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Clinical and research applications of magnetic resonance imaging in the study of CADASIL

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Abstract

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is an inherited small vessel disease that leads to early cerebrovascular events and functional disability. It is the most common single-gene disorder leading to stroke. Magnetic resonance imaging (MRI) is a central component of the diagnosis and monitoring of CADASIL. Here we provide a descriptive review of the literature on three important aspects pertaining to the use of MRI in CADASIL. First, we review past research exploring MRI markers for this disease. Secondly, we describe results from studies investigating associations between neuroimaging abnormalities and neuropathology in CADASIL. Finally, we discuss previous findings relating MRI markers to clinical symptoms. This review thus provides a summary of the current state of knowledge regarding the use of MRI in CADASIL as well as suggestions for future research.

Keywords

CADASIL; Magnetic Resonance Imaging; Neuroimaging; Diagnosis; Biomarkers

Introduction

Cerebral small vessel disease (SVD) is a broad term used to describe consequences of pathological processes affecting small vessels of the brain [57]. SVD is a significant underlying cause of ischemic strokes and intracerebral hemorrhage. It is also major contributor to dementia, mood disorders, gait disturbances and disability [49]. SVD is found in high frequency in the elderly population and is usually sporadic in nature. However, inherited forms of SVD exist, including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

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Declarations of interest

None.

CADASIL is a unique type of SVD caused by mutations in the NOTCH3 gene [29]. This disorder is characterized by the occurrence of subcortical ischemic events, such as transient ischemic attacks (TIA) and strokes, at early age and often in the absence of typical risk factors for cerebrovascular disease [6, 28]. It is recognized as the most prevalent monogenic cause of stroke and vascular dementia. The pathological hallmarks of CADASIL include the degeneration of vascular smooth muscle cells and pericytes as well as the presence of granular osmiophilic material (GOM) within vessels [6, 28]. Macroscopic examinations of affected brain tissues have revealed the presence of diffuse myelin rarefaction, lacunes mostly affecting subcortical areas, and cortical apoptosis [6, 28]. CADASIL presents with various neurological and psychiatric symptoms including migraines with aura, cognitive impairment, gait abnormality and mood disturbance [6]. Although the clinical presentation of CADASIL varies considerably between affected individuals, the mean age of onset of clinical symptoms is around 35 to 40 years [14, 17].

Genetic testing is the gold standard for the clinical diagnosis of CADASIL. Additionally, the clinical investigation generally involves the combined examination of clinical, metabolic and radiological characteristics, together with a review of family history [14]. Magnetic Resonance Imaging (MRI) is a central component of the diagnosis of CADASIL and is routinely used to document SVD in patients [66]. To provide an overview of the utility of MRI in CADASIL, this review article summarizes the past scientific literature on three main aspects relevant to this topic: 1) the use of MRI in the diagnosis of CADASIL; 2) the associations between MRI markers and pathological processes in CADASIL and 3) the associations between MRI markers and clinical manifestations of CADASIL.

1) The use of MRI in the diagnosis of CADASIL

The core MRI abnormalities observed in CADASIL have been described in several reports and include the presence of white matter hyperintensities (WMH), subcortical infarcts and cerebral microbleeds (CM) [66]. The radiological presentation of CADASIL varies considerably between affected individuals [14, 17]. Likely contributing to this variability, growing evidence suggests that the clinical and radiological presentations in CADASIL are dependent on the genotype [26, 35, 44–46, 61, 62]. While MRI abnormalities appear at a variable age in CADASIL, they can be observed in the vast majority of patients aged above 35 years [6]. Age is an important factor in predicting the extent of brain alterations in patients and is positively correlated with the prevalence and severity of changes observed on MRI [7, 19]. It has further been estimated that MRI signal irregularities in CADASIL can be detected 10–15 years prior to the onset of clinical manifestations [6]. MRI signal abnormalities in asymptomatic individuals are less severe and less diffuse than in symptomatic patients, suggesting an association between the severity of these abnormalities and increasing symptomatology [6]. T2-weighted images, a type of sequence often used to detect the presence of pathology and ischemic events, appears to be more sensitive than T1-weighted images to early manifestations of CADASIL. Accordingly, the earliest reported MRI changes in CADASIL consist in areas of increased signal on T2-weighted or fluid-attenuated inversion recovery (FLAIR) images, frequently in the periventricular white matter [6]. In an attempt to characterize the neuroimaging characteristics of CADASIL, studies have contrasted MRI findings from NOTCH3 mutation carriers and age-matched non-

