocephalus and **f** GRE-T2* images show typical changes associated with cerebral amyloid angiopathy

assessment. The failure to improve was attributed to the longstanding nature of his symptoms. He died at age 81 from aspiration related to progressive dysphagia.

Lewy Body Dementia

The diagnosis of probable Lewy body dementia was made in this 80-year-old gentleman independently by a senior psychiatrist, a cognitive neurologist, and a neuropsychologist, prior to obtaining an MRI with evidence of CAA. His symptoms began around age 70 and came to clinical attention at about age 76, after approximately 2 years of cognitive and psychiatric decline. This followed a car accident in which he sustained a small subdural hemorrhage. His deficits seemed greatly out-of-proportion to the trauma he sustained, prompting our evaluation. He had significant deficits in short-term memory, orientation, and language, with prominent difficulty with naming and repetition. Additionally, he suffered from paranoia, nightmares, and non-antagonistic hallucinations. He would often forget that deceased family members were no longer living. His family reported a decline in his sense of humor. He had inappropriate spending habits and acquired a substantial credit-card debt. While he did not provide a history of falls, his gait was broad-based and unsteady. His MMSE was 9/30, and he had deficient semantic and phonemic fluency (for instance, when asked to name as many zoo animals as he could in 60 s, he responded slowly, "Rabbit .... uh … anything that moves ... let's see.... all sorts of things that get around"). Object naming on the short form of the Boston Naming Test was impaired at 2.7 standard deviations below the mean; there were paraphasic errors without neologisms. A brain MRI showed enlarged ventricles and a pattern of cerebral microhemorrhages characteristic of CAA (Fig. 3). He was treated with acetylcholinesterase inhibitors which neither he nor his family felt were helpful.

Our final case was that of a gentleman with a medical history of depression and recurrent spontaneous pneumothoraxes due to bullous emphysema, complicated by delirium. He presented to neurological care at age 71 when he developed diplopia after a fall. At this evaluation, his family complained that he had developed short-term memory loss gradually over the preceding decade, was unable to manage finances, and was having trouble driving. His MMSE was 25. He had nightmares, often about snakes, for the prior 2–3 years with occasional thrashing in his sleep and acting out vivid dreams. He also complained of intermittent left-hand numbness. Neuropsychological testing confirmed moderate impairments in executive functioning, memory, and visual perceptual reasoning. An MRI of the brain was unremarkable, aside from scattered white matter hyperintensities. He had progressive worsening of mood symptoms (family was astonished when he seemed uninterested after the birth of a grandchild), and his symptoms overall fluctuated dramatically from day-to-day.

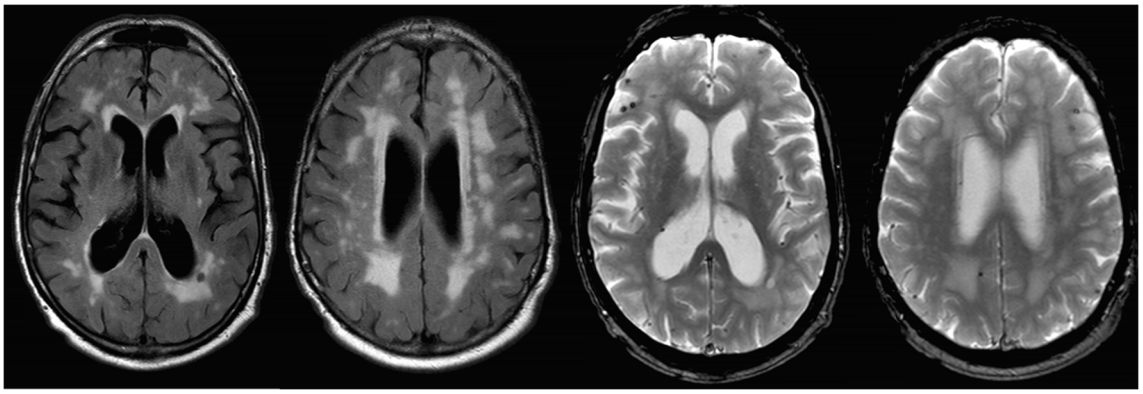

Fig. 3 Lewy body dementia with cerebral amyloid angiopathy. This patient who was clinically diagnosed with Lewy body dementia had extensive white matter hyperintensities on FLAIR (left two images) and scattered cerebral microhemorrhages in a pattern typical of cerebral amyloid angiopathy

