[ LITERATURE REVIEW ]

# Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

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## ABSTRACT

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephelopathy is an autosomal dominant disease affecting small vessels and often resulting in subcortical infarcts. A skin biopsy may facilitate its diagnosis as the cutaneous surface is much easier to sample than the central nervous system's tissue. Unfortunately, there is no effective treatment available today. (*J Clin Aesthet Dermatol.* 2013;6(3):29–33.)

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal dominant, small-vessel disease characterized by multiple subcortical ischemic infarcts. These infarcts mainly involve the central nervous system and can lead to disability and dementia.[1,2] Linkage studies identified a mutation in the NOTCH3 gene on chromosome 19 as the genetic defect in CADASIL.[3] The prevalence of the NOTCH3 gene mutation is 4.14 per 100,000 adults as estimated in a registry for CADASIL in Scotland.[4] CADASIL is caused by mutations in one of the exons (from 2 to 24 out of the 33 exons) of the NOTCH3 gene within the epidermal growth factor receptor (EGFR)-like repeats in the extracellular domain of the NOTCH3 protein.[5–7] More than 150 mutations have been identified so far and clustering of mutations on exons 3,4,5,8, and 11 has been reported.[8,9] The missense mutations lead to a cysteine substitution in the EGFR on the extracellular N-terminal domain.[8] This is thought to cause a defect in transendothelial exchange. Besides familial occurrence, sporadic cases are known to occur, which are more likely to go undiagnosed or misdiagnosed.[10] In 70 percent of families, the mutations are located on exons 3 and 4 that encode the first 5 EGF domains.[8]

A skin biopsy from a normal appearing cutaneous area can be very helpful in diagnosing CADASIL as the vascular changes can be observed using electron microscopy.[11,12] The knowledge of CADASIL among dermatopathologists is important as patients with CADASIL may be referred by neurologists to carry out and interpret skin biopsies, ultimately providing a key diagnostic input. Additionally, a skin biopsy also helps to detect a carrier status.

## CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of CADASIL mainly consists of a migraine with an aura, subcortical ischemic events, mood disturbances, motor disability, cognitive impairment, and apathy (Table 1).[13–16]

For the purpose of diagnosis, the history of multiple early-onset ischemic events is generally an important clue. These can be detected upon magnetic resonance imaging (MRI) and cerebral angiography and seen as lacunar infarcts in the basal ganglia and brainstem. MRI on T2-weighted images or fluid attenuated inversion recovery (FLAIR) sequences may demonstrate hyperintensity in the white matter associated with areas of focal hyperintensity in the basal ganglia, thalamus, and brainstem (Figure 1).[17,18] The extent varies greatly and generally worsens rapidly with age. Cerebral angiography can reveal intracranial stenosis, but it is not recommended due to a high rate of complications.[19,20] CADASIL should be suspected with a high level of suspicion in the presence of a suspicious family history. Genetic testing is the gold standard for the diagnosis of CADASIL. A screening of the 23 exons that

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**TABLE 1. Neurological symptoms in CADASIL syndrome**

