CADASIL, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy: Navigating the Genetic and Clinical Complexity Implications

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Abstract

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a genetic condition affecting the central nervous system (CNS), primarily linked to mutations in the Notch3 gene located on chromosome 19. CADASIL is characterized by recurrent strokes, cognitive decline, and migraines, often leading to severe disability. Characteristically, CADASIL presents with clinical symptoms that include transient ischemic attacks (TIAs), subcortical infarcts, mood disturbances, and progressive cognitive impairment. These clinical features are typically observed in middle-aged adults and progress over time. The disease has a distinctive appearance on magnetic resonance imaging (MRI), which often reveals white matter hyperintensities, especially in the subcortical regions, as well as lacunar infarcts and microbleeds.

The diagnosis of CADASIL is primarily based on genetic testing to identify mutations in the Notch3 gene, supported by neuroimaging findings.. There is currently no cure for CADASIL, and treatment focuses on managing symptoms and preventing complications, such as stroke and cognitive decline. Lifestyle modifications and control of vascular risk factors are essential components of the management strategy.Due to its hereditary nature, family members of affected individuals may also be at risk and should consider genetic counseling and testing. Clinicians and radiologists need to be aware of CADASIL as early diagnosis can help in managing the disease and improving the quality of life for affected individuals. This analysis reviews the clinical features, genetic aspects, and differential diagnoses of CADASIL, emphasizing the importance of recognizing and diagnosing this condition in a timely manner.

Contents

1. Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is more commonly known by its acronym, 'CADASIL', and was introduced to the scientific world in the early 1990s. It is often confused with other forms of vascular dementia, and since it has a distinct genetic basis and pathophysiology, understanding this specific disease is particularly important. The fundamental mechanisms underlying the pathogenesis of CADASIL involve mutations in the Notch3 gene on chromosome 19, leading to abnormal protein accumulation in the blood vessels of the brain. Despite advances in genetic testing, the exact neural mechanisms and pathways affected by these mutations are not fully elucidated. There is currently no cure for CADASIL, and treatment focuses on managing symptoms and preventing complications, such as stroke and cognitive decline. Managing CADASIL poses challenges due to its progressive nature and the lack of specific therapies targeting the underlying genetic defect(Lesnik Oberstein & Haan, 2004), (Lapoint et al., 2000),

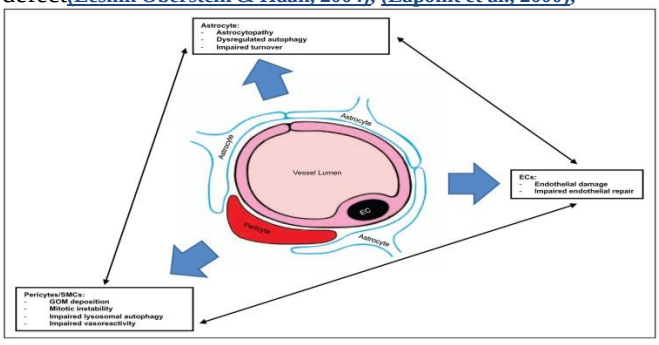

Figure 1 : schematic of a cerebral capillary shows the effects on multiple molecular systems on the dothelial, pericyte,smooth muscle and neural cell levels because of CADASIL

2.Main characteristics of CADASIL

CADASIL syndrome is identified by a few clinical aspects and a particular typical neuroimaging feature: recurrent strokes, migraines, and progressive cognitive decline. These symptoms are caused by small vessel disease in the brain, which can lead to subcortical infarcts and leukoencephalopathy. MRI images often show white matter hyperintensities, particularly in the subcortical regions, along with lacunar infarcts and microbleeds. Genetic testing reveals mutations in the Notch3 gene on chromosome 19, leading to abnormal protein accumulation in the blood vessels. This syndrome has been added to the class of hereditary small vessel diseases of the brain **(Chen et al., 2014)**. Patients with CADASIL show characteristic, but nonspecific, changes on neuroimaging and genetic testing that serve as evident pathological proof of the disease. Differential diagnoses include other causes of vascular dementia, such as hypertensive vasculopathy, cerebral amyloid angiopathy, multiple sclerosis, and inflammatory or infectious vasculopathies. The three mentioned aspects (clinical features, neuroimaging, and genetic testing) are adequately distinguishable in diagnoses without the use of brain biopsies. Differential diagnoses include multiple sclerosis, neurosarcoidosis, primary CNS vasculitis, and infectious vasculitis of the central nervous system (CNS) **(Desmond et al., 1999)**.