carriers [15, 25, 27, 38, 43, 51, 58, 65, 70, 76]. In CADASIL patients, these studies have reported the presence of WMH predominantly in the periventricular region, anterior temporal pole, external capsule as well as frontal and parietal areas. The pattern of lesions is often described as symmetrical. White matter in the posterior temporal and occipital lobes, the basal ganglia, the thalamus, the pons and the internal capsule is considerably less affected. Arcuate fibers, also known as cortical association or U-shape fibers, are generally spared. Involvement of the corpus callosum, which is rare in sporadic forms of SVD, has been described in CADASIL individuals, but often in a small proportion of cases. A higher frequency of dilated perivascular space (PVS), measured on T2 images using pre-established criteria, has also been highlighted in this population [13, 70]. The vast majority of structural MRI studies performed CADASIL patients have exposed the presence of diffuse and regional brain atrophy [31, 34, 60, 67]. In contrast, a previous study on members of a single family carrying a CADASIL mutation concluded that atrophy was rather rare [12]. This discrepant finding can be explained by methodological limitations, including the use of a small number of patients with a genetically confirmed diagnosis of CADASIL and a subjective assessment of brain atrophy. Diffusion tensor imaging (DTI), a MRI technique providing an estimate of the microstructural integrity of cerebral white matter, is of great potential relevance to the field of CADSIL. Using DTI, studies have described important diffusion changes in the white matter of CADASIL patients [8, 47, 55]. Significant differences in histograms representing the whole-brain trace of the diffusion have been observed between CADASIL patients and age-matched controls, pointing to the presence of widespread microstructural tissue damage in this disease [48]. The microstructural integrity of the basal nuclei and the thalamus appears to be particularly affected [47, 55]. To aid the differential diagnosis, an important focus has been given to the description of specific MRI markers allowing to distinguish CADASIL from other conditions presenting similar clinical and/or radiological features (e.g. sporadic SVD or multiple sclerosis). Studies comparing genetically confirmed CADASIL patients to non-carriers presenting with CADASIL-like presentations reveal largely similar imaging characteristics between groups [1–3, 27, 51, 58, 68]. Previous evidence suggests that anterior temporal lobe involvement on MR images is highly specific and allows for distinguishing CADASIL from other conditions [1, 2, 10, 27, 43, 52, 54, 64, 68–70, 76]. For example, O'Sullivan et al. (2001) reported a sensitivity of 90% and specificity of 100% of anterior temporal WMH to differentiate CADASIL from sporadic forms of leukoaraiosis [54]. A different study highlighted a sensitivity of 89% and specificity of 86% for "moderate" or "severe" anterior temporal pole WMH in the diagnosis of CADASIL [43]. These results are in agreement with a study from Van den Boom et al. (2003) demonstrating that the presence of WMH in the anterior temporal lobe was the only MRI feature consistently seen in the youngest CADASIL patients (aged 20–30 years) [69]. The presence of lesions in the external capsule has also been proposed as a potential diagnostic feature of CADASIL [1, 3, 9, 10, 43, 52, 54, 58, 64, 65, 76], although it has been reported in a lower proportion of patients and has been associated with a lower diagnostic specificity [69]. Despite the identification of MRI differences between CADASIL patients and non-carriers, these differences are overall limited and not consistently found across studies. MRI features described as specific to CADASIL, including temporal pole WMH, have been observed in a considerable proportion of subjects without NOTCH3 mutations, limiting their specificity [51, 58, 63]. Previous findings also demonstrate that these features

may be absent at early stages of the disease [64, 67]. Adding to the complexity of establishing specific MRI markers for CADASIL, several studies indicate that the MRI presentation of patients may vary depending on the genotype. For example, anterior temporal involvement appears to be less common in subjects with cysteine-sparing NOTCH3 mutations, although the role of cysteine-sparing mutations in the pathogenesis of CADASIL remains a matter of debate [26, 35, 44–46, 62]. As such, at the present time, CADASIL cannot be reliably differentiated from other forms of SVD on the sole basis of MRI. While the involvement of the anterior temporal pole and external capsule may hint the presence of CADASIL, these features are not sufficient to confirm its diagnosis. This emphasizes the importance of considering additional information in the diagnostic process.

