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CADASIL: new advances in basic science and clinical perspectives

Elisa A. Ferrante, Cornelia D. Cudrici, Manfred Boehm

National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland, USA

Abstract

Purpose of review—Recent advances in genetic evaluation improved the identification of several variants in the *NOTCH3* gene causing Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL). Despite improved diagnosis, the disease mechanism remains an elusive target and an increasing number of scientific/clinical groups are investigating CADASIL to better understand it. The purpose of this review is to summarize the current knowledge in CADASIL.

Recent findings—CADASIL is a genotypically and phenotypically diverse condition involving multiple molecular systems affecting small blood vessels. Cerebral white matter changes observed by MRI are a key CADASIL characteristic in young adult patients often before severe symptoms and trigger *NOTCH3* genetic testing. *NOTCH3* mutation locations are highly variable, correlate to disease severity and consistently affect the cysteine balance within extracellular Notch3. Granular osmiophilic material deposits around blood vessels are also a unique CADASIL feature and appear to have a role in sequestering proteins that are essential for blood vessel homeostasis. As potential biomarkers and therapeutic targets are being actively investigated, neurofilament light chain can be detected in patient serum and may be a promising circulating biomarker.

Summary—CADASIL is a complex, devastating disease with unknown mechanism and no treatment options. As we increase our understanding of CADASIL, translational research bridging basic science and clinical findings needs to drive biomarker and therapeutic target discovery.

Keywords

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; dementia; Notch3; small vessel disease; stroke

INTRODUCTION

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a monogenic hereditary small vessel disease (SVD) and currently considered the most common genetic cause of stroke and dementia in adults. It

Correspondence to Elisa A. Ferrante, PhD, National Institutes of Health, 10 Center Drive, Bldg 10-CRC 5E-3256, Bethesda, MD 20892, USA. Tel: +1 301 402 3577; elisa.ferrante@nih.gov.

Conflicts of interest

There are no conflicts of interest.

is caused by mutations, commonly heterozygous missense (95%), in the *NOTCH3* gene on Chromosome 19p13.2-p13.1 that are inherited in an autosomal dominant pattern. The disease is of slow onset, with initial clinical manifestations in the third and fourth decade of life. Predominant clinical features include migraines with aura, recurrent strokes of ischemic nature, transient ischemic attacks, progressive white matter degeneration, memory loss, debilitating dementia and disability and multiple psychiatric symptoms [1–3].

The path to diagnosis for most CADASIL patients is complex and often lengthy because of lack of awareness about the disease in the general clinical community. Adding complexity is the symptomatic heterogeneity of the disease, frequently even between family members that carry the same mutation but develop different clinical features. Diagnosis generally occurs through a combination of family history of migraines/strokes/dementia, MRI findings of white matter changes characteristic of CADASIL and *NOTCH3* genetic testing. Prior to the availability of a genetic test and sometimes still used for diagnostic confirmation, electron microscopy of skin biopsies from CADASIL patients were the gold standard for the identification of deposits near blood vessels called granular osmiophilic material (GOM), which are unique to CADASIL and, the composition and function of which has not yet been fully characterized.

Notch3 is a transmembrane receptor expressed by vascular smooth muscle cells (VSMCs) and pericytes in vasculature throughout the body. The majority of CADASIL *NOTCH3* mutations affect one of the 34 extracellular domain epidermal growth factor repeats (EGFr) of the Notch3 protein by either adding or removing a cysteine residue, resulting in accumulation within the extracellular space/within GOMs and, ultimately, leading to degradation of the VSMC layer in blood vessels. Through this process, subjects with CADASIL become susceptible to strokes but the exact mechanism has not yet been elucidated. The disease is progressive and fatal. There are currently no treatment options for patients with CADASIL as a therapeutic target has not been identified. This review focuses on recent research and clinical advances that increase our understanding of CADASIL as well as recent efforts to identify biomarkers for the disease.