There is currently no cure for CADASIL, and treatment focuses on managing symptoms and preventing complications. It's crucial to control vascular risk factors as hypertension and hyperlipidemia as well as Antiplatelet agents may be used to reduce the risk of stroke, although their efficacy in CADASIL is still under investigation. In the literature, it has been theorized that CADASIL is often underdiagnosed, and patients may be misdiagnosed with other forms of stroke or dementia before the correct diagnosis is made. Genetic counseling is recommended for affected individuals and their families due to the hereditary nature of the disease. Increased understanding of this clinical-genetic syndrome is particularly significant for early diagnosis and appropriate management, improving the quality of life for affected individuals.**(Baudrimont et al., 1993)**

3. Imaging Characteristics of CADASIL

CADASIL typically presents with diffuse white matter hyperintensities, known as leukoaraiosis, which are an early finding. Multiple lacunar infarcts are also characteristic, with highly sensitive and specific locations including the anterior temporal pole, external capsule, and paramedian superior frontal lobe. Diffusion restriction is observed in acute lacunar infarcts. Recommended imaging modailites include MRI with T2, FLAIR, and DWI sequences.. The best diagnostic clue for CADASIL is the presence of characteristic subcortical lacunar infarcts and leukoencephalopathy in young or middle-aged adults. Key locations include the anterior temporal lobe, external capsule, and paramedian superior frontal lobe, along with lacunar infarcts in the basal ganglia and subcortical regions. In younger patients, the frontal lobe, parietal lobe, external capsule, and anterior temporal lobe are most commonly involved, while older patients may additionally show involvement of the posterior temporal and occipital lobes .**(Ferrante et al., 2019)**

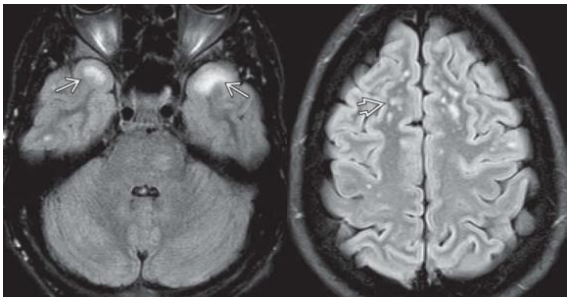

Figure 2 **: (Left) Axial FLAIR MR in a young patient with headaches shows hyperintensity in the anterior temporal lobes, highly suggestive of CADASIL .(Right) Axial FLAIR MR in the same patient shows subcortical hyperintense foci in the superior frontal gyri .**

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.

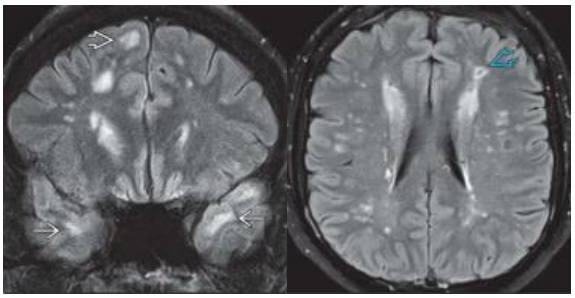

Figure 3: (Left) Coronal FLAIR MR shows multiple hyperintense white matter lesions in the anterior temporal lobes ſt, frontal lobes, and periventricular location in this 38-year-old man with CADASIL.(Right) Axial T2/FLAIR MR in a young patient with CADASIL shows multifocal white matter hyperintensities .

