GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(REVIEW ARTICLE)

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CADASIL: An overview of a rare cerebrovascular disease

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GSC Advanced Research and Reviews, 2025, 23(03), 103-109

Publication history: Received on 04 May 2025; revised on 11 June 2025; accepted on 14 June 2025

Article DOI: https://doi.org/10.30574/gscarr.2025.23.3.0165

Abstract

The Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) it's a genetic disorder that affects the small blood vessels in the brain for a pathological variant in the *NOTCH3* gene, located on chromosome 19. It is of great interest to know its correct diagnosis based on expression and variable clinical symptomatology due to episodes of migraine, dementia, cerebral ischemic episodes, psychiatric disorders and motor difficulties. Factors involved in the differential diagnosis of this genetic disorder will be discussed, based on general international criteria like Neuroimaging Findings and Genetic Testing. In addition, its clinical manifestations will be analyzed in various patient contexts to identify specific features related to individual genetic variations.

Keywords: Hereditary cerebral arteriopathy; $NOTCH_3$ gene mutations; Recurrent subcortical strokes; Progressive chronic leukoencephalopathy; CADASIL; Variable neuropsychiatric symptoms

1. Introduction

CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) *(OMIM: 125310)* is a rare cerebrovascular disease with a global prevalence of 2–5 per 100,000 people. It is the most common hereditary cause of stroke and vascular dementia. [1, 2, 3,]

This genetically inherited disease is primarily characterized by multiple cerebrovascular accidents, beginning with migraine as an initial symptom between the ages of 20 and 30 in one-third of patients. This is followed by episodes of focal neurological deficits caused by transient ischemic attacks or cerebral infarctions, ultimately progressing to major neurocognitive impairment. [1, 2, 3,]

1.1. Genetic Basis and Pathophysiology

CADASIL is a rare genetic disease and the most frequent hereditary cause of small vessel disease in the brain. It results from a pathological variant in the *NOTCH3* gene, located on the short arm of chromosome 19 (19p13.2–p13.1). This gene encodes a receptor-type transmembrane protein that belongs to the NOTCH receptor family. The NOTCH3 protein is predominantly expressed in vascular smooth muscle cells and pericytes, playing an essential role in intercellular signaling during development and in maintaining vascular integrity. [3]

CADASIL follows an autosomal dominant inheritance pattern, meaning that each affected individual has a 50% chance of passing on the pathogenic mutation to their offspring. However, sporadic cases due to de novo mutations have been reported, indicating that the absence of family history does not exclude the diagnosis. [3]

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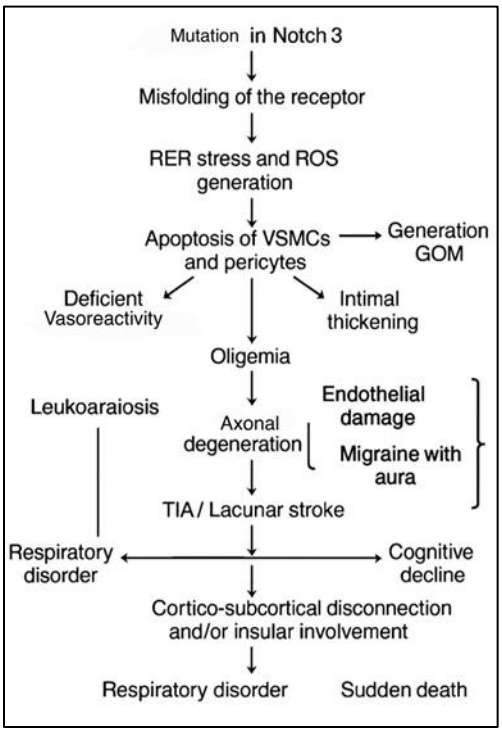
At the molecular level, the most common pathogenic mutations affect exons that encode the cysteine-rich EGF-like repeat domains of the NOTCH3 protein. These mutations alter the number and arrangement of cysteine residues, disrupting the protein's three-dimensional conformation and promoting the accumulation of granular osmiophilic material (GOM), visible under electron microscopy. These deposits are found in the basal membrane of smooth muscle cells in the media layer of small- and medium-sized cerebral arteries, triggering a progressive arteriopathy. [3]

Histopathological changes include arterial wall thickening, smooth muscle cell loss, fibrosis, and luminal narrowing, leading to chronic cerebral hypoperfusion. These alterations contribute to recurrent subcortical infarctions and progressive leukoencephalopathy, the hallmark clinical features of the disease. The progression of these chronic ischemic events is associated with neurological symptoms such as migraine with aura, cognitive decline, psychiatric disorders, and ultimately subcortical dementia. [3]

