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CADASIL MUTATION AND BALO CONCENTRIC SCLEROSIS: A LINK BETWEEN DEMYELINATION AND ISCHEMIA?

A 26-year-old man of Portuguese descent with no significant past medical history presents with sub-acute onset of right-sided hemiparesis and aphasia, with marked expressive aphasia, word-finding difficulty, and rare paraphrasic errors. Examination demonstrated right central facial weakness, 2–3/5 strength in the right arm and leg, and dysmetria in the right upper and lower extremities. Reflexes were hyperactive on the right with a right-sided Babinski response. MRI of the brain showed multiple bilateral concentric ring-like structures in the centrum semiovale and the corona radiata on T2 imaging (figure, A), consistent with the pattern of Balo concentric sclerosis. There was associated restricted diffusion in 3 lesions and incomplete ring enhancement in 1 lesion. CSF analysis showed 30 leukocytes (79% lymphocytes, 4% monocytes), erythrocyte count was 850, and oligoclonal bands were absent. He was treated with 1 g of IV methylprednisolone daily for 5 days, with little improvement. He then underwent 5 plasmapheresis exchanges, with significant improvement of motor, sensory, speech deficits, and gait. Forty-five days after discharge, his examination showed 4+/5 strength in the right intrinsic muscles of the hand and a right-sided positional tremor. Gait and tandem gait were normal. He was placed on β-interferon-1a 44 μg subcutaneously 3 times a week, for treatment of presumed clinically isolated syndrome, with good response. One year later, his neurologic examination was essentially normal.

There was no family history of demyelinating or autoimmune disorders. His mother has a significant history of headaches and early-onset strokes, and was found to be a carrier of the *Notch3* mutation consistent with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). His sister had a stroke in her 30s, and a history of migraine headaches, but has not undergone medical evaluation.

Testing for CADASIL in the patient showed the *Notch3* mutation associated with CADASIL (transition C>T, nucleotide position 1750, codon 558). Skin biopsy showed electron-dense extracellular material in close apposition to the smooth muscle of the vascular media[1] (figure, B).

Discussion. This patient's clinical presentation, neuroimaging findings, disease course, and response to therapy are consistent with Balo concentric sclerosis. However, the presence of the *Notch3* mutation associated with CADASIL in this patient raises questions about disease pathogenesis in this particular patient, and of possible relationships between the 2 disorders.

Balo concentric sclerosis is rare, and has been associated with demyelinating diseases including multiple sclerosis (MS) and neuromyelitis optica.[2] It is thought to represent the host tissue response to injury, and is associated with restricted diffusion on MRI.[3] Of note, restricted diffusion on MRI has also been described in more "typical" MS lesions.[4] A recent neuropathologic analysis of brain tissue from 14
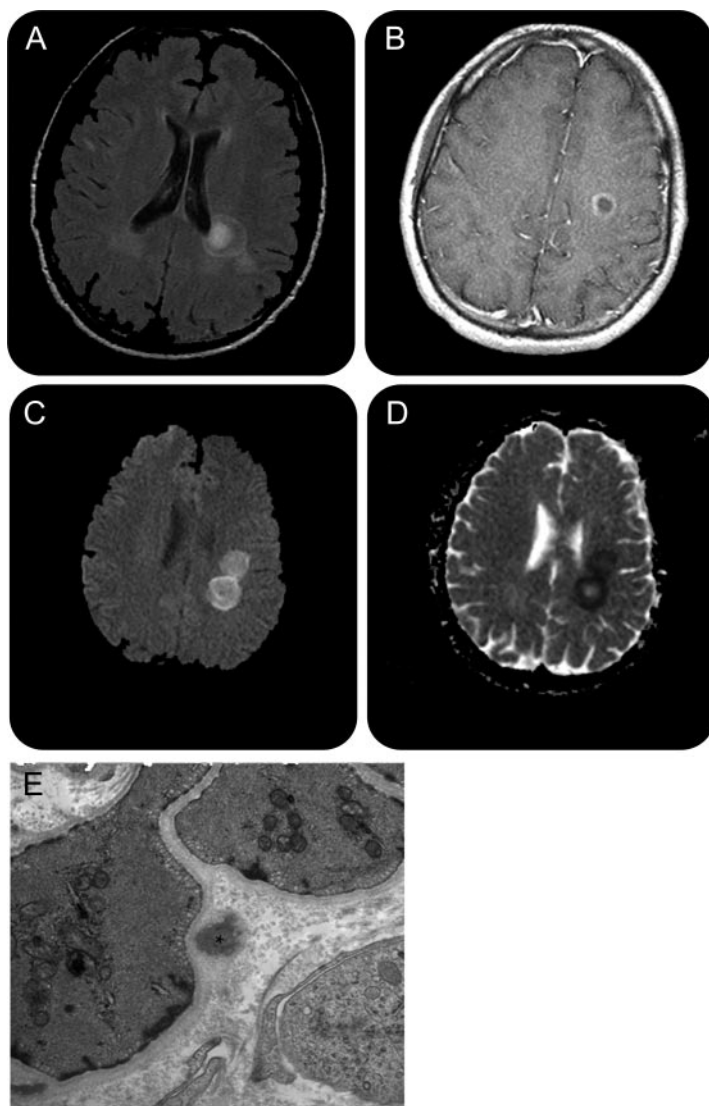
Comment:
Ischemia or demyelination—or both?

