

# Inherited Cerebral Small Vessel Disease, Vascular Cognitive Impairment, Classical Cardiovascular Risk Factors, and Preventive Measures - Lessons from Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

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## ABSTRACT

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is caused by mutations in *NOTCH 3* gene, and it is the most common cause of inherited cerebral small vessel disease and vascular cognitive impairment (VCI). There are many new insights on the mechanisms of cognitive decline, relevant to the evolution of VCI of any cause. The most important issue is that, although being a genetic disease, the phenotype may be worsened by classical cardiovascular risk factors, especially hypertension and smoking. Control of these risk factors may delay disease progression and disability in CADASIL and, currently, is strongly recommended.

**Key words:** Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, diabetes, dyslipidemia, hypertension, smoking, lacunar stroke, microbleeds, vascular cognitive impairment, white matter hyperintensities

## INTRODUCTION

Vascular cognitive impairment (VCI) is the second most common cause of cognitive impairment in the elderly,<sup>[1]</sup> and among many mechanisms and causes, subcortical small vessel disease (SSVD) is probably the most frequent.<sup>[2]</sup> It is usually a sporadic disorder of the elderly, due to classical cardiovascular risk factors, including hypertension, diabetes and dyslipidemia.<sup>[3]</sup> Studies on VCI may recruit such patients, and this is frequently done. However, up to two-third of such elderly patients may harbor concomitant Alzheimer's disease pathology,<sup>[4]</sup>

which may contribute significantly to symptoms and the degree of cognitive impairment, and thus, they suffer from mixed rather than pure VCI.<sup>[5]</sup> The use of biomarkers, including cerebrospinal fluid biomarkers for Alzheimer's disease, may help in the correct patient selection.<sup>[2,3]</sup> However, such diagnostic procedures are costly and not available in all clinical settings. On the other hand, SSVD due to inherited causes, although much rarer, may offer not only animal models<sup>[6]</sup> but also homogeneous patient samples, usually with no additional pathology, more suitable for studying pure VCI and understanding the mechanisms of and relationship between SSVD, lacunar stroke, and VCI.<sup>[7]</sup>

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Inherited cerebral small vessel diseases comprise a group of rare monogenic disorders leading to cerebrovascular disease and stroke.<sup>[8]</sup> Among these, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is considered to be the most common (or least rare) monogenic cause of inherited stroke, subcortical vascular disease, and vascular dementia,<sup>[9]</sup> comprising ~60% of genetic microischemic leukoencephalopathies.<sup>[10]</sup> It is due to mutations in the *NOTCH3* gene at chromosome 19q12,<sup>[11]</sup> which causes alterations in vessel wall of arterioles (including deposition of granular osmiophilic material), resulting in brain tissue ischemia.<sup>[12]</sup>

Typically, migraine (usually with aura) at about the age of 30 or early ischemic events (transient ischemic attacks and lacunar stroke) at 41–50 years are the presenting symptoms.<sup>[13]</sup> Neuroimaging features include multiple and, later on, confluent ischemic lesions in the white matter (WM) and basal ganglia with characteristic involvement of the anterior temporal WM and external capsule.<sup>[14]</sup> As the disease progresses and ischemic lesion load increases, behavioral-psychiatric manifestations and cognitive decline become evident as well as bilateral pyramidal and pseudobulbar signs lead to vascular dementia, significant motor disability, and premature death usually at or before 65–70 years.<sup>[15]</sup> A significant variation in phenotypic presentation, disease severity, and rate of deterioration exists among different families carrying the same mutation and even among patients of the same family. Thus, patients with normal-appearing magnetic resonance imaging at the 4<sup>th</sup> decade of life,<sup>[16]</sup> with a later age of disease onset,<sup>[17]</sup> with a later onset of stroke,<sup>[18]</sup> sometimes as late as the 8<sup>th</sup> decade,<sup>[19]</sup> or with oligosymptomatic presentations<sup>[20]</sup> are increasingly being recognized. On the other hand, rapid deterioration with severe psychiatric symptoms and dementia at the 4<sup>th</sup>–5<sup>th</sup> decades is not uncommon.<sup>[21]</sup>

