3-14-2017

CADASIL accelerated by acute hypotension: Arterial and venous contribution to leukoaraiosis

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ABSTRACT

Objective: To underline the importance of blood pressure regulation in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) and to describe changes that occur in the veins in this condition, specifically venous collagenosis associated with leukoaraiosis.

Methods: Case report with neuroimaging and pathologic data.

Results: A 61-year-old man with genetically confirmed CADASIL was initially lucid following a motor vehicle accident but subsequently became hypotensive (60/40 mm Hg) due to an open femur fracture and required intubation. Multiple new white matter infarcts appeared on brain imaging. A second hypotensive episode days later was associated with new coin-sized infarcts in the bilateral corona radiata and cerebellar peduncles, and resulted in quadriplegia. No embolic source was found on cardiac or vascular imaging. He died 5 weeks post trauma. Autopsy revealed extensive subcortical and periventricular leukoencephalopathy and multiple cavitations involving deep subcortical gray and white matter. Small arteries had thickened walls, disruption of the muscularis, and intimal periodic acid–Schiff (PAS)–positive material. Both larger periventricular and small caliber veins had thickened walls that were PAS-negative and trichrome-positive, consistent with venous collagenosis. There was no pathologic evidence of global hypoxia or diffuse axonal injury.

Conclusions: The findings suggest rapid acceleration of CADASIL pathology from acute hypotension in the setting of impaired vasoreactivity. In addition, collagenosis of veins in the affected white matter regions suggests that the veins may play an important, though largely overlooked, role in maintaining white matter integrity. *Neurology*® 2017;88:1077–1080

GLOSSARY

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; **GOM** = granular osmiophilic material; **PAS** = periodic acid–Schiff.

Imaging[1,2] and pathologic studies[3] in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) have demonstrated impaired vascular reactivity in subcortical vessels, in part due to arterial changes of thickened hyalinized walls, smooth muscle degeneration, and accumulation of granular osmiophilic material (GOM). This "earthen pipe" state of vessels impairs autoregulation with dependence on systemic blood pressure for perfusion of subcortical regions. Chronic hypoperfusion can cause ischemic damage and cognitive decline,[4] but less is known about the effects of acute hypotension. One such report described multiple simultaneous infarctions on MRI in 3 patients, each of whom experienced an acute decline in blood pressure,[5] but pathologic studies are lacking.

In addition, the contribution of veins has been largely overlooked in conditions with leukoaraiosis, including Alzheimer disease and CADASIL. While we are not aware of any pathologic studies examining the veins in CADASIL, a recent report suggests loss of venous integrity in this

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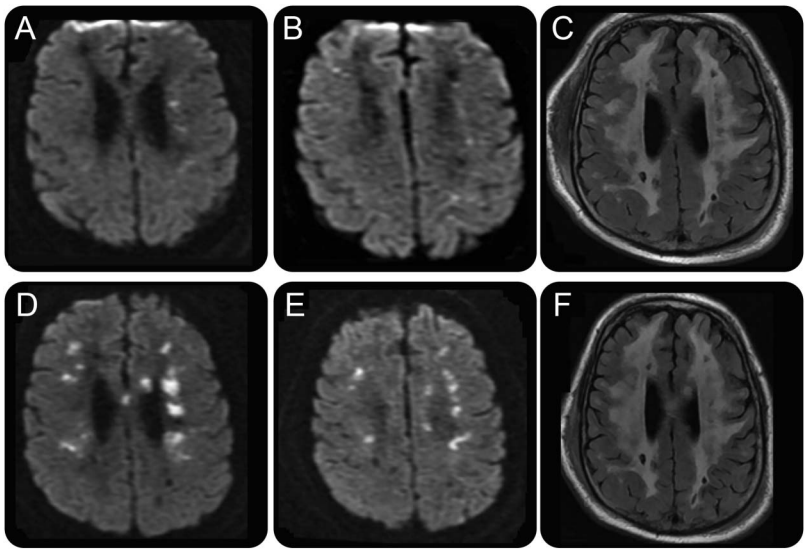
Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Figure 1 MRI findings following hypotensive episodes



Axial MRI reveals multiple acute-on-chronic infarcts on diffusion-weighted imaging (DWI) (A, B) and fluid-attenuated inversion recovery (FLAIR) (C) images after a first hypotensive episode and on DWI (D, E) and FLAIR (F) images after a second hypotensive episode, days later.

condition using 7T MRI.[6] Interestingly, 2 independent research groups, using pathologic[7] and in vivo imaging,[8,9] have observed a close association between venous collagenosis and periventricular leukoaraiosis in normal aging and Alzheimer disease and speculate that venous wall disease leads to increased vascular resistance and hydrostatic vasogenic edema, which can compromise white matter integrity. Whether venous collagenosis also occurs in CADASIL and is associated with leukoaraiosis has not yet been elucidated.

