

CADASIL and Cavernomas: A Common Mechanism

Sir,

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant, noninflammatory, non-atherosclerotic microangiopathy affecting the central nervous system predominantly; presenting typically with migraine-like headaches, young-onset strokes followed by cognitive decline. The strokes in CADASIL are usually infarcts, but MRI evidence of microbleeds is found in around 35% of the patients.^[1] Also, major symptomatic hemorrhages are described rarely in some patients.^[2] But, cerebral cavernous malformations (CCMs) have never been described in patients with CADASIL. We report an atypical genetically confirmed case of CADASIL presenting with recurrent seizures and imaging evidence of multiple CCMs and tried to put forward a common pathophysiological association.

A 45-year-old lady presented to our hospital with recurrent episodes of tingling in the right hand for the last 3 years. She also had two episodes of loss of awareness in the last 2 years. The right-hand tingling would last for a few minutes, sudden in its onset and cessation, not associated with the loss of awareness or weakness during those episodes and would occur once in 2–3 months. 2 years before presentation, she had an episode of behavioral arrest preceded by epigastric rising sensation, associated with intact comprehension and speech arrest lasting for 5–10 min without any involuntary movements or automatisms. 8 months ago, she had sudden loss of consciousness and tonic posturing of all four limbs lasting for 10 min with postictal confusion for half an hour. She did not have any history of migraine-like headaches, stroke-like episodes, and cognitive decline. Her symptoms were suggestive of focal seizures. She was evaluated elsewhere before coming to us where she was told to have multiple CCMs and was prescribed levetiracetam. Following this, her symptoms resolved. She came for a second opinion to our hospital. We reviewed her family history, which was significant. Her 70-year-old mother had two episodes of stroke;

first being left hemiparesis at the age of 35 years, second being sudden onset slurring of speech at 63 years of age. Later, she developed insidious onset gradually progressive cognitive decline for the past 2 years.

MRI brain [Figures 1–4] of the index patient showed multiple CCMs involving bilateral cerebral and cerebellar hemispheres, the largest measuring 2.1 × 2.8 cm noted in the left parietal region. Also, there were confluent T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensities noted in subcortical and deep periventricular white matter including bilateral anterior temporal lobes and external capsules suggestive of CADASIL. An axillary skin biopsy was done which did not show any periodic acid-Schiff (PAS) positive diastase-resistant material. Exons 2–6 of the Notch3 gene were sequenced which showed heterozygous mutation for NM_000435: c. 268C >T; p.R90C confirming the diagnosis of CADASIL. Digital subtraction angiography was done to rule out any arteriovenous malformations and it was negative. Her mother's MRI brain was done which had features classical of CADASIL.

We report an atypical case of CADASIL with multiple CCMs. This case is peculiar in several aspects. First, our patient did not

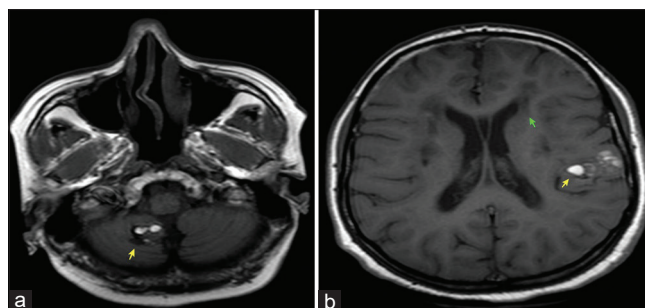


Figure 1: Axial T1 image of brain showing cavernomas (yellow arrows) in the right cerebellar hemisphere (a) and left parietal region (b), hypo-intensities (green arrow) in bilateral periventricular and subcortical regions (b)