The diagnosis is confirmed through genetic analysis identifying a mutation in the *NOTCH3* gene and may be supported by characteristic findings on brain MRI, such as white matter hyperintensities—particularly in the anterior temporal poles, external capsule, and basal ganglia. [3]



Available from Del Rio Espínola et al [4]

Figure 1 CADASIL Physiopathology

2. Clinical Manifestations

CADASIL presents with a heterogeneous clinical picture, predominantly neurological, with symptoms typically beginning in early adulthood and progressing over time. The most common manifestations are cerebrovascular events, reported in up to 85% of cases, including transient ischemic attacks and lacunar infarctions, in the absence of traditional vascular risk factors. [5, 6, 7, 8]

Migraine with aura, which may precede ischemic events, typically appears between the ages of 20 and 30 and is present in 20–40% of patients. Over time, the disease progresses to cognitive impairment, initially presenting as executive dysfunction and slowed processing speed, with preserved episodic memory, and later evolving into major neurocognitive disorder (NCD) with a pseudobulbar component. [5, 6, 7, 8]

Seizures occur less frequently (5–10%), typically generalized tonic-clonic seizures around the age of 50. Rare systemic manifestations include acute myocardial infarction, arrhythmias, alopecia, gingivitis, periodontal disease, skin lesions, and visual symptoms (aura, diplopia, oscillopsia). Psychiatric disorders affect 20–40% of patients, with apathy and

mood disorders (depression, mania) being the most common, followed by psychotic or adjustment disorders. [5, 6, 7, 8]

Motor involvement (gait disturbances, urinary incontinence, pseudobulbar palsy) is usually correlated with the progression of lesion burden in the central nervous system, reflecting the chronic and degenerative course of the disease. [5, 6, 7, 8]

Table 1 Most Common Clinical Manifestations

History of recurrent lacunar ischemic strokes (84–87%).
Subcortical dementia (31–60%) (its incidence increases up to 80% after age 60).
Migraine with or without aura (22–38%).
Sensorineural hearing loss (33%).
Neuropsychiatric disorders such as severe depression, manic episodes, or psychosis (20%).
Epilepsy (7%).

[9]

2.1. Diagnostic Criteria

CADASIL diagnosis can be classified into three levels: possible, probable, and definite, each with specific criteria to guide diagnosis and differentiate from other pathologies. [10]

2.2. Possible CADASIL

Considered in patients with late onset (>50 years), mild symptoms such as affective disorders or global dementia, and the presence of minor vascular risk factors (mild hypertension, dyslipidemia, smoking). Family history may be unclear and MRI findings are atypical, requiring consideration of alternative diagnoses. [10]

2.3. Probable CADASIL

Applies to cases where symptoms begin before age 50, with at least two key clinical features: stroke-like episodes with persistent deficits, migraine, or subcortical dementia. There is an absence of significant cardiovascular risk factors, a dominant inheritance pattern, and MRI findings of white matter changes without cortical infarcts. It is crucial to differentiate from conditions like Binswanger's disease or multiple sclerosis. [10]

2.4. Definite CADASIL

Requires fulfilling criteria for probable CADASIL plus genetic confirmation (mutation in the *NOTCH3* gene) or histopathological findings (GOM in small vessels). This level of diagnosis excludes other conditions with certainty and confirms the disease. [10]

Table 2 Diagnostic Criteria for CADASIL

Types	Characteristics
Possible CADASIL	Late onset (>50 years). Stroke-like episodes without permanent signs (minor affective disorder or global dementia). Minor cardiovascular risk factors (mild hypertension, mild hyperlipidemia, smoking, oral contraceptives). Unknown or incomplete family lineage. MRI showing atypical white matter changes.
Probable CADASIL	Onset before age <50 years. At least two of the following findings: Stroke-like episodes with permanent neurological signs. Migraine. Subcortical dementia. Absence of etiologically related cardiovascular risk factors.

	Evidence of autosomal dominant inheritance. MRI showing white matter changes without subcortical infarcts.
Definite CADASIL	Criteria for probable CADASIL plus any of the following: Demonstration of *NOTCH3* gene mutation. Pathological findings consistent with small vessel arteriopathy with GOM (granular osmiophilic material) deposits
Exclusion Criteria	Onset after age >70 years. Severe hypertension or hypertension complicated by cardiac or systemic vascular disease. Absence of documented familial cases. Normal MRI findings after age 35.

Available from P. Davous et al [10]

3. Neuroimaging Findings

Brain MRI is a key diagnostic tool, often detecting changes before clinical symptoms appear. Typical findings include:

Table 3 Typical findings in Brain MRI

Findings	**Location or Imaging Feature**
White matter hyperintensities.	Anterior temporal lobes and external capsule on T2 and FLAIR sequences.
Lacunar infarcts	Basal ganglia, thalamus, and brainstem.
Microbleeds	Seen in GRE or SWI sequences.
Progressive brain atrophy	Noticeable in advanced stages.