| SYMPTOMS | FREQUENCY IN CADASIL PATIENTS | APPROXIMATE AGE OF ONSET (RANGE) | POSSIBLE PRESENTATIONS | OTHER COMMENTS |
|---|---|---|---|---|
| Migraine with aura (M/A) | 20–40%[18,35,36] | 30 years (6–48 years)[15,37] | • Visual aura: scintillating scotomas or photopsia, lateral homonymous hemianopia, blurred vision, optic ataxia, or prosopagnosia<br>• Sensory symptoms<br>• Aphasic symptoms (in one-fifth of CADASIL patients with M/A)<br>• Atypical aura: confusion, fever or coma | 1) MRI usually shows variable involement of white matter as hyperdense areas, which progress with age<br>2) The distribution and extent of white matter hyperintensities appear similar in patients of CADASIL with or without M/A except in the occipital white matter, where interestingly, the findings may be less severe in migraine sufferers.[37]<br>3) The pathophysiology of M/A in CADASIL is unkown, but is presumed to be due to vascular disorder that affects the excitability in the cortex inducing cortical spreading depression. |
| Subcortical ischemic events (stroke/transient ischemic attacks [TIA]) | 60–80%[2,14,38,39] | 45–50 years (20–70 years) in case of absence of conventional vascular risk factors[14,35,36,40] | • Two-thirds of ischemic events are classical lacunar syndromes:<br>– Pure motor stroke<br>– Pure sensory stroke<br>– Ataxic hemiparesis<br>– Sensory motor stroke<br>• Other focal neurological deficits of sudden onset:[13]<br>– Dysarthria (either isolated or associated with motor/sensory deficit)<br>– Monoparesis<br>– Paresthesia of single limb<br>– Isolated ataxia<br>– Nonfluent aphasia<br>– Hemianopia | |
| Mood disturbance | 20% mainly severe depressive episodes[13,41] | Not described | • Severe depression<br>• Depression alternating with typical manic episodes (bipolar mood disorder) | |
| Cognitive impairment, dementia, apathy | Dementia: 60% of patients >60 years of age[42–44]<br>Apathy: 40%[16] | Not described | • Alteration in attention and memory suggesting subcortical-frontal networks dysfunction[7,42,43]<br>• The cognitive impairment can be sudden or gradual[13,40,45]<br>• Often associated with apathy (lack of motivation with decreased voluntary behavior) | 1) The Wisconsin test or trail-making test is very sensitive to detect early cognitive impairment[43]<br>2) Two-thirds of CADASIL patients with dementia show improvement with cues, indicating towards a preserved encoding process.[42,44]<br>3) The apathy is presumed to occur due to accumulation of several ischemic lesions causing sub-cortical-cortical and interhemispheric disconnections.[46–49] |
| Motor disability | • Gait disturbances: 90% of individuals with dementia[50]<br>• Urinary incontinence: 80–90% of individuals with dementia[50]<br>• Pseudobulbar palsy: 50% of patients with dementia[50] | Median age for inability to walk without assistance: 59 years in males and 62 years in females[51] | • Gait disturbances<br>• Urinary incontinence<br>• Pseudobulbar palsy | Age at death has been noted to be significantly lower in men (median age—64.6 years) than in women (median age—70.7 years)[51] |
| Other neurological manifestations | | | Seizures (focal/generalize): 5–10% of the patients[14,52] | |

encode for the 34EGFR was shown to possess 100-percent specificity and almost 100-percent sensitivity,[7,8,21] but 90 percent of mutations occur in exons 2 and 6.[7]

## PATHOLOGY

The pathognomonic features of CADASIL observed on histology consist of an arteriopathy, mainly affecting small penetrating cerebral and lepto-meningeal arteries, which show wall thickening with subsequent stenosis of the lumen and ultimately ischemia. The ultrastructural features exhibit a typical granular osmiophilic material (GOM) deposited around the smooth muscle cells and pericytes of small- and medium-sized arterioles of mainly the brain, but could also involve skeletal muscles, myocardium, peripheral nerves, liver, kidney, intestines, and the skin (Figure 1).[22–24] The chemical nature of GOM is unknown. The GOM in CADASIL stains with periodic acid–Schiff (PAS) suggesting that it has acid polysaccharide, while it was demonstrated that the GOM does not contain amyloid, elastin, chromatin, calcium, or iron.[22] The GOM has not been found to be consistent with metal, mineral, immunoglobulins, complement proteins, heat shock protein 70 (HSP70), cystatin C, transthyretin, gelsolin, fibrinogen, ubiquitin, cathepsin D, or α1-antichymotrypsin.[22,25] Positive staining has been observed with aB crystallin, which is found within myocytes suggesting depositions from degenerating myocytes.[26] The nonpathognomonic ultrastructural findings reported in CADASIL include reduplication of the basal lamina of the dermal capillaries, attenuation of endothelial cells, and abnormal elastic fibers.[27,28]