## CORRELATES OF DEMENTIA SEVERITY

### Types of lesions

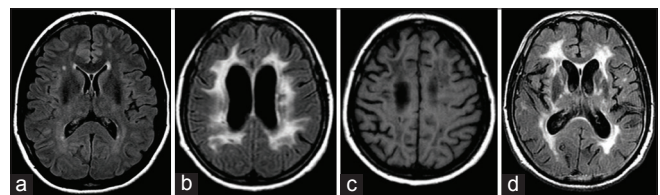
Very early in the disease process, when patients are still asymptomatic or have only migraine and show no evidence of cognitive impairment, MRIs may initially seem normal. However, deposition of protein material in the lymphatic drainage pathways in the walls of cerebral vasculature may impair drainage of interstitial fluid.<sup>[22]</sup> Venous vasculature is also decreased,<sup>[23]</sup> while decreased contrast between gray and WM in T1 images has been reported,<sup>[24]</sup> possibly related to signal alterations in normal appearing WM. Alterations in WM that is normal appearing in conventional images have been shown by calculating magnetization transfer values<sup>[25]</sup> and may be observed by diffusion tensor imaging.<sup>[26]</sup> As decreased drainage of interstitial fluid becomes more severe

and, additionally, some degree of ischemia is present, WM (probably intramyelinic) edema occurs<sup>[27]</sup> and WM hyperintensities (WMH) appear [Figure 1a] and become progressively numerous. The load of WMH alone showed a negative correlation with global cognitive measures, frontosubcortical and/or executive function tests, verbal fluency, and delayed memory scores.<sup>[28]</sup> However, despite executive and attentional deficits, patients at this stage usually show no more than mild disability and no frank dementia.<sup>[28]</sup>