BASIC AND CLINICAL ADVANCES IN CEREBRAL AUTOSOMAL DOMINANT ARTERIOPATHY WITH SUBCORTICAL INFARCTS AND LEUKOENCEPHALOPATHY

As more CADASIL patients are identified because of advances in genetic testing and whole exome/genome sequencing becomes more available, increasing efforts are being made to better understand the pathophysiology of the disease and to increase awareness throughout the clinical community. As of 2014, there were more than 230 unique CADASIL mutations already reported [4], a number that has likely increased in the last several years, and it is estimated that two to five people in 100 000 carry a CADASIL mutation, although this number varies depending on population nationality [5,6■]. Approximately 98% of these mutations occur within exons 2–23 of *NOTCH3* and result in a gain or loss of a cysteine residue within one of the 34 EGF repeats of the Notch3 Receptor [7]. Even though mutations have been reported throughout all 33 *NOTCH3* exons, high clustering is

documented for exons 1 through 6, particularly within exons 3–4 [8]. This high genotypic variability is likely responsible, at least partially, for the high phenotypic variability of the disease, although progress is still being made to better characterize known mutations. Most recently, Rutten *et al.* [9] assessed a cohort of 664 CADASIL patients with pathogenic variants in EGFr domains 1 through 34 and found that individuals with EGFr 1–6 variants have an earlier stroke onset, higher brain lesion load and lower survival rates than those with variants in EGFr 7–34 that had a much milder version of the disease. This points to the location of the mutation potentially being critical for how CADASIL develops and progresses, although an effect might also be present through modifier genes, environmental effects or other concomitant risk factors to explain the phenotypic variability observed in CADASIL subjects, even when carrying the same mutation.

Upon ligand binding, the Notch3 receptor is activated by proteolytic cleavages that lead to release of the extracellular domain (Notch3^{ECD} or N3ECD) into the interstitial space between cells. This also frees the intracellular domain (Notch3^{ICD} or N3ICD), which translocates to the nucleus to regulate gene expression in a process that helps maintain VSMC homeostasis [10,11]. In CADASIL, mutant Notch3^{ECD} accumulates in the extracellular space and eventually leads to VSMC degeneration in a mechanism that is poorly understood. However, work by several investigators suggests that Notch3^{ECD} has binding affinity for a variety of molecules in a way that sequesters them from physiological pathway signaling to cause pathological dysfunction in blood vessel homeostasis [12].

In support of this hypothesis, GOMs have been identified near the surface of VSMCs and pericytes of brain, skeletal muscle, retina, kidney, pericardium and skin of CADASIL patients [13]. It remains unclear whether GOMs are merely accumulated deposits that result from smooth muscle cell degradation or if they also impart toxicity to the cells further causing vessel degeneration by sequestering molecules that are important for normal physiological regulation. It has been established that extracellular Notch3, tissue inhibitor of metalloproteinases 3 (TIMP-3), vitronectin (VTN) and latent TGF- β binding protein 1 (LTBP-1) co-localize within these deposits by immunohistochemistry and mass spectroscopy of CADASIL brains and arteries obtained by microvessel isolation [12,14,15]. TIMP-3, VTN and TGF- β , regulated by LTBP-1, are proteins that have important roles in blood vessel formation and maintenance. Using a combination of laser microdissection, liquid chromatography-tandem spectrometry and immunohistochemistry, Nagatoshi *et al.* [16] recently found co-localization of serum amyloid P component (SAP) with Notch3 in GOM-enriched blood vessels as well as annexin 2 and periostin within GOMs. SAP has been implicated in cognitive diseases such as Alzheimer's as having a role in the stabilization of amyloid plaques and may have a similar role in the formation and stabilization of GOMs in CADASIL [16,17]. All combined, these findings point to a possibility that a variety of molecules having key roles in blood vessel homeostasis become sequestered by Notch3^{ECD} into GOMs, leading to a dysregulation of critical pathways.

