A 48-year-old white man was seen in November in the emergency room of a county hospital in Houston with cold blue toes on both feet after exposure to temperatures that were above freezing, and with no snow on the ground. Besides the blue toes, the foot pulses were diminished. The skin over the feet was intact. An arteriogram revealed the absence of flow in multiple digital arteries (Figure 1). Subsequently over the following 2 months, the worst affected toes developed dry gangrene (Figure 2).

One month earlier, in October, the patient had been admitted to the same hospital with migranous headaches and memory loss. He had severe dementia on cognitive testing, ataxia, and resting tremors. He had mildly impaired renal function that reversed with hydration. We noted transient, easy to control hypertension and asymptomatic bradycardia. A 12-lead ECG showed sinus bradycardia with no evidence of conduction pathway abnormalities or ongoing acute ischemia (Figure 3). A pharmacological stress test suggested nonreversible single vessel disease in the right coronary artery territory. MRI of the brain showed chronic ischemic changes involving the watershed areas of the frontal and the parietal lobes (Figure 4). On direct questioning, the patient recalled a half-brother who volunteered that they shared the same father, also with severe dementia.

With this history of a familial dementia, and ruling out other commoner causes of dementia, a skin biopsy was performed. Electron microscopy showed granular osmiophilic material, confirming the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL; Figure 5).

At 3 months follow-up after the first encounter, the patient was still severely demented and with dry gangrene of the right 1st through 3rd toes. Unfortunately, he left unannounced from a personal care home before completion of the process of making him a ward of state.
CADASIL is the most common cause of genetic vascular dementia in adults and is attributable to Notch3 gene mutations. It is characterized by 5 main symptoms: migraines, subcortical ischemia, mood disturbances, apathy, and dementia. Notch3 receptors are important in the cell-signaling pathways during vascular development and repair of inflammatory conditions such as atherosclerosis, arteriosclerosis, and angiogenesis. Clinical syndromes associated with Notch pathway defects include patent ductus arteriosus, pulmonary arterial hypertension, Alagille syndrome, and CADASIL. In CADASIL, there is degeneration of smooth muscle cells in blood vessels with the accumulation of electron-dense vascular deposits (granular osmiophilic material) in the extracellular space close to vascular smooth muscle cells of the small arteries in multiple vascular territories. This pathological feature is unique to CADASIL, thus detection of granular osmiophilic material by electron microscopy in skin biopsies is 100% congruent with genetic testing, however genetic testing for Notch3 gene mutations remains the gold standard for the diagnosis.

CADASIL mainly involves the brain causing stroke and dementia. However, it has been shown that the vasculopathy is generalized and is associated with a dysfunction in vasoreactivity secondary to endothelial and vascular smooth muscle cell abnormalities. The peripheral ischemia triggered by exposure to moderate cold observed in this patient is unusual, and suggests that alterations in the Notch3 signaling pathway predispose patients to developing disproportionately severe cold–associated injuries, possibly related to dysfunctional vasoreactivity.

This extreme response to cold may have implications in situations such as postarrest therapeutic hypothermia protocols.

Figure 3. ECG showing sinus bradycardia and nonspecific ST-segment changes.

Figure 4. MRI of the brain demonstrating chronic ischemic changes (FLAIR sequence). A, Confluent WMH spanning the frontal and parietal white matter bilaterally (yellow arrows). Note involvement of arcuate/subcortical “u” fibers. B, SLL are correlated microscopically with widening of perivascular space of perforating arteries and spongiosis of surrounding parenchyma (red arrows). C, Widened perivascular space contains CSF, therefore SLL and CSF are similar in signal (red arrows). CSF indicates cerebrospinal fluid; FLAIR, Fluid Attenuated Inversion Recovery; SLL, subcortical lacunar lesions (red arrows); U, subcortical “u” fibers of the white matter; and WMH, white matter hyperintensities (yellow arrows).
coronary artery bypass, and valve replacement surgery, especially in patients with family history of early dementia. Testing for vascular reactivity in young patients with possible CADASIL before elective procedures involving hypothermia may be beneficial in predicting possible postprocedure complications.

Currently there is no proven pharmacological therapy for CADASIL other than controlling the symptoms and offering preventive measures for general cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, smoking cessation, and low-dose aspirin. Otherwise, the mainstay of treatment is rehabilitation, physiotherapy, psychological support, and nursing care. Genetic counseling is also crucial, mainly for asymptomatic members at risk of carrying the mutation.1

This case not only illustrates the presentation of CADASIL but also shows the long-term clinical complications of the generalized vasculopathy that affects these patients. Thus, understanding the mechanisms by which Notch signaling affects endothelial function and vascular development is essential to optimize preventive measures and develop new targets for pharmacological intervention in CADASIL patients.

Disclosures

None.

References


Figure 5. Electron micrograph of a dermal vessel showing many deposits of granular osmiophilic material (arrows) in the vessel wall.
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