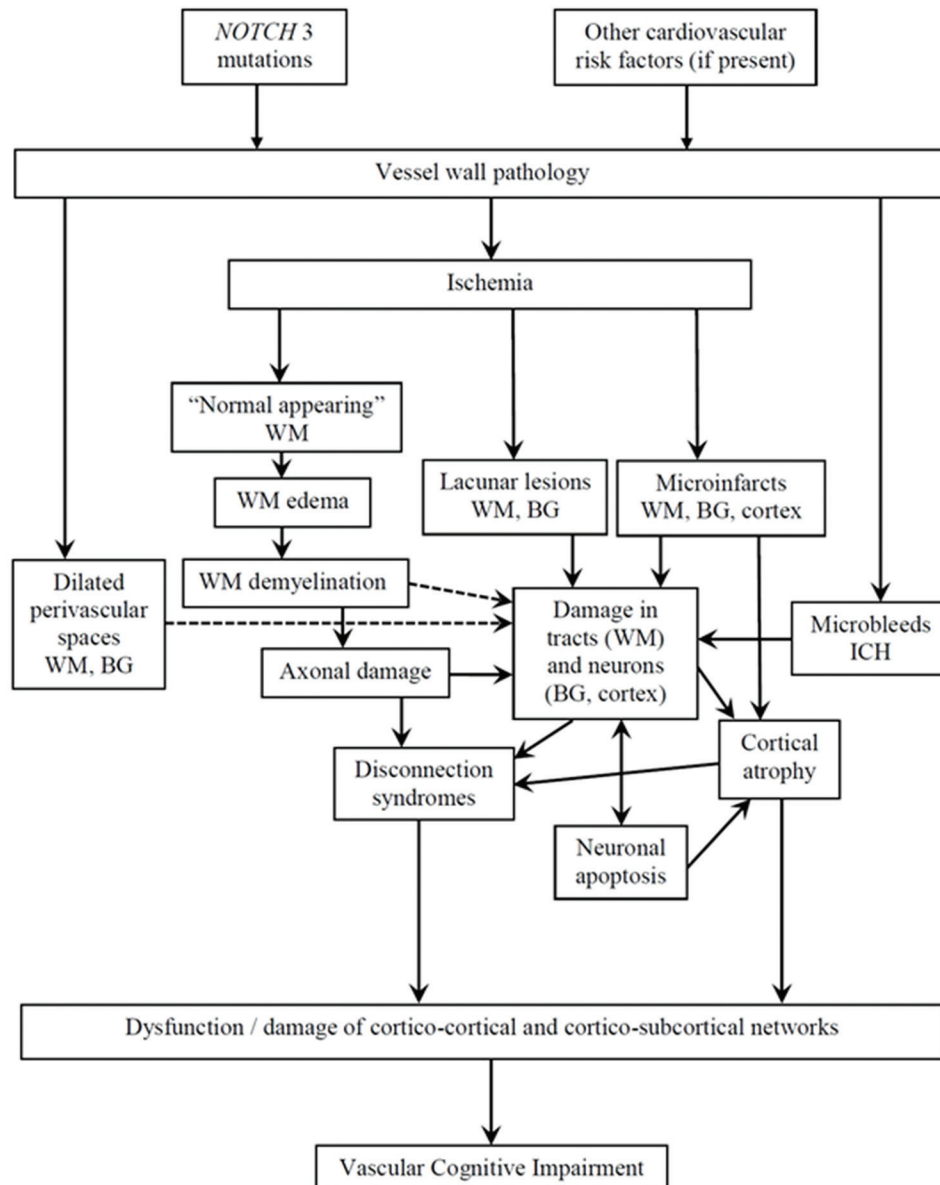
Dilated perivascular spaces increase with age in the entire brain, and it has been suggested that dilated spaces located in temporal lobes and subinsular areas are strongly and specifically associated with WMH, while dilated spaces in the WM independently correlate with cognitive decline.<sup>[29]</sup> Microbleeds in deep or cortical locations may also be present and they are independently associated with executive and frontosubcortical dysfunction.<sup>[28]</sup> Emotional symptoms of any type (depressive or non-depressive) seem to be associated with microbleeds in thalamus and cortex.<sup>[30]</sup> However, WMH alone, even in the presence of microbleeds, produces subclinical or mild cognitive impairment, usually reaching no more than the threshold of mild dementia.<sup>[28]</sup> Significant axonal damage in addition to demyelination<sup>[31]</sup> and, especially, lacunes<sup>[32]</sup> [Figure 1b and c] is usually required for more severe cognitive dysfunction, since such lesions are more able to interrupt important cortico-cortical and cortico-subcortical circuits and produce disconnection syndromes.

### Location of lesions

It seems that the type and extent of lesions are not only the parameters affecting the severity of cognitive impairment but also their “strategic” location [Figure 2].



**Figure 1:** Magnetic resonance imaging of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy patients. (a) Fluid-attenuated inversion recovery (FLAIR) image in a young female patient with headaches only and no cognitive impairment. Only a few white matter lesions are present. (b) FLAIR image and (c) T1 image in a female patient with dementia bilateral pyramidal signs and severe disability. Diffuse ischemic white matter disease is present and lacunes are evident as “holes” with the intensity of cerebrospinal fluid. (d) FLAIR image of a male patient with dementia and severe cognitive and motor disability. The diffuse leukoencephalopathy affects significantly both frontal lobes, including the anterior thalamic radiation and, partly, the fornice minor. White matter involvement in posterior locations is also present



**Figure 2:** Mechanisms of vascular cognitive impairment in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (based on Refs 22–34). Mutations of *NOTCH3* cause structural and functional disorder of arteriolar vessel wall, resulting in partial ischemia (edema) or complete (lacunar) infarction. Gradual increase of vascular lesions leads to cognitive impairment. Classical cardiovascular risk factors, if present, enhance the above process and increase the risk of disability. WM: White matter, BG: Basal ganglia, ICH: Intracranial hemorrhage