Early stages of CADASIL show a loss of contrast between gray matter and white matter. T2WI reveals diffuse white matter hyperintensities (leukoaraiosis) as an early finding, along with discrete, hyperintense lacunar infarctions. The anterior temporal pole and paramedian superior frontal lobe are particularly sensitive and specific locations. FLAIR sequences show discrete hyperintense lacunar infarcts and white matter hyperintensities. T2* GRE sequences detect microhemorrhages in 25-50% of patients, with the frequency increasing with age. DWI shows diffusion restriction in acute lacunar infarcts. PWI indicates reduced cerebral blood flow (CBF) and cerebral blood volume (CBV) in areas of white matter signal abnormality without significant mean transit time (MTT) changes. diminished CBF may precede abnormalities within the white matter and after acetazolamide challenge decrease hemodynamic reserve would be observed. **(O'Sullivan et al., 2001).**

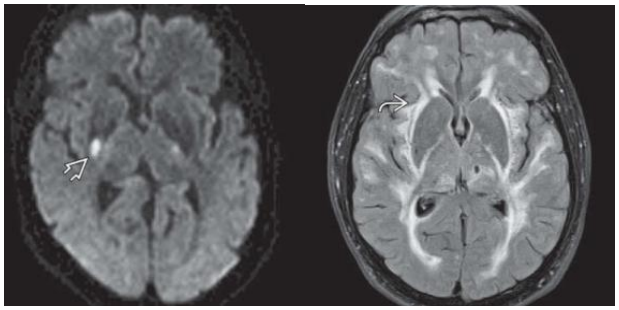

Figure 4 : **(Left) Axial DWI trace MR in a young woman shows an acute lacunar infarct in the right basal ganglia. CADASIL was diagnosed by the presence of a NOTCH3 mutation.(Right) Axial FLAIR MR shows extensive white matter hyperintensities with involvement of the external capsule and temporal lobes**

.4. Cases from the literature

We performed a narrative review of the literature and reviewed studies about CADASIL syndrome to describe the symptomatology and the prevalent cases in the literature. MEDLINE and ScienceDirect were searched for original articles and reviews of literature published between January 1990 and February 2021 describing studies that involved patients and results observed on CADASIL syndrome symptomatology, imaging findings, and presentations of the cases. The keywords used for the search were: 'CADASIL syndrome' and 'cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy'**(Choi, 2015) (Shao et al., 2014)**

We have included 30 articles in our study. The inclusion criteria were the presence of CADASIL syndrome, and the exclusion criteria were the absence of CADASIL syndrome. Our study included 30 articles.

The main clinical features described in the literature include recurrent strokes, migraines, and progressive cognitive decline. Radiological features are described as follows: white matter hyperintensities, particularly in the subcortical regions, along with lacunar infarcts and microbleeds. Additionally, lesions can be located in the basal ganglia, thalamus, or brainstem but may be less consistent with growing distance from the subcortical areas. Responsiveness to treatment is varied, focusing on managing symptoms and preventing complications, such as stroke and cognitive decline.**(Kaplan et al., 2000)**

The differential diagnosis is conducted against other causes of vascular dementia, such as hypertensive vasculopathy, cerebral amyloid angiopathy, multiple sclerosis, and inflammatory or infectious vasculopathies.**(Young et al., 2021)** The mean age at onset is 45 years (range 20 to 70 years), and prevalent studies from the literature have revealed an equal sex distribution. Regarding the patients that did not follow chronic management strategies or lifestyle modifications, CADASIL was demonstrated to have a progressive course. During periods of attacks, even though clinical and neurological deterioration can occur, the preservation of the disease within remission might avoid intensification of impairment.**(Fletcher, 2003).**

5.Demographics and Epdimyology

Casadil syndrome typically manifests ischemic symptoms in mid-adulthood, with MRI changes often appearing around the age of 30, preceding stroke or transient ischemic attacks (TIA) by 10 to 15 years. Migraines, when present, usually precede other clinical findings. There is no sex preference for the syndrome; however, prognosis and life expectancy differ between female and male patients.**(Joutel et al., 1996)**

The prevalence of Casadil syndrome remains unknown, though over 500 families have been documented worldwide. A small study in Scotland indicated a minimum prevalence of 1.98 per 100,000, with a predicted prevalence of about 4 per 100,000. This likely underestimates the true prevalence due to various factors. Casadil syndrome is the most frequent hereditary small-vessel disease affecting the brain. The average age of stroke onset is slightly earlier in men (50.7 years) compared to women (52.5 years), though this difference is not significant. Disease progression is typically more rapid in men, leading to earlier mortality.