METHODS We describe imaging and pathologic findings of a patient in whom CADASIL was dramatically accelerated following acute episodes of hypotension and profile venous, as well as arterial, changes.

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from the patient's wife, his substitute decision-maker.

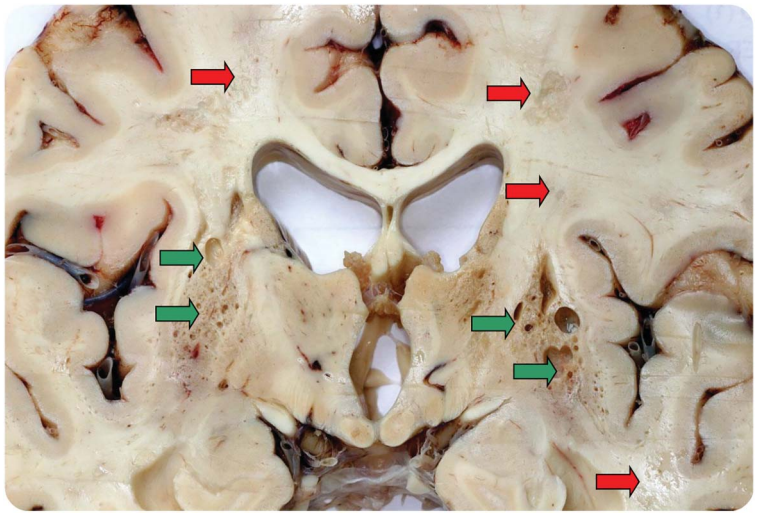
RESULTS A 61-year-old man had been followed medically by one of the authors (J.D.S.) since 1978, when he first presented at 34 years of age with a stroke. He continued to have stroke-like episodes with transient encephalopathic features over the ensuing years along with recurrent migraine headaches and gradual cognitive decline; however, he had been relatively stable for the previous decade, with intensive medical therapy to support the endothelium. A CT scan early in his disease course was "suspicious for multiple sclerosis." Serial MRI scans between 1987 and 2005 revealed progressive periventricular white matter hyperintensities extending into subcortical white matter regions of the parietal and frontal lobes bilaterally, as well as involving external capsules and temporal horns and sparing U-fibers. Infarcts involving the right lentiform, corona radiata, and left caudate, along with enlarged perivascular spaces in bilateral lentiform nuclei, were observed. A skin biopsy showed GOM and genetic testing revealed a mutation in the *Notch3* gene at exon 6 with heterozygosity for the missense mutation 1072C>T at Arg 332 Cys, confirming a diagnosis of CADASIL. Vascular risk factors including mild hypertension, impaired glucose tolerance, dyslipidemia, and homocysteinemia were well-managed up to the patient's last appointment in early 2006, the day preceding a motor vehicle accident that led to his death.

Following a motor vehicle collision, the patient was initially lucid but subsequently became hypotensive (60/40 mm Hg) due to an open femoral fracture, requiring intubation and ventilation. Level of consciousness remained depressed. An MRI 4 days post trauma revealed multiple punctate foci of restricted diffusion in bilateral corona radiata and centrum semiovale, consistent with ischemic infarction. A second hypotensive episode days later with a mean arterial pressure as low as 40 mm Hg left the patient quadriplegic and unresponsive but with spontaneous eye opening. Multiple new bilateral coin-sized infarcts in the corona radiata and cerebellar peduncles were revealed on MRI (figure 1). No embolic source was found on cardiac or vascular imaging. His clinical status failed to improve and at 5 weeks post trauma, care was withdrawn and he died.