In an effort to better understand the process leading to vessel degradation in CADASIL, several groups are focusing on how the disease affects blood vessels on a molecular level. In a recent study, Dziewulska *et al.* [18] analyzed blood vessels isolated from CADASIL brain, skeletal muscle and skin tissue with immunohistochemistry and electron microscopy. They

found that VSMCs within the tissues often had nuclei with very condensed chromatin, in irregular shapes and sizes and that were also multinucleated. In combination with positive staining for proliferative markers, this group suggested that there may be a mitotic instability in CADASIL VSMCs because of poor regulation by mutant Notch3 that potentially leads to degeneration. Also focusing on VSMC, Hanemaaijer *et al.* [19] investigated whether Notch3^{ECD} accumulation is a result of impaired lysosomal autophagy in CADASIL patient derived cerebral VSMCs. Confocal imaging with labeling for Notch3 and lysosomal markers pointed to a defect in the autophagosome-lysosome fusion step, resulting in reduced clearance of Notch3^{ECD} by CADASIL VSMCs as compared with healthy controls.

Endothelial dysfunction also appears to play a role in CADASIL as plasma levels of endothelial damage/repair markers such as vonWillebrand factor, endothelial progenitor cells and circulating progenitor cells appear to be affected in CADASIL. While vonWillebrand factor levels were significantly elevated in patient plasma samples, endothelial progenitor cells and circulating progenitor cells levels were lower but the later appeared to correlate with worsened outcomes as measured by neuropsychometric testing and MRI [20]. These results point to impaired endothelial homeostasis playing a role in the CADASIL pathophysiology.

Also implicating the gliovascular unit, astrocyte damage has been observed within the white matter of CADASIL patients at different stages of the disease and CADASIL brain tissue had a higher percentage of astrogliopathy and astrocyte turnover with evidence of a dysregulation in autophagy particularly within the anterior temporal lobe [21]. Using a combination of electroencephalograms and arterial spin labeling MRI, Huneau *et al.* [22] focused on the coupling of neural activity and hemodynamic changes (neurovascular coupling or NVC) in response to visual and motor stimuli in CADASIL patients as compared with healthy controls. They found that, even at early stages of the disease, there was a significant difference in the dynamic of blood flow responses in CADASIL patients but not in neural activity, hypothesizing that this may be because of an early dysfunction in the cerebral vasculature. These results have been since confirmed in an additional cohort of 21 CADASIL patients by using functional MRI while performing go/No-go tasks and implicate an observed reduction of blood oxygen levels in several areas of the brain, possibly because of impaired vasoreactivity in CADASIL [23].

Biomarker discovery is particularly important in CADASIL as a tool to diagnose, track progression and measure therapeutic effectiveness in CADASIL. In the recent years, neurofilament light chain (NfL) has emerged as a promising circulating biomarker. NfL is a structural protein in the axons of neurons and appears in blood and cerebrospinal fluid upon neuronal damage in diseases such as multiple sclerosis and Alzheimer's [24,25]. In 2018, Tiedt *et al.* [26] investigated serum NfL as a marker of ischemic stroke in a cohort of patients recruited within 24 h of ischemic stroke symptoms and followed over a period of 6 months. They found that serum NfL levels were not only elevated and peaked immediately after ischemic stroke but that they remained elevated at 3 and 6 months after ischemic stroke. Additionally, NfL levels correlated with infarct volumes as well as recurrent ischemic lesions and secondary neurodegeneration on MRI at 6 months and they independently predicted clinical outcomes at 3 months post-ischemic stroke. In a comparison study

between CADASIL individuals, sporadic SVD patients and healthy controls, serum NfL was confirmed to correlate with SVD MRI markers for both patient groups but also with clinical neurological features such as impaired processing speed performance, focal neurological deficits and disability for the CADASIL patient cohort only [27]. Gravesteijn *et al.* [28] obtained similar results with serum NfL and found a strong correlation not only in measured MRI neuroimaging but also with cognitive function and long-term disease outcomes. These studies show a strong association between serum NfL and several clinical characteristics of CADASIL and is a good marker in patients with ischemic stroke during the acute phase but also several months after ischemic stroke. However, serum NfL levels can become elevated in aging as well as any situations leading to axonal damage because of other diseases, lacking specificity for CADASIL and lead to confounding conclusions. Further studies are needed to completely characterize how NfL serum levels can be used in combination with other clinical measures and biomarkers of the disease rather than on its own.