6. Additional information

CADASIL syndrome leads to a distinct pathology involving small blood vessels in the brain. leading to arteriopathy affecting penetrating cerebral and leptomeningeal arteries. This results in narrowed lumens and decreased cerebral blood flow (CBF) and metabolism. Even in patients with minor white matter hyperintensities (WMHs), total CBF is reduced despite preserved cerebral vasodilatory capacity. The NOTCH3 gene, located on chromosome 19p13, encodes a large transmembrane receptor expressed in vascular smooth muscle cells, featuring 34 epidermal growth factor repeats (EGFR) with six cysteine residues. Over 150 CADASIL mutations have been identified, often causing an odd number of cysteine residues on the affected EGFR. De novo mutations are also reported. While small vessels in other organs like the skin, muscle, liver, and spleen can be affected, clinical manifestations are predominantly cerebral**. (Young et al., 2021)**

Pathologically, CADASIL is characterized by chronic small artery disease, including diffuse myelin pallor, periventricular and centrum semiovale white matter rarefaction, lacunar infarcts in the white matter and basal ganglia, dilated perivascular spaces, and cortical atrophy. Microscopically, it presents with specific arteriopathy in small penetrating cerebral and leptomeningeal arteries, marked by arterial wall thickening leading to luminal stenosis with a normal endothelium, non-amyloid extracellular granular osmiophilic deposits in the media extending into the adventitia, and morphologically altered smooth muscle cells that can disappear from the vessel wall. Widespread cortical apoptosis, particularly in layers 3 and 5, is also observed. Brain biopsies are generally not required for the diagnosis of CADASIL due to the availability of less invasive diagnostic methods such as skin biopsies and genetic testing **(Ferrante et al., 2019)**. However, in atypical cases, a brain biopsy may be considered, though it carries the risk of complications, particularly when targeting areas such as the deep white matter, brainstem, or thalamus.**(UCHINO et al., 2002)**

Potentioal pharmacological intervention is Neuromodulin, or GAP-43, plays a crucial role in neural development, synaptic plasticity, and nerve regeneration. While it is not currently an established therapy for CADASIL syndrome, its involvement in neural repair and plasticity suggests it could be a promising target for future research. CADASIL is characterized by small vessel damage in the brain, leading to strokes and cognitive decline. Enhancing neural repair mechanisms through neuromodulin could potentially mitigate some of this damage. Additionally, neuromodulin's influence on synaptic plasticity may help improve cognitive functions, addressing a significant symptom of CADASIL. Although there are no current clinical trials targeting neuromodulin for CADASIL, its potential benefits highlight the need for further investigation into its efficacy and safety in preclinical models and eventual human trials.**(Elliott, 2005)**

Future investigations should focus on a better definition of the molecular mechanisms underlying CADASIL, and the development of biomarkers that can aid in the early diagnosis and monitoring of disease progression. Research on cytokine and chemokine profiles in serum and cerebrospinal fluid (CSF) could provide insights into the inflammatory processes involved in the disease. Although CADASIL is primarily a genetic disorder, secondary factors such as hypertension and lifestyle can influence disease progression. Studies have documented elevated serum markers of inflammation in CADASIL patients, suggesting a possible link between systemic inflammation and disease severity. Advanced imaging techniques, including magnetic resonance spectroscopy and diffusion tensor imaging, have been employed to study CADASIL. These techniques may help in identifying subtle changes in brain structure and function that precede clinical symptoms **(Chabriat et al., 2009)**

In the literature, a possible relationship between CADASIL and increased risk of stroke has been well documented. The characteristic arteriopathy in CADASIL leads to chronic ischemic damage, predisposing patients to recurrent strokes and transient ischemic attacks. The understanding of CADASIL as a small vessel disease with distinct genetic underpinnings provides a framework for exploring targeted therapies and interventions. By utilizing advanced genetic, molecular, and imaging techniques, future research can further elucidate the pathophysiology of CADASIL and pave the way for novel therapeutic approaches aimed at mitigating the impact of this debilitating disease.**(Karmon et al., 2011)**