[11]

These imaging features help differentiate CADASIL from other leukoencephalopathies such as multiple sclerosis or cerebral amyloid angiopathy. [11]

Table 4 Evolutionary Stages of CADASIL (Association Between Clinical Features and MRI Findings)

Stage	**Stage I**	**Stage II**	**Stage III**
Age (years)	20-40	40-60	>60
Clinical Features	Migraine (with or without aura)	Stroke episodes and/or neuropsychiatric disorders	Subcortical dementia
MRI Findings	Lesions confined to the white matter	Coalescent white matter lesions and well-defined lesions in the basal ganglia	Diffuse leukoencephalopathy and multiple well-defined lesions in the basal ganglia

Available from M. Verin et al [12]

4. Diagnostic Genetic Testing

As mentioned above, the gold standard for the diagnosis of CADASIL is molecular genetic analysis of the *NOTCH3* gene, which has a sensitivity close to 100%. A scoring system (Table 3) was developed to assess patient selection for this test. A score higher than 15 is considered indicative of a candidate for testing. [13]

Table 5 Patient Selection Scale for *NOTCH3* Gene Analysis

Feature	Score
Migraine	1
Migraine with aura	3
Stroke	1
Stroke Onset before age 50	2
Psychiatric disorders	1
Major neurocognitive disorder	3
Leukoencephalopathy	3
Leukoencephalopathy extending to the temporal pole	1
Leukoencephalopathy extending to the external capsule	5
Subcortical infarcts	2
Family history in at least 1 generation	1
Family history in at least 2 generations	1

Available from Pescini F et al[13]

5. Further Relevant Clinical and Diagnostic Considerations

CADASIL has been described as a multisystemic disease, with involvement extending beyond the central nervous system. Documented cases have included cardiovascular abnormalities (such as arrhythmia and acute myocardial infarction), neuromuscular symptoms including myopathies and polyneuropathies, as well as atypical dermatological and ophthalmological manifestations, suggesting a more generalized compromise of the vascular endothelium. [11]

Another significant observation is the early clinical onset, with migraines with aura potentially presenting in the second or third decade of life—often decades before cerebrovascular events or cognitive decline. This early presentation may lead to diagnostic delays or confusion with primary headache disorders, underscoring the importance of a thorough evaluation in young patients with a suggestive family history. [11]

Psychiatric manifestations should also be recognized as part of the clinical spectrum of CADASIL. Disorders such as depression, apathy, emotional lability, and even psychotic symptoms may precede neurological deterioration, sometimes resulting in misdiagnoses such as schizophrenia or major affective disorders. This phenotypic variability highlights the need for a multidisciplinary diagnostic approach. [11]

From an imaging standpoint, brain magnetic resonance imaging (MRI) may reveal characteristic lesions up to 15 years before clinical onset. T2-weighted and FLAIR hyperintensities located in the external capsule, anterior temporal lobes, and pons are highly predictive of CADASIL and help distinguish it from other causes of leukoencephalopathy. [11]

Regarding genetic diagnosis, although most cases follow an autosomal dominant pattern due to mutations in the *NOTCH3* gene, de novo mutations have been reported. Therefore, the absence of family history should not preclude the diagnosis. In this context, genetic testing remains the diagnostic gold standard and is particularly warranted in patients with suggestive clinical and imaging findings. [11]

Currently, there is no curative treatment for CADASIL. Therapeutic strategies focus on symptomatic management and secondary prevention of ischemic events. The use of anticoagulants or thrombolytics requires special caution due to the potential risk of hemorrhage stemming from the inherent vascular dysfunction in this disease. Consequently, therapeutic approaches must be carefully individualized. [11]

5.1. Differential Diagnosis

The differential diagnosis should include entities such as Binswanger's disease, primary central nervous system angiitis, and multiple sclerosis. Additionally, various genetic disorders must be considered, including CARASIL, MELAS syndrome, Fabry disease, and small vessel vasculopathies associated with COL4A1 gene mutations. [14, 15, 16]

6. Conclusion

CADASIL is a rare but clinically significant hereditary cerebrovascular disease and the leading genetic cause of stroke and vascular dementia. It arises from mutations in the NOTCH3 gene, resulting in progressive arteriopathy with severe neurological consequences. The broad spectrum of symptoms—from early-onset migraines to cognitive decline and psychiatric disturbances—makes diagnosis challenging. Thus, a comprehensive clinical approach supported by neuroimaging and, crucially, genetic testing is essential. Early and accurate recognition of this condition improves clinical management, genetic counseling, and patient quality of life. Further research into disease mechanisms will help identify therapeutic targets and develop effective treatments, as current management remains limited to symptomatic relief.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Sepúlveda V, Varela J, Villaseñor J. CADASIL: arteriopatía cerebral autosómica dominante con infartos subcorticales y leucoencefalopatía. Rev Confluencia. 2022;5(1):109–111. doi:10.52611/confluencia.num1.2022.721.