2) Associations between MRI markers and pathological processes in CADASIL

Studies investigating relationships between neuropathology and MRI markers provide valuable information on pathological processes underlying MRI signal abnormalities. As such, they allow a more valid and comprehensive interpretation of MRI findings. Only a few studies have systematically investigated these relationships in CADASIL patients. Dichgans and colleagues (2002) attempted to link in-vivo MRI to autopsy findings [19]. MRI scans were acquired in 16 CADASIL patients, while postmortem pathological examinations were performed on seven different patients. Because none of the autopsied cases had available MRI data, this study was mostly observational and relationships between imaging and pathological variables were not directly assessed. Autopsy findings revealed lacunes and diffuse white matter changes resulting from demyelination, axonal loss, gliosis, and extracellular space enlargement. The authors further described focal accumulations of hemosiderin-containing macrophages in six of the seven autopsied brains. They hypothesized that homogenous rounded foci of signal loss apparent on T2*-weighted images likely corresponded to hemosiderin deposits after the occurrence of CM, although other causes could not be excluded due to methodological limitations. Viswanathan et al. (2006) studied neuronal apoptosis in four CADASIL patients who died from complication of the disease and had an MRI performed the year prior to death [72]. Apoptotic neurons were observed in all cases at autopsy. Neuronal apoptosis was not found within or close to cortical microinfarcts. Subsequent analyses showed that the number of apoptotic neurons in layers 3 and 5 was associated with the extent of subcortical WMH and axonal damage. In two patients with available quantitative MRI data, the authors observed that the patient with more severe apoptosis also presented greater volumes of WMH and lacunes. The severity of the apoptosis was related to normalized brain volumes, suggesting that it likely contributes to cerebral atrophy in CADASIL. In a single case study, Jouvent et al. (2011) studied a 53 year-old CADASIL patient using both postmortem neuropathological examination and high-resolution 7-T MRI (HR-MRI) [32]. The results of this combined investigation showed that hypointensities of a linear shape with regular edges, of a few hundred micrometers in diameter, crossing the cortical mantle on consecutive slices on T2* images, corresponded to microvessels. The authors further identified two subtypes of intracortical infarcts, as confirmed by histological examination. On T2* images, these infarcts were observed as small hypointense foci of irregular shape and of signal intensity similar to that of white matter. Some of these lesions were circular and did not reach the edges of the cortical mantle, whereas others were pyramidal with their bases resting on the gray/white matter

border. Both types of lesions were present across all cerebral lobes. The authors argued that the use of high-resolution MRI could contribute to the detection of intracortical infarcts, which can be difficult based solely on pathological examination or low-resolution MRI. Iron deposition has been proposed as a biomarker for various neuropathological processes, including cerebral small vessel disease. For this reason, Liem et al. (2012) investigated the presence of iron deposition in relation to small vessel disease in three CADASIL patients using combined high-resolution 7-T MRI and histopathological examination of postmortem brains [39]. Histochemistry revealed the presence of iron deposition in the caudate nucleus, putamen and, to a lesser degree, in the globus pallidus. The observed pattern of iron accumulation matched the pattern of signal loss on postmortem MRI. The authors conclude that MRI signal hypointensity is linked to progressive iron accumulation. Yamamoto et al. (2009) simulated MR images by juxtaposing digital pictures of serial in-vitro slices of the temporal pole from a single CADASIL patient [74]. They proposed that MRI temporal pole hyperintensities in CADASIL patients reflect enlarged PVS, together with myelin depletion and axonal damage. Using indirect measures, other studies have reported links between pathology and MRI signal abnormalities in CADASIL. For examples, in both CADASIL and sporadic small-vessel disease patients, Duering (2018) demonstrated significant associations between serum neurofilament light chain (a blood marker for axonal damage) and measures of brain volume, WMH, lacunes and CM [22]. Studies have also relied on high-resolution 7-T MR technologies to estimate underlying pathological processes in CADASIL. Liem et al. (2010) used 7-T MR angiography to characterize the luminal diameters of lenticulostriate arteries in-vivo [41]. Luminal diameters were unaffected in CADASIL patients. The authors found no associations between luminal diameters and lacunes in the basal ganglia, suggesting that these lesions were not caused by a narrowing of lenticulostriate arteries. De Guio et al. (2014) measured the white matter venous density in CADASIL patients using HR 7-T MRI [16]. They showed a reduction in the density of visible venous vasculature in both normal appearing white matter and WMH. Fang et al. (2017) examined changes in retinal vessel using Enhanced Depth Imaging Optical Coherence Tomography in relation to 7-T MRI markers [24]. They found moderate, but significant, correlations between the presence of CM or small infarcts and measures of retinal vessels integrity. Taken together, these results support the validity of MRI investigation in the detection of pathological alterations in CADASIL patients. Future systematic studies combining MRI and examinations of post-mortem tissues to characterize pathological mechanisms underlying MRI signal abnormalities in CADASIL patients could promote the optimization of MRI sequences to detect and classify brain lesions in-vivo.