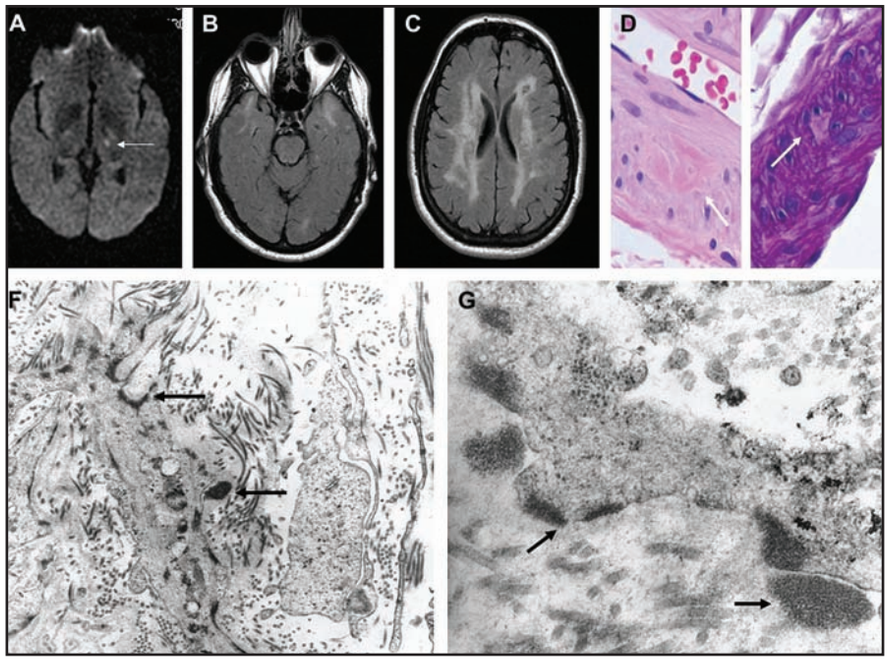


**Figure 1.** Radiologic findings in patient with CADASIL disease. (A) Magnetic resonance imaging (at age 43 years, when patient developed acute-onset right hemiparesis and dysarthria), revealed left internal capsule lacunar infarct (arrow). On T2-weighted images, there were symmetric hyperintense signals in white matter of both temporal lobes (B), and diffuse hyperintense signals in subcortical and deep white matter (C). Light microscopic examination of skin biopsy specimen fixed in formalin revealed rare dermal arteriole exhibiting focal aggregates of eosinophilic material (D), which was PAS positive diastase resistant, and focally replaced smooth muscle cells of media (E). (F) and (G) On transmission electron microscopic examination of tissue fixed in glutaraldehyde, GOM deposits (black deposits marked by arrows) were identified in extracellular matrix, adjacent to and within smooth muscle cells of dermal arterioles. Some of the extracellular deposits appeared to indent cell membranes of atrophic/degenerated smooth muscle cells of media. (F and G, Original magnifications: F, × 23,000; G, × 73,000.) Reproduced with permission from Elsevier.

## CADASIL AND THE SKIN

Walsh et al[28] reported a case involving a 47-year-old woman who presented with a history of several early-onset ischemic strokes and a similar family history. Besides MRI and cerebral angiography that suggested CNS vasculitis, brain and skin biopsies were obtained. The specimen for skin biopsy was obtained from an area of normal-appearing abdominal skin. The electron microscopy of this biopsy showed scattered granular, electron dense material abutting the vascular smooth muscle cells in cutaneous arterioles.

Clinically evident skin lesions in CADASIL are almost never observed. However, Ratzinger et al[29] reported a case of a 47-year-old man who presented with generalized, asymptomatic, reddish-brown, round-to-oval, well-defined, focally hemorrhagic macules and patches.[29] The patient had continuously developed more skin lesions from the age of 25 years and had suffered from recurring transient ischemic attacks, multiple ischemic strokes, and cerebral bleeding as well as grand mal epilepsy with one episode of status epilepticus. Biopsies of lesional and nonlesional skin from the patient's trunk revealed prominent superficial vascular plexus with an increased number of elongated and dilated vessels and a mild perivascular infiltrate of lymphocytes. The walls of capillaries, postcapillary venules and small arteries were thickened and hyalinized by a homogeneous, eosinophilic material that stained positive for PAS. GOM was observed on electron microscopy. Direct immunofluorescence showed an increased number of vessels with markedly thickened walls by deposits of fibrin, C3, immunoglobulin (Ig) M, and IgA. These findings were consistent with a diagnosis of CADASIL with cutaneous involvement, reported for the first time.

## MANAGEMENT

The management of CADASIL is multidisciplinary with involvement of neurologists, neurosurgeons, dermatologists, dermatopathologists, family practitioners and internists. Awareness of this condition can lead to its early recognition and hence prevent complications mainly related to ischemic events. Genetic testing in asymptomatic patients is a topic of debate due to associated ethical and psychological impacts, as seen with other familial neurological diseases.[30]

Currently, there is no effective treatment of CADASIL. The use of aspirin is common as a secondary prevention to reduce the risk of cerebral ischemic phenomena. However, it can cause hemorrhagic events and should be used with caution.[31–33] Migraine with an aura should be managed with nonsteroidal anti-inflammatories (NSAIDs) and analgesics. Vasoconstrictors (such as triptans) are not recommended due to the possibility of inducing an ischemic event. For prophylaxis, the usual antiepileptic drugs and beta blockers can be used. Caution should be used to avoid hypoperfusion in ischemic locations. Statins can be used in patients with hypercholesterolemia and may also be helpful in preventing/delaying arterial disease. Donepezil showed no effect on cognitive scales, but demonstrated improvement of executive functions.[34] Rehabilitation, physiotherapy, and support from family and relatives is an important component.

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