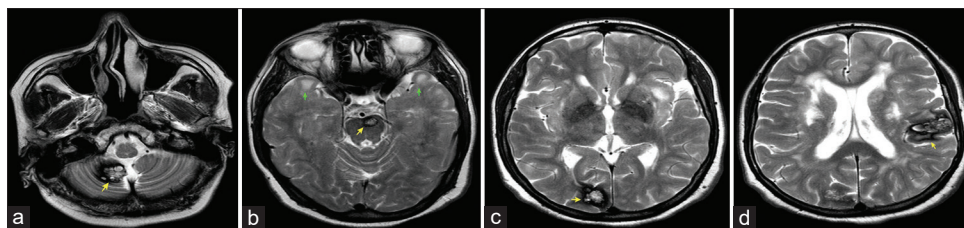


Figure 2: Axial T2 image of brain showing multiple cavernomas (yellow arrows) in the right cerebellar hemisphere (a), left pons (b), right occipital region (c) and left parietal region (d). Note bilateral anterior temporal hyperintensities (green arrows) characteristic of CADASIL (b)



Figure 3: Axial fluid-attenuated inversion recovery image of the brain showing multiple cavernomas (a, b and c) (yellow arrows). Note bilateral external capsule (a) and periventricular (c) hyperintensities (green arrows)

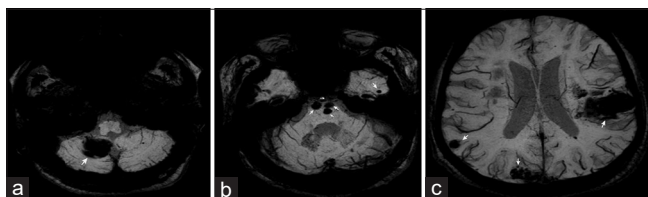


Figure 4: Susceptibility-weighted imaging of the brain showing multiple cavernomas (a, b and c) (white arrows)

have any classical symptoms suggestive of CADASIL. Second, she presented because of multiple CCMs causing recurrent seizures and not because of the underlying CADASIL. Third, the cause of CCMs in this patient was not known. CCMs are either sporadic or familial.^[3] Sporadic CCMs can be idiopathic or may be secondary to radiation in some instances.^[4] This patient with multiple CCMs might have had a coexisting familial CCM disorder along with CADASIL, but this would be less likely because none of the other family members had similar manifestations. Her mother whose imaging was available with us showed features classical of CADASIL but did not have any CCMs. It might not be a case of sporadic CCM either, because, usually sporadic CCMs are single and do not cause symptoms in the majority. We suppose, in this case, that the multiple CCMs might be due to Notch3 gene mutation leading to generalized microangiopathy involving arterioles and pericytes of capillaries. There has been recent evidence that DLL4 ligand present in endothelial cells binds to Notch3 protein present in pericytes and prevents angiogenesis. This prevents the formation of CCMs, thus, making Notch3 important in the pathogenesis of cavernous malformations as well.^[5] Classically, CADASIL is considered to be a disease of vascular smooth muscle affecting small arterioles, and CCMs are considered to be a disease of endothelial cells. But, Notch3 protein is expressed in both vascular smooth muscle cells and pericytes. Also, recent research showed that pericyte loss and basement membrane degeneration are

integral parts of the pathogenesis of CADASIL.^[6] An autopsy series of 13 CADASIL patients also showed that pericytes are damaged in CADASIL along with vascular smooth muscle cells.^[7] This interesting observation of multiple CCMs coexisting with CADASIL raises important questions on the pathophysiological basis of both CADASIL and CCMs and the same has to be studied in detail in both animal and human models further. This proposed common mechanism involving Notch3 protein and pericytes might have important therapeutic implications for both the disorders for which there is no definite pharmacological therapy at present.

We report a rare case of CADASIL with multiple CCMs and tried to explain the co-occurrence with the proposed common pathophysiological mechanisms involved in them. Pericytes appear to play an important role in both CADASIL and CCMs. More basic and clinical research is required to elucidate their role further and to develop future potential therapeutic agents.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her names and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Nil.

Conflict of interest

The authors declare that they have no conflict of interest.

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