3) The associations between MRI markers and clinical manifestations of CADASIL

To identify and validate MRI markers for CADASIL, the characterization of associations between these markers and clinical symptoms or disease progression is crucial. For this purpose, a large number of studies have explored clinical correlates of MRI abnormalities in CADASIL. The overall lesion load observed on T1-weighted MR images has been associated with the degree of global disability, often quantified using the modified Rankin Scale [4], and with performance on different cognitive domains [18, 76]. Conversely, O'Sullivan (2004) failed to find significant correlations between the total lesion load on T2-weighted images and global cognition, suggesting that the examination of specific types of

lesions might be of greater interest [55]. Accordingly, numerous studies have instead focused on the associations with specific MRI markers of CADASIL. As described in the previous section, the presence of WMH is a common and early MRI feature of CADASIL. Studies investigating relationships between WMH and clinical symptoms have produced mixed results. While the severity of WMH has been linked to the presence and severity of depressive symptomatology in CADASIL patients [59, 64], most studies highlight a lack of independent influence of WMH on cognitive performance and disability [36, 71, 73]. Congruently, in a 7-year follow-up study, changes in WMH volume over time was not associated with decline in global cognition [37]. A potential factor contributing to the lack of association between WMH and cognitive or functional outcomes consists in the great variability in the spatial distribution of WMH across patients. A recent study from Duchesnay (2018) highlighted distinct regional patterns of WMH, each associated with different clinical outcomes [20]. According to the authors, considering regional WMH burden, rather than adopting a whole-brain approach, allowed a superior prediction of clinical outcomes. As such, previous studies measuring the global WMH burden might have underestimated its clinical relevance. Cerebral microbleeds is another central neuroimaging features of CADASIL. Studies examining relationships between CM and clinical symptoms have also reached mixed findings. Several studies have outlined significant associations between the number of CM and indices of disease progression, including advancing age [56], greater global disability [11, 72, 73], lower score on the mini-mental state examination (MMSE) [72] and poorer performance in executive function [5]. The increase in the number of CM over time has further been linked with a decrease in global cognitive functioning, memory and executive function [37]. In opposition, other studies have failed to find an independent influence of CM on cognition [56, 73] or depressive symptoms [59]. Potentially contributing to discrepancies in findings across studies, it has been proposed that CM may not have a direct effect on disability in CADASIL but rather represent a consequence of the severity of other lesions [72]. In contrast with WMH or CM, a larger volume of lacunes has been consistently linked with poorer clinical outcomes or cognitive performances in CADASIL patients [11, 36, 40, 50, 53, 59, 71, 73]. In a longitudinal study, the baseline volume of lacunes was found to predict subsequent global cognitive functioning and disability [30]. Furthermore, increases in lacunes over time have been associated with a worsening of performance in executive function [37, 42]. As such, the burden of lacunes has been proposed as the most relevant MRI maker with regards to cognitive impairments in CADASIL [36, 40, 73]. Brain atrophy is a well-documented consequence of CADASIL. The vast majority of studies investigating associations between clinical symptoms and global volumetric brain measures, such as the brain parenchymal fraction (BPF), have revealed significant relationships with cognitive scores and functional outcomes in CADASIL patients [34, 50, 53, 60, 71]. Using multimodal imaging in a large cohort, Viswanathan et al. (2010) established that brain atrophy corresponded to the main determinant of disability and global cognitive function in CADASIL [71]. In comparison, Benisty et al. (2012) failed to find significant correlations between scores on multiple cognitive measures and the BPF [5]. However, this group studied a specific CADASIL subpopulation presenting without lacunes, potentially contributing to this divergence in findings. Baseline brain volumes, or changes in brain volumes over time, also appear to contribute to the prediction of subsequent cognitive functioning and disability [30, 42, 60]. While they did not find significant associations with