Vascular pathology and, more specifically, compromised capillaries have long been implicated in the pathogenesis of Balo concentric sclerosis (BCS).[1] More recently, hypoxia-like tissue injury and corresponding counter-regulatory mechanisms, such as upregulation of heat shock proteins and HIF1α in oligodendrocytes, have been proposed as underlying the conspicuous concentric lesion formation.[2] And although classic BCS is clearly considered a demyelinating disease, it should be kept in mind that purely ischemic lesions may present with a concentric ring formation, pointing toward a more general pattern of tissue reaction. How does the present report by Chitnis and Hollmann on a patient with a Balo-like lesion and concomitant Notch3 *mutation fit into the picture? Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a cerebral small vessel occlusive disease with pathognomonic granular osmiophilic deposits of aggregated* Notch3 *extracellular domain in the walls of small arteries. A dysfunction of vascular smooth muscle cells is central to the pathogenesis of CADASIL; however, the detailed effects of the CADASIL mutation on* Notch3 *function remain elusive. Is BCS, after all, an arteriolar disease? Or are we looking here at an extraordinary presentation of CADASIL? The clinical response to plasmapheresis still very much suggests a demyelinating disease—whose presentation in this case might be substantially altered by concomitant vascular pathology. Further clinical, pathologic, and cell biological work will be needed before the comeback of the vascular hypothesis for BCS is ultimately warranted.*

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(A–D) Concentric rings on brain MRI with restricted diffusion. (A) Axial brain MRI shows a lesion adjacent to the left lateral ventricle, which demonstrates a ring and central core hyperintensity on T2 fluid-attenuated inversion recovery image. (B) Axial T1 image of a gadolinium ring-enhancing lesion adjacent to the left lateral ventricle. (C) Axial diffusion-weighted image (DWI) shows high signal within 2 lesions. (D) Axial apparent diffusion coefficient map confirms the presence of restricted diffusion of lesions seen on DWI in (C). (E) Electron microscopy photomicrograph of skin biopsy: skin punch biopsy of the right deltoid was performed. A dermal arteriole with one definite granular osmiophilic material (GOM) deposit marked with an asterisk. The GOM deposit is in close apposition to the pinocytic vesicles of the vascular smooth muscle cell plasma membrane (magnification ×25,000).

in the cytoplasm. Additionally, expression of molecules involved in tissue preconditioning, including hypoxia-inducible factor 1-α, heat-shock protein 70, and D-110 epitope, were increased at the edge of active concentric lesions. These molecules were mainly expressed in oligodendrocytes, astrocytes, microglia, and cortical neurons. CADASIL mutation has been shown to be absent in patients with typical MS.[7]

Although these findings may be entirely coincidental, the presence of CADASIL *Notch3* mutation in our patient with a clinical presentation of Balo concentric sclerosis raises the following hypotheses regarding pathogenesis.

- Hypothesis 1. Balo is caused by mutations predisposing to hypoxic tissue injury, which includes the CADASIL mutation: Balo concentric sclerosis is due to mutations which affect vascular smooth muscle and lead to hypoxic-like injury in tissue. Such mutations may include the *Notch3* mutation associated with CADASIL.
- Hypothesis 2. CADASIL can present as Balo: CADASIL may present as Balo in some patients who are genetically predisposed to limited tissue injury, resulting in areas of preserved myelin.
- Hypothesis 3. Vascular risk factors may modify demyelinating presentation: *Notch3* mutation and other vascular risk factors could influence the presentation of a primary demyelinating disease, thus changing its phenotype toward the concentric Balo pattern.

Based on this case observation, we suggest systematic testing for the CADASIL mutation in patients with a demyelinating presentation consistent with Balo concentric sclerosis or significant restricted diffusion on MRI. Further genetic and biological studies are required to investigate the relationship between these 2 conditions.

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patients with concentric lesions consistent with Balo found that all active concentric lesions followed the type III pattern of demyelination,[5] which was not seen in any of the 18 MS cases reviewed.[6] The type III pattern shares common features with hypoxia-like tissue injury. Lesions with a type III pattern as well as Balo lesions are characterized by preferential loss of MAG, with initial relative preservation of PLP and MOG. Oligodendrocytes display occasional nuclear shrinkage and fragmentation, and expressed CNPase

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Classification scheme requirements for therapeutic questions

Class I. A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

Class II. A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a-e in Class I or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b-e in Class I. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.

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A = Established as effective, ineffective, or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)

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U = Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.