He had terrifying visual hallucinations, often of snakes, and had an emergence of sexually inappropriate behavior, treated effectively with progesterone. The REM behavior disorder symptoms improved for a while with treatment with clonazepam, although he continued to have occasional injuries, once when he thought he was leaping from a car and jumped out of bed, striking his head. By age 74, his gait was slowed, he developed a hunched posture, lost his sense of smell, and became physically aggressive. He moved into a memory care center and continued to hallucinate, thinking he was in a war zone, or that he was incarcerated, or that his wife was unfaithful to him. Later that year, he required several psychiatric hospitalizations for hallucinations and suicidality, and he was eventually treated with ECT which had limited beneficial effect. He expired shortly thereafter. His autopsy was striking for the complete absence of Lewy bodies, absence of β-amyloid plaques or neurofibrillary tangles; the only neuropathology observed was CAA.

Discussion

Of the cases discussed, all received the diagnosis of CAA after presenting with a classical clinical dementia syndrome not typically associated with CAA: primary progressive aphasia, dementia with Lewy bodies, or normal pressure hydrocephalus. These cases were selected because they are striking and illustrate the range of presentations which can be associated with CAA. These cases also raise hypotheses regarding disease mechanisms.

CAA is frequently comorbid with AD and 36% of patients with AD also have cerebral microhemorrhages [23, 24]. Cerebral microhemorrhages have been described in primary progressive aphasias in three prior studies and are particularly linked to the logopenic variant [25, 26, 27••]. In these studies, the prevalence of cerebral microhemorrhages ranged from 30 to 50%, and the distribution tended to be lobar, in a pattern typical of CAA. Both logopenic variant primary progressive aphasia and CAA are associated with AD pathology; thus, it is not clear whether CAA contributes to the clinical presentation or is a bystander. In the final case, it is striking that the patient's language symptoms preceded the hemorrhagic pathology by several years; yet, all of the hemorrhagic changes occurred in brain areas relevant to language function, suggesting that the underlying vasculopathy may be a driver of the symptoms even prior to hemorrhage. All three of our cases had focal CAA-related hemorrhagic and/or atrophic changes in areas of the brain associated with language function, which suggests the hypothesis that CAA can directly contribute to primary progressive aphasia, although this will need to be evaluated in a larger study with a neuropathological confirmation.

A significant proportion (33 to 70%) of patients with LBD have some neuropathological evidence of CAA, and 13 to 20% have severe CAA (which we would expect to detect on MRI) [5, 28, 29]. While this association has been consistently documented over several decades, there remains little insight into how or whether CAA contributes to the pathobiology and symptomatology of LBD. However, emerging data confirms our clinical observation that distressing hallucinations are an underrecognized symptom of severe CAA and can adversely impact patient and family quality of life [30••].

Finally, a recent study found that 9% of biopsies performed for NPH also showed CAA [31•]. The pathological mechanism of NPH is poorly understood, making it difficult to predict the role of CAA in this process. However, it is understood that post-hemorrhagic conditions (subarachnoid hemorrhage, trauma, and some intraparenchymal hemorrhages) may be complicated by a communicating hydrocephalus with normal or low pressure, which has been attributed to scarring of the arachnoid granulations. It is possible that the microhemorrhagic changes of CAA recapitulate this mechanism. It is not known whether acute blood circulating within the CSF, or hemoglobin breakdown products, or products of oxidative stress related to Fenton-cycling of the elemental iron released during hemoglobin breakdown are the essential steps in

leading to NPH, but these mechanisms are all active in patients with CAA [32]. The issue is also important because CAA may be considered to carry an increased risk of bleeding with shunt procedures.

Conclusions

These clinical observations demonstrate that CAA can have a varied presentation complicating the differential diagnosis of dementia syndromes and may share and/or contribute to the pathological mechanisms underlying a variety of neurodegenerative disorders. The mechanistic links between AD, LBD, NPH, and CAA remain incompletely understood. Nevertheless, recognizing the breadth of CAA's clinical associations is necessary to ensure effective treatment and to guide further inquiry into its mechanism.

Compliance with Ethical Standards

Conflict of Interest Carolyn Akers, Lealani May Y. Acosta, Ciaran Considine, Daniel Claassen, Howard Kirshner, and Matthew Schrag each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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