

✦ Case report

Unusual Predominant Memory Decline in an Early-Stage CADASIL Patient: A Four-Year Longitudinal Follow-Up of Hereditary Vascular Dementia

Carolina Ospina,^{1‡} Dorothee Schoemaker,^{2,3‡} Lina Marcela Velilla,¹ Yesica Zuluaga,¹ Francisco Lopera,¹ Joseph F. Arboleda-Velasquez,³ Yakeel T. Quiroz^{1,2,4,5*}

1. Grupo de Neurociencias, Universidad de Antioquia, Medellín (Colombia)

2. Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston (USA)

3. Schepens Eye Research Institute of Mass Eye and Ear | Department of Ophthalmology, Harvard Medical School, Boston (USA)

4. Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston (USA)

5. Department of Psychological and Brain Sciences, Boston University, Boston (USA)

* **Corresponding author:** Yakeel T. Quiroz, yquiroz@mgh.harvard.edu, 39 1st Avenue, Suite 101, Boston, MA 02129

‡ Authors contributed equally to this work

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Abstract

Introduction: Deficits in executive function and processing speed have traditionally been viewed as the chief cognitive manifestation of vascular contributions to cognitive impairment and dementia. This case study describes the longitudinal progression of cognitive symptoms in a 42-year-old Colombian woman with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a hereditary condition leading to the early onset of cerebral small vessel disease. Because of the young age of onset of vascular cognitive impairment, CADASIL allows examining the early cognitive consequences of cerebrovascular changes in the absence of age-related comorbidities.

Methods: We followed the neuropsychological progression of a non-demented and stroke-free patient carrying a CADASIL mutation, in parallel to that of 13 non-carrier control subjects. At baseline, all subjects completed detailed clinical, neurological, and neuropsychological evaluations as well as an MRI scan. After a period of four years, subjects completed a follow-up neuropsychological evaluation.

Results: Examination of the patient's baseline MRI revealed the presence of significant areas of white matter hyperintensity. The patient did not present cerebral microbleeds, lacunes, notable brain atrophy, or evidence of previous strokes. In contrast to non-carrier subjects, the patient experienced predominant memory decline, with relatively preserved executive function and processing speed.

Conclusions: This case highlights the heterogeneity of cognitive deficits associated with cerebrovascular disease.

1. Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare autosomal-dominant disease linked to NOTCH3 mutations and leading to the early and progressive onset of cerebral small vessel disease.¹ Typical CADASIL mutations involve a cysteine residue within one of the EGF-like repeats in the extracellular domain of Notch3, which result in an odd number of cysteine residues. This change is believed to alter the formation of disulfide bridges, therefore affecting the stability of Notch3 and potentially leading to abnormal aggregation and function of the receptor.² Patients with CADASIL often suffer from recurrent strokes and develop vascular cognitive impairment at a relatively young age.³ CADASIL is recognized as the most common monogenic cause of strokes and vascular dementia.³

The diagnosis of CADASIL is based on evidence of a mutation on the NOTCH3 gene upon genotyping and can be further corroborated by the presence of a positive family history of early strokes and dementia or by skin biopsy supporting the presence of granular osmiophilic material (GOM) on electron-microscopy. Clinical examination often includes neuroimaging, such as magnetic resonance imaging (MRI), to evaluate the severity of the disease. Radiological features of CADASIL are similar to those observed in sporadic forms of small vessel disease, at least in the early stages of the disease, and include the presence of extensive white matter hyperintensity, cerebral microbleeds, and lacunes of presumed vascular origin.⁴

The clinical presentation of CADASIL is highly heterogeneous, with substantial variation in the age of onset, clinical symptoms, disease severity, and progression. CADASIL can be accompanied by diverse neurological symptoms, including migraines with aura, gait disturbance, motor dysfunction, seizure, or apathy. Vascular-related cognitive impairment and dementia is a central feature of the disease, with signs of cognitive decline apparent in most CADASIL subjects aged over 35 years.³ Deficits in executive function and processing