One of the most distinctive characteristics of CADASIL are the white matter hyperintensities (WMH) in the brain tissue that can be visualized by MRI and are often present as an early sign of the disease before a patient, usually in their 30s, develops many severe symptoms. However, CADASIL patients are often misdiagnosed as having multiple sclerosis or other types of SVDs despite similar but unique neuroimaging differences. Characteristics of CADASIL are symmetry, morphology and location of WMH with involvement of the anterior temporal lobe, the external capsule and the superior frontal gyrus [6]. Figure 1 shows the typical CADASIL MRI findings for an acute ischemic event and the longer-term white matter changes. Other MRI features often observed in CADASIL are incident lacunes, cerebral microbleeds, enlarged perivascular space and brain atrophy [5], although these features can be observed in a variety of other SVDs. In an MRI neuroimaging comparison between CADASIL and myotonic dystrophy type 1 (DM1) patients, which are sometimes confused with one another, the CADASIL cohort appeared to have more involvement of the temporal lobes, external capsule and basal ganglia as well as a significantly higher incidence of microbleeds than DM1 [29]. Similarly, in an effort to differentiate MS from CADASIL patients, Vinciguerra *et al.* [30] have shown that a novel automated MRI marker, peak width skeletonized mean diffusivity (PSMD), correlates with the white matter lesion load in both conditions but is higher in MS than in CADASIL.

Aiming to determine clinical correlations with conventional MRI markers, a study following 160 CADASIL individuals with confirmed genetic diagnosis over 3 years, established that brain atrophy and the number of incident lacunes independently and sensitively correlated with clinical changes (strokes, dementia, disability) in the patient cohort and can be used as markers of disease progression on conventional MRI [31]. The extent of WMH changes in patients, however, has consistently been found to not have strong correlations with disease severity in CADASIL. Hypothesizing that regional rather global WMH changes in CADASIL contribute to differences clinical outcomes, Duchesnay *et al.* [32] divided the brain in different spatial sections and found that higher WMH associated with the temporal lobes and frontal gyri correlated with a milder version of the disease as compared with WMH in the pyramidal tracts in 301 CADASIL patients.

CONCLUSION

While CADASIL has been extensively studied over the last several decades, our understanding increases as research and clinical techniques evolve. With whole exome and genome testing, we can now sequence entire families and identify individuals that are affected by the disease before development of symptoms. With proteomics, we can investigate how molecules and signaling pathways are dysregulated as a result of CADASIL, but we can also see how they interact to modulate its pathophysiology. Genomics and proteomics have opened the door to the critical and much needed possibilities of identifying biomarkers and potential therapeutic targets for this disease. Yet, this remains a complex condition, the mechanism of which still has to be elucidated.

It has become clear that this is a genotypically and phenotypically diverse disorder as more case studies appear in the scientific literature. Notch signaling is a highly conserved pathway that regulates blood vessel formation during development and vessel homeostasis in adulthood [33]. In CADASIL, *NOTCH3* mutations and their effect on the Notch3 receptor appear to set off a cascade of imbalances with a profound effect at multiple levels as extracellular accumulation of Notch3^{ECD} can sequester other molecules from their normal physiological functions. CADASIL vessel disorder, shown in Fig. 2, similarly involves multiple molecular systems on the endothelial, smooth muscle and neural cell levels related to maintenance of cellular health, delivery of important nutrients and vasoreactivity. Advances in MRI neuroimaging techniques and postprocessing are also enabling us to better discern regional differences in white matter changes within areas of the brain making MRI a better marker to track disease progression.

Although quick progress has been made and as we move forward, translational research combining basic science advances and clinical findings as well as long-term clinical studies enrolling large cohorts of CADASIL patients at different disease stages will be critical to help fully elucidate its pathophysiology and have the power to identify appropriate biomarkers and therapeutic agent options for patients.