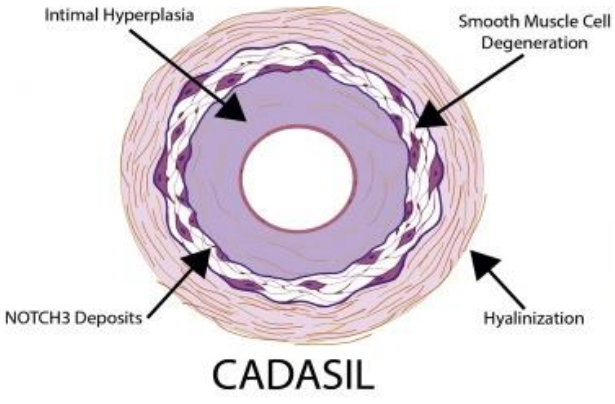

***Figure 5** : Vascular changes and Smooth muscle cell degeneration in CADASIL*

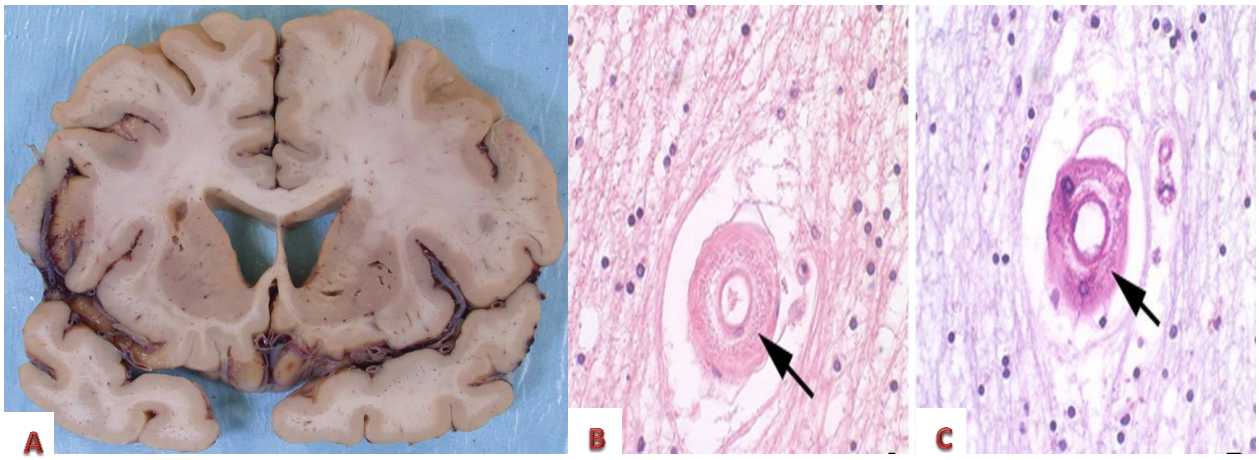

Figure 6: (A) **White matter changes with status cribrosus and small subcortical and basal ganglia lacunes** ***(B),(C)*** **Representative images of arterioles demonstrating differential degeneration of vessel walls**

Histologically, CADASIL is characterized by a distinctive vasculopathy primarily affecting small arteries within the brain parenchyma, particularly in the white matter and subcortical regions. The hallmark pathological feature is the accumulation of granular osmiophilic material (GOM) within the tunica media of affected vessels. This GOM appears as electron-dense granules on electron microscopy and stains positive with periodic acid-Schiff (PAS) stain. GOM deposition leads to thickening and degeneration of the vessel wall, ultimately resulting in luminal narrowing and impaired blood flow .Additionally, loss of vascular smooth muscle cells (VSMCs) and perivascular fibrosis are observed in later stages of the disease process facilitated by these vascular alterations , chronic ischemic injury in the brain will develop , which results in the clinical manifestations of CADASIL.(Desmond et al., 1999)

Table 1: : **Clinical Features and Outcomes of CADASIL Syndrome in Younger versus Older Patients**

Symptoms	Percent	Younger	Older
Location of injury		Frontal lobe, parietal lobe, external capsule, and anterior temporal lobe	posterior temporal and occipital lobes
TIA Stroke	60-80%	rare	present
Migraine with aura	20-40%	present	absent
Cognitive deficits	Dementia:60% Apathy :40%	rare	Present (dementia)
Motor disability	1-Gait disability:90% 2-Urinary incontinence: 80-90% 3-pseudobulbar palsy: 50%	rare	Present (with dementia)
Behavioral disturbance	20% (severe depression)	present	present