Arteriolar pathology, WM pathology, and axonal abnormalities, although widespread, may severely affect the WM of the frontal lobe [Figure 1d], affecting frontosubcortical and/or frontocortical networks.<sup>[31]</sup> Based on neuroimaging, five areas show the maximum influence in processing speed: lacunar load in the left anterior thalamic radiation and left cingulum and WMH in the left forceps minor, left parahippocampal WM and left corticospinal tract.<sup>[33]</sup> Since these areas are related with important frontosubcortical neuronal circuits (especially, dorsolateral prefrontal and cingulate circuits), it is not surprising that the

above lesions in these areas roughly explain one-third of the total variance in processing speed.<sup>[33]</sup> In addition, lacunar lesion load in anterior thalamic radiation is associated with the reduced thickness of medial frontal cortex (which, in turn, is associated with deficits in processing speed) and reduced thickness of right occipitotemporal cortex, the latter (lingual, fusiform, and parahippocampal cortices) also being associated with abnormal processing speed.<sup>[34]</sup> It has been suggested that, within the WM of the frontal lobe, the superior longitudinal fasciculus may be affected even earlier than the cingulum bundle.<sup>[31]</sup> This may result in a frontal

disconnection syndrome that gradually involves the parietal and temporal lobes.

## CAUSES OF CLINICAL VARIABILITY AND CORRELATES OF ISCHEMIC LESION LOAD

Although it is generally accepted that most of the different *NOTCH3* mutations have little effect in phenotypic variability, a minority of mutations affecting the *NOTCH3* ligand binding domain (EGFR10-11) may be associated with the decreased load of WMH and better cognitive function.<sup>[35]</sup> Multiple variants of other genes, each with small effect, may also influence the load of WM lesions, partly explaining some of the phenotypic variations among patients.<sup>[36]</sup> Sex affects clinical presentation. In males, migraine onset occurs 6 years later, and the first lacunar stroke occurs 7 years earlier than in females.<sup>[13]</sup> Unfortunately, the above factors are non-modifiable.

It is long known that, in the appropriate clinical setting, the absence of cardiovascular risk factors increases the diagnostic probability of CADASIL. This should not be interpreted that patients with CADASIL have no cardiovascular risk factors. The presence of hypertension, diabetes, dyslipidemia, and thrombophilia has been reported in many patients and should not preclude the diagnosis of CADASIL.<sup>[37,38]</sup> If present, such factors may modify the clinical features.<sup>[38]</sup> Hypertension independently increases the risk for stroke<sup>[38-40]</sup> and disability due to dementia.<sup>[41]</sup> Smoking also increases the risk of stroke<sup>[38,42]</sup> and dementia.<sup>[42]</sup> Hypertension<sup>[40]</sup> and diabetes with increased HbA1c may increase the risk for microbleeds.<sup>[40,43]</sup>

The above observations lead to suggestions for controlling these risk factors, especially hypertension and smoking, in an attempt to delay lacunar stroke, disease progress, and functional disability.<sup>[38,42]</sup> Such a disease modifying approach is being followed during the last decade and is currently recommended.<sup>[44]</sup>

Recently, it has been shown that the epidemiology of CADASIL is changing.<sup>[18]</sup> The median age of first stroke is higher than previously estimated, especially in men. Men diagnosed after 2006 experiences their first stroke at a median age of 56 and 10 years later than those diagnosed before 2006.<sup>[18]</sup> Furthermore, in patients over 58 years old, 38% remain independent,<sup>[18]</sup> as compared to 14% of patients over 60 years, before 2000.<sup>[45]</sup> Such a favorable change in the natural history of CADASIL may be partly due to a better knowledge of the disorder, resulting in increased suspicion, better diagnosis, and identification of more “benign” cases. However, control of risk factors may have also contributed. Indeed, in two monozygotic twins with CADASIL, the one

that followed preventive measures such as physical activity and early control of dyslipidemia with statin showed less severe imaging findings and experienced his first stroke 14 years later than the one which was smoker and delayed controlling dyslipidemia.<sup>[46]</sup>

## CONCLUSIONS

Despite being a genetic disease, the phenotype of CADASIL may be worsened by classical cardiovascular risk factors. Control of such risk factors may delay disease progression and disability and, currently, should be strongly recommended.

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