Autopsy revealed no embolic source. Macroscopic examination of the brain showed numerous regions of softening and discoloration of white matter and multiple cavitations involving deep subcortical gray and white matter (figure 2). On microscopy, small arteries had thickened walls, disruption of the media, and deposition of granular periodic acid–Schiff (PAS)–positive material, consistent with the diagnosis of CADASIL (figure 3A). There was no widespread ischemic neuronal necrosis observed throughout the brain or in regions of selective vulnerability to support a diagnosis of a diffuse hypoxic injury. Axonal spheroids were not seen on routine staining or β–amyloid precursor protein immunohistochemistry in the long white matter tracts to support a diagnosis of traumatic axonal injury. Interestingly, both larger periventricular and small caliber veins had thickened walls that were PAS-negative and trichrome-positive, consistent with venous collagenosis (figure 3, B and C).

DISCUSSION This case directly demonstrates the vulnerability of the microvascular disease–affected

Figure 2 Coronal brain section findings



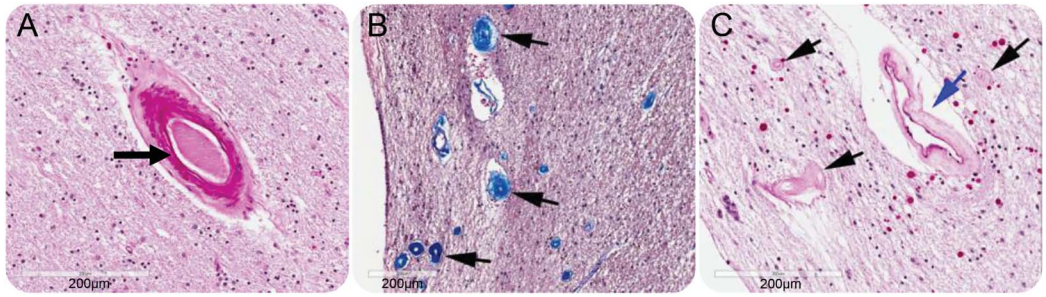
Extensive subcortical and periventricular leukoencephalopathy (red arrows) and multiple subcortical cavitations, lacunes, and enlarged perivascular spaces (green arrows) are evident on coronal brain sections.

brain to sudden acute episodes of hypotension. CADASIL has long been recognized as a disease affecting arteries and arterioles, with changes including thickened hyalinized walls, smooth muscle degeneration, and accumulation of GOM. The resulting lack of cerebral vasoreactivity from this earthen pipe state is presumed to be a major cause of cerebral ischemia in these patients, as well as a key contributor to development and progression of leukoaraiosis.

Venous collagenosis has been strongly associated with leukoaraiosis in aging and Alzheimer disease.[7,8] These collagenized and often stenotic vessels may be associated with increased vascular resistance and blood–brain barrier leakage, with exudation of fluid into extravascular (interstitial) spaces, i.e., vasogenic edema. Indeed, in support of vasogenic edema at least partly underlying leukoaraiotic changes seen on MRI, our group[9] has demonstrated a partial regression and even disappearance of some focal white matter hyperintensities over time—changes that would not be expected to occur with ischemia. Further, these areas of leukoaraiosis were closely associated with medullary venules as revealed by coregistered imaging. Interstitial edema may, itself, have toxic effects on nearby neuropil, leading to degeneration, demyelination, gliosis, and even venular infarction.[7]

Whether venous collagenosis contributed to the ischemic changes associated with acute hypotension in our case is uncertain. However, we suspect that the smooth muscle arteriopathy of penetrating arterioles in CADASIL, which lack collateral supply, results in underperfusion of the centrum semiovale and periventricular deep medullary system. The resulting chronic oxidative stress would be a stimulus to collagenosis, similar to what has been described in elderly individuals with extensive periventricular hyperintensities, driven by hypertensive arteriopathy and other vascular risk factors.[7,8] Venous collagenosis would presumably increase venous pressure, making the periventricular and deep white matter regions even more vulnerable to ischemic injury. Recent findings from an animal model add plausibility to this hypothesis. Stroke-prone hypertensive rats were shown to develop not only arterial changes, but also venous collagenosis, presumably as a downstream effect.[10] These veins with thickened, collagenized walls were most frequently found in ischemic regions. The authors hypothesized that these affected veins play a role in further development of cerebral ischemic lesions, with oxidative stress driving venous collagenosis, and venous resistance further reducing perfusion. We speculate that collagenization of veins is driven by arterial disease, whether it is due to CADASIL, hypertension, or amyloid angiopathy. In turn, by increasing vascular

Figure 3 Cerebral arterial and venous pathology in white matter hyperintensities in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy



(A) Arteriole containing periodic acid–Schiff (PAS)–positive granular material within the media (arrow). (B) Collagenosis of periventricular veins (arrows) highlighted by Masson trichrome. (C) The collagenized veins (arrows) do not contain the PAS-positive material within their walls.

resistance, venous collagenosis further exacerbates underperfusion, leading to ischemic changes as well as vascular leakage and vasogenic edema.