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- of special interest
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KEY POINTS

- CADASIL is the most common genetic cause of stroke and dementia in adults but a genotypically and phenotypically diverse disease.
- The disease mechanism has not been elucidated but significant progress has been made to better understand the genotype and phenotype of the disease, including mutation type/location, variant effect on protein function, protein accumulation into GOMs and vascular dysfunction extending to VSMC, endothelium and the gliovascular unit.
- Research on biomarkers is ongoing and promising with newly identified NfL.
- MRI advances allow us to discern the effect of the location within the brain of white matter changes and correlate to disease severity.
- Translational research is essential for the identification of treatment options still not identified and much needed for patients with CADASIL.

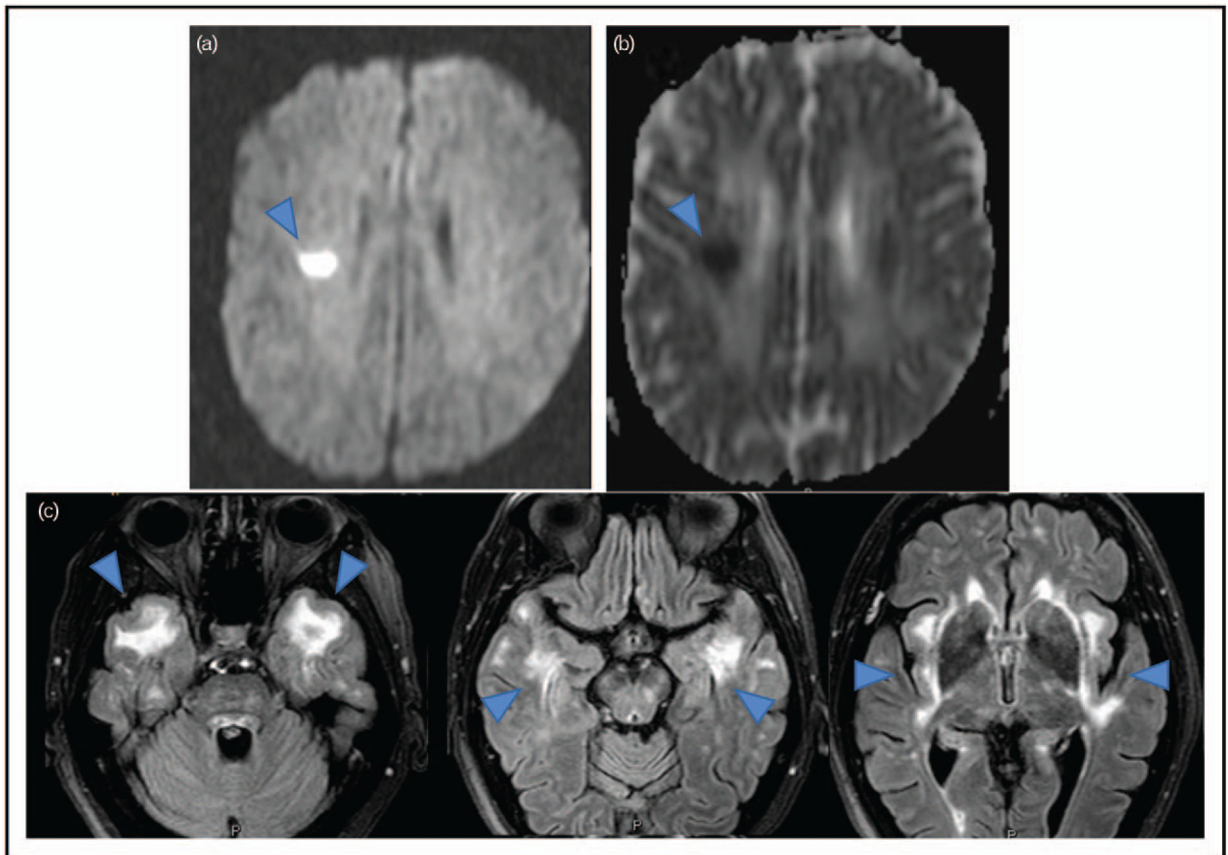


FIGURE 1. Typical Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) MRI findings: panels a and b show typical acute ischemic changes in a CADASIL patient after stroke. Panel c consists of three cross-sectional MRI images to show typical white matter changes in a CADASIL patient. Blue arrows point to the typical changes.

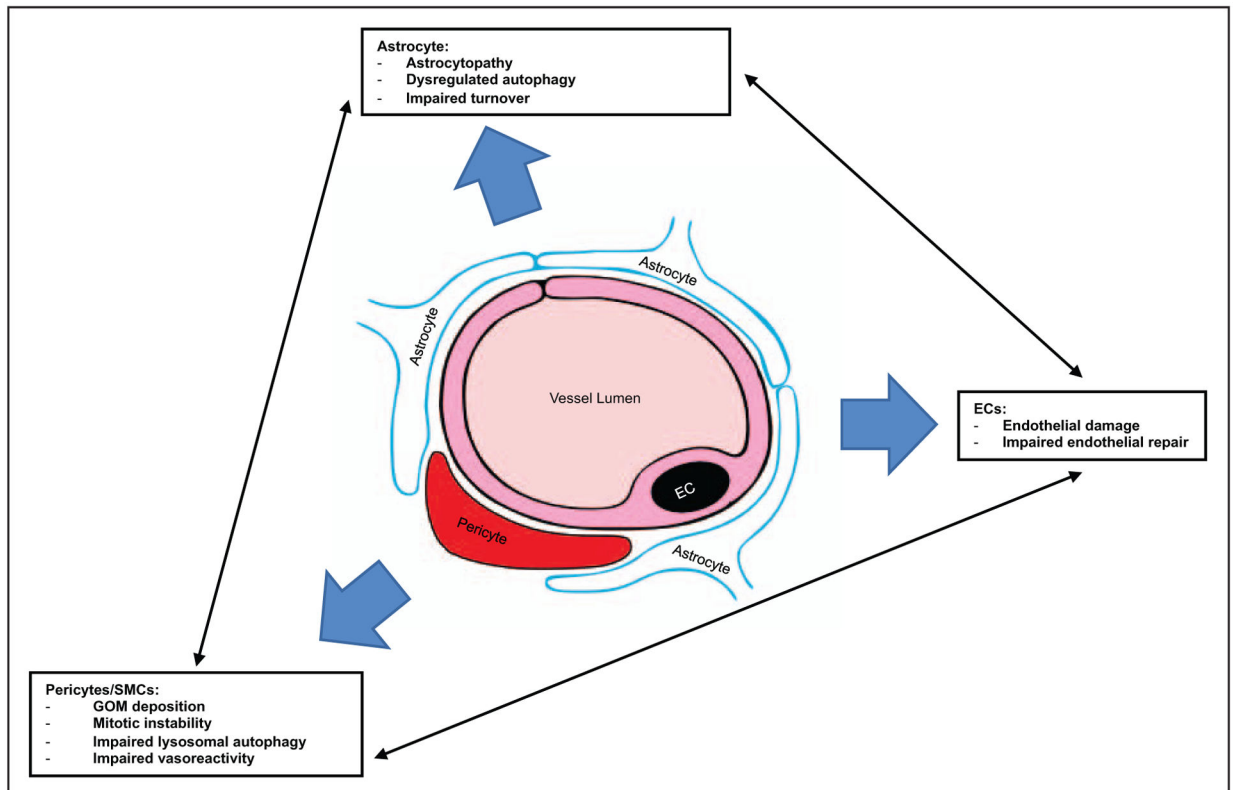


FIGURE 2. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) vessel disorder: schematic of a cerebral capillary shows the effects on multiple molecular systems on the endothelial, pericyte/smooth muscle and neural cell levels because of CADASIL.