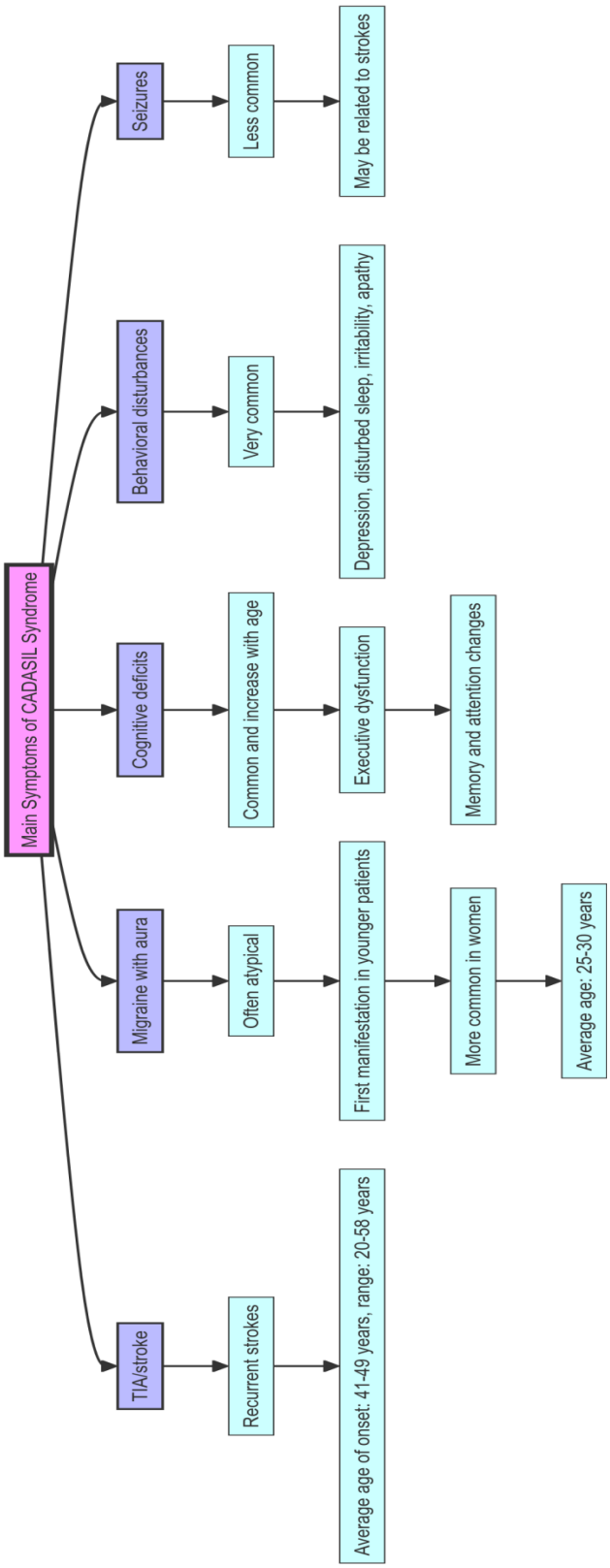

Figure 7: **Chart Flow Diagram Representing Symptoms of CADASIL Syndrome**

7.Conclusions

Although CADASIL is a hereditary small vessel disease, it is not a benign condition. In studies reported in the literature, no patient has fully recovered, and without proper management, the disease can progress, leading to significant morbidity. Marked white matter hyperintensities and lacunar infarcts accompany or follow the onset of the disease and can be measured by clinical parameters and MRI. These factors contribute to long-term neurological morbidity. Although the exact pathophysiological mechanisms of the disease are linked to mutations in the Notch3 gene, there appear to be overlaps with other small vessel diseases.

Neurologists should be aware of the typical conditions and manifestations of CADASIL, as prompt and appropriate management may limit permanent neurological effects. In differential diagnoses of neurodegenerative diseases and vascular diseases with similar CT and MRI images, CADASIL should be considered. The pathogenesis of CADASIL has been linked to elevated levels of CSF proteins without significant pleocytosis, the characteristic white matter changes on MRI, and the genetic mutation in the Notch3 gene suggest that it is a genetically mediated disease. Although there is no specific biomarker beyond genetic testing, careful exclusion of other conditions is necessary to diagnose CADASIL.

Clinicians are advised to consider this disorder in the diagnostic area, as early diagnosis and appropriate management can result in better long-term functional outcomes. More data are needed to understand the diagnostic and prognostic value of MRI findings and genetic testing in CADASIL. Continued research and longitudinal studies are essential to further elucidate the pathophysiological mechanisms, identify potential therapeutic targets, and improve the management and prognosis of patients with CADASIL.

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