brain atrophy, Liem et al. (2009) revealed strong correlations between ventricular enlargement, likely secondary to central cortical atrophy, and decline in global cognitive functioning over time [37]. Looking at regional patterns of brain atrophy, a study demonstrated significant hippocampal volume reduction in patients meeting clinical criteria for dementia, as opposed to non-demented patients [53]. Hippocampal volumes were also found to independently predict scores on a global cognitive performance scale. In two articles looking at regional morphometric characteristics of CADASIL patients, Jouvent et al. showed strong correlations between sulci morphology and clinical measures of apathy, global cognitive functioning and disability [31, 33]. Multiple studies have explored associations between white matter tract integrity, as estimated via DTI, and clinical symptoms in CADASIL [8, 47, 48, 55, 71]. Overall, these studies support significant correlations between measures of disability or global cognitive functioning and diffusion parameters. O'Sullivan (2004) et al. noted particularly strong associations between executive function performance and DTI measurements, one of the most salient cognitive impairment in CADASIL [55]. Additionally, Molko et al. (2002) reported larger changes in whole-brain diffusion parameters in patients experiencing clinical deterioration over time than in patients maintaining a stable status [48]. Finally, more uncommon MRI markers have been studied in relation to clinical symptoms in CADASIL. For example, Yao et al. (2014) demonstrated that the severity of PVS dilatation was worsened in demented CADASIL patients and was associated with global cognitive functioning, regardless of the age [75]. In a different study, the presence of intracranial atherosclerosis, as estimated with MR angiography, was independently linked to increased disability [11]. Moreton et al. (2018) found that CADASIL patients with lower cerebral vasoreactivity, as estimated using Arterial Spin Labeling (ASL), tended to present greater levels of disability, depressive symptoms and impaired processing speed [50]. To summarize, many studies have related MRI markers to clinical symptoms in CADASIL. However, these results are at times inconsistent across studies and need replication. In this literature, the presence and extent of lacunes and brain atrophy has been the most consistently associated with cognitive and/or functional outcomes in CADASIL. Yet, certain factors merit further consideration. For example, in two articles, Duering et al. proposed that the regional pattern of distribution of MRI lesions is an important factor in the explanation of observed deficits [21, 23]. Furthermore, in agreement with the notion of cognitive reserve, the education level appears to mediate the relationship between MRI lesions and clinical symptoms in CADASIL [77]. To provide a better understanding of the clinical relevance of MRI signal abnormalities in CADASIL, factors influencing the relationship between MRI markers and the presentation or progression of symptoms need to be investigated more thoroughly.

Conclusion

Magnetic resonance imaging is a core component of the clinical diagnosis of CADASIL, a genetic condition leading to early cerebrovascular changes and strokes. Here, we reviewed and summarized the literature on three aspects relevant to the use of MRI in CADASIL. Although the imaging characteristics of CADASIL have been previously described in a review article [66], the present review adds to the existing literature by further exploring relationships between MRI markers and clinical or pathological features of CADASIL. The

review of studies investigating potential MRI markers for CADASIL indicates that it shares largely similar radiological features with other diseases affecting white matter integrity, such as multiple sclerosis or sporadic forms of SVD (as an illustration, see Figure 1). Accordingly, while the involvement of the anterior temporal pole and external capsule can suggest the presence of CADASIL, none of the proposed MRI markers is sufficiently sensitive or specific to support the differential or accurate diagnosis of this disease. This review also points to the lack of research systematically examining associations between MRI markers and pathology in CADASIL. This type of work is needed to obtain a better understanding of pathogenic mechanisms underlying MRI signal abnormalities and may promote the development of more precise imaging biomarkers for this disease. Finally, the review of studies investigating relationships between MRI markers and clinical symptoms in CADASIL indicates that lacunes and brain atrophy are the most robustly related to disability and cognitive status. However, associations between clinical and imaging variables appear to fluctuate depending on the type of symptoms examined as well as other modulating factors, such as the cognitive reserve or the regional distribution of brain lesions. Future research is needed to better characterize factors influencing the interplay between radiological and clinical presentations in CADASIL, including the effects of the genotype or various lifestyle/environmental factors. A thorough understanding of factors associated with neuroimaging findings in CADASIL is necessary to promote accurate diagnosis, improve disease management and facilitate the validation of new therapeutic strategies.