[2] Turnpenny PD, Ellard S, Cleaver R. CADASIL. En: Turnpenny PD, Ellard S, Cleaver R, editores. *Elementos de genética médica y genómica de Emery.* 16ª ed. Barcelona: Elsevier; 2021. p. 291.

[3] Latorre C, Barra B. CADASIL: arteriopatía cerebral autosómica dominante con infartos subcorticales y leucoencefalopatía. Una revisión narrativa. Psiquiatr Salud Ment (Santiago). 2023;40(3-4):68–75.

[4] del Río Espínola A, Solé E, Montaner J. Fisiopatología del CADASIL. Med Clin (Barc). 2010 Jul;135(5):222–30. doi:10.1016/j.medcli.2009.10.034.

[5] Chabriat H, Joutel A, Tournier-Lasserve E, Bousser MG. CADASIL: yesterday, today, tomorrow. Eur J Neurol. 2020;27(8):1588–95. doi:10.1111/ene.14993. PMID: 39348626.

[6] Xiromerisiou G, Marogianni C, Dadouli K, Zompola C, Georgouli D, Provatas A, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy revisited: Genotype-phenotype correlations or all published cases. Neurol Genet. 2020 May 11;6(3):e434. doi:10.1212/NXG.0000000000000434.

[7] Shi Y, Li S, Li W, Zhang C, Guo L, Pan Y, et al. MRI lesion load of cerebral small vessel disease and its correlation with cognition in patients with CADASIL. Front Neurol. 2018;9:862. doi:10.3389/fneur.2018.00862.

[8] Choi JC. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy: a genetic cause of cerebral small vessel disease. J Clin Neurol. 2010;6(1):1–9. doi:10.3988/jcn.2010.6.1.1

[9] Palomeras i Vilches A, Picas Jufresa A, Ramió Torrentà L, Cristóbal Buñuel Álvarez J. CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Med Fam Semergen. 2010;36(3):170–3. doi:10.1016/j.semerg.2010.01.006.

[10] P. Davous. CADASIL: a review with proposed diagnostic criteria. Eur J Neurol, 5 (1998), pp. 219-233

[11] National Institute of Neurological Disorders and Stroke (NINDS). CADASIL [Internet]. Bethesda (MD): National Institutes of Health; 2018 [cited June 1, 2025]. Available from: https://www.ninds.nih.gov/health-information/disorders/cadasil

[12] M. Verin, Y. Rolland, F. Landgraf, H. Chabriat, B. Bompais, A. Michel, et al. New phenotype of the cerebral autosomal dominant arteriopathy mapped to chromosome 19: migraine as the prominent clinical feature. J Neurol Neurosurg Psychiatry, 59 (1995), pp. 579-585

[13] Pescini F, Nannucci S, Bertaccini B, Salvadori E, Bianchi S, Ragno M, et al. The Cerebral Autosomal-Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL) Scale: a screening tool to select patients for NOTCH3 gene analysis. Stroke. 2012;43(11):2871-6. doi: 10.1161/STROKEAHA.112.665927.

[14] Uemura M, Nozaki H, Onodera O. [Arteriopatía cerebral autosómica recesiva con infartos subcorticales y leucoencefalopatía (CARASIL)]. Nervio cerebral. Enero de 2017; 69(1):25-33. Japonés. doi: 10.11477/mf.1416200631. PMID: 28126975.

[15] Bougea A, Velonakis G, Spantideas N, Anagnostou E, Paraskevas G, Kapaki E, Kararizou E. The first Greek case of heterozygous cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy: An atypical clinico-radiological presentation. Neuroradiol J. 2017 Dec;30(6):583-585. doi: 10.1177/1971400917700168. Epub 2017 Apr 12. PMID: 28402226; PMCID: PMC5703136.

[16] Mukai M, Mizuta I, Watanabe-Hosomi A, Koizumi T, Matsuura J, Hamano A, Tomimoto H, Mizuno T. Genotype-phenotype correlations and effect of mutation location in Japanese CADASIL patients. J Hum Genet. 2020 Aug;65(8):637-646. doi: 10.1038/s10038-020-0751-9. Epub 2020 Apr 10. PMID: 32277177.