Our case illustrates the vulnerability of the microvasculature in CADASIL to declines in blood pressure and suggests the potential contribution of venous-related pathology to decline. Whether venous collagenosis commonly occurs in CADASIL or is a one-off finding in our case requires replication in other autopsy studies. Venous collagenosis in CADASIL may have been overlooked previously, possibly due to underrecognition as a pathologic entity and misidentification of collagenized veins for arteriosclerotic, hyalinized arteries.[7] Interestingly, venous collagenosis has been shown to be highly associated with leukoaraiosis in both aging and Alzheimer disease and this suggests that the pathophysiologic processes underlying leukoaraiosis in CADASIL may be similar to what occurs in these conditions.

AUTHOR CONTRIBUTIONS

Jacqueline A. Pettersen: study concept and design, acquisition of data, manuscript draft, and critical revision of manuscript for intellectual content. Julia Keith: acquisition of data, critical revision of manuscript for intellectual content. Fuqiang Gao: study concept and design, acquisition of data, critical revision of manuscript for intellectual content. J. David Spence: acquisition of data, critical revision of manuscript for intellectual content. Sandra E. Black: study concept and design, acquisition of data, critical revision of manuscript for intellectual content.

ACKNOWLEDGMENT

The authors thank the patient's wife, who was a proactive, devoted caregiver for the 27 years that this gentleman suffered from the effects of CADASIL and who consented to the autopsy to advance knowledge of CADASIL. They also thank Dr. Juan Bilbao from the Department of Anatomic Pathology, Sunnybrook Health Sciences Centre, University of Toronto, for performing the original neuropathologic examination; and Canadian Institute of Health Research and the Alberta Health Foundation in Medical Research (J.A.P.), Canadian Partnership for Stroke Recovery (F.G.), Campbell Cognitive Neurology Unit (L.C.), Department of Medicine, Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, and Brill Chair in Neurology, Sunnybrook Health Sciences Centre, and University of Toronto (S.E.B.) for support.

STUDY FUNDING

This study was supported by funding from CIHR MOP 131129, which enabled our work on venous collagenosis.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received July 14, 2016. Accepted in final form December 19, 2016.

REFERENCES

1. Chabriat H, Pappata S, Ostergaard L, et al. Cerebral hemodynamics in CADASIL before and after acetazolamide challenge assessed with MRI bolus tracking. Stroke 2000;31:1904–1912.
2. Pfefferkorn T, von Stuckrad-Barre S, Herzog J, Gasser T, Hamann GF, Dichgans M. Reduced cerebrovascular CO_2 reactivity in CADASIL: a transcranial Doppler sonography study. Stroke 2001;32:17–21.
3. Okeda R, Arima K, Kawai M. Arterial changes in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) in relation to pathogenesis of diffuse myelin loss of cerebral white matter. Stroke 2002;33:2565–2569.
4. Rufa A, Dotti MT, Franchi M, et al. Systemic blood pressure profile in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Stroke 2005;36:2554–2558.
5. Gobron C, Viswanathan A, Bousser MG, Chabriat H. Multiple simultaneous cerebral infarctions in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Cerebrovasc Dis 2006;22:445–446.
6. De Guio F, Vignaud A, Ropele S, et al. Loss of venous integrity in cerebral small vessel disease: a 7-T MRI study in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Stroke 2014;45:2124–2126.
7. Moody DM, Brown WR, Challa VR, Anderson RL. Periventricular venous collagenosis: association with leukoaraiosis. Radiology 1995;194:469–476.
8. Black SE, Gao FQ, Bilbao J. Understanding white matter disease: imaging-pathological correlations in vascular cognitive impairment. Stroke 2009;40(suppl 1):S48–S52.
9. Gao FQ, van Gaal S, Levy-Cooperman N, et al. Does variable progression of incidental white matter hyperintensities in AD relate to venous insufficiency? Alzheimers Dement 2008;4:T368–T369.
10. Zhou M, Mao L, Wang Y, et al. Morphologic changes of cerebral veins in hypertensive rats: venous collagenosis is associated with hypertension. J Stroke Cerebrovasc Dis 2015;24:530–536.