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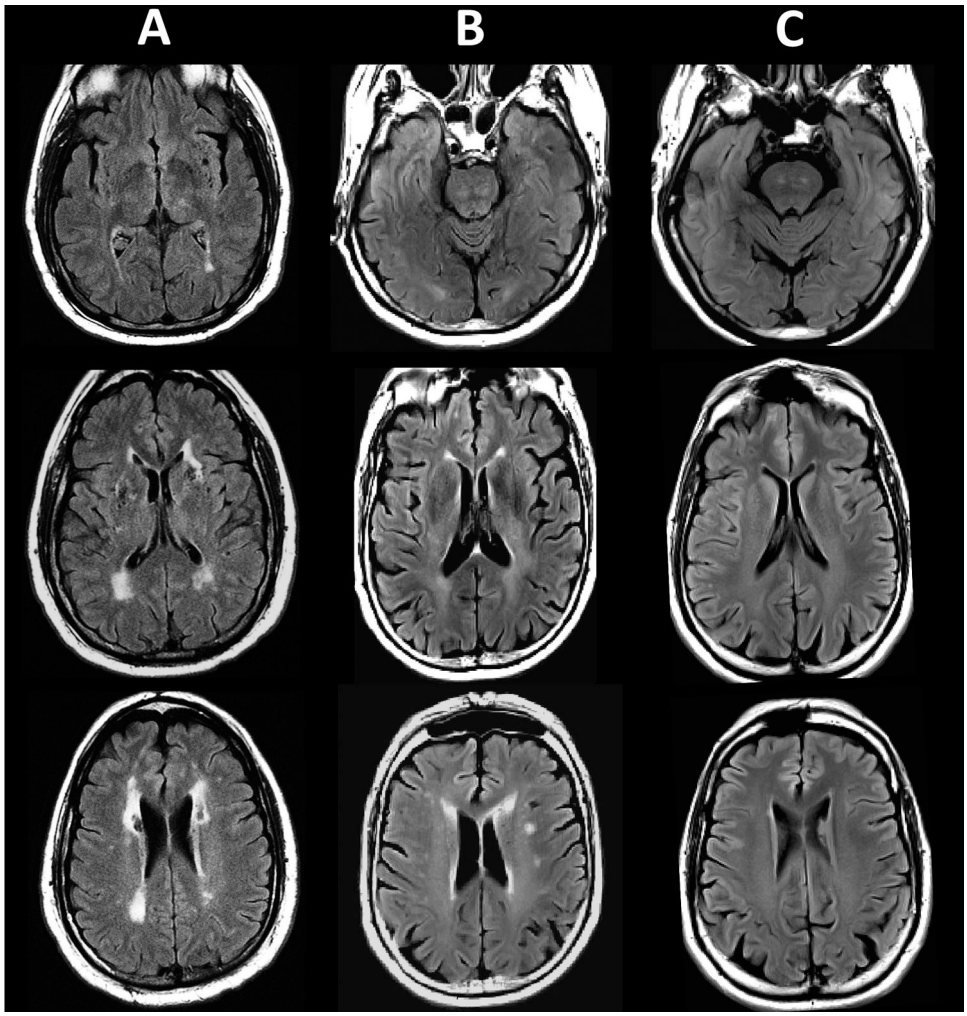

Figure 1.

Fluid-attenuated inversion recovery (FLAIR) images of white matter signal abnormalities in: A) a 61 year old male subject with CADASIL (*image courtesy of Dr. Anand Viswanathan, J. Philip Kistler Stroke Research Center, Massachusetts General Hospital, Boston, USA*); B) a 58 male subject with sporadic cerebral small vessel disease (SVD) and C) a 58 male subject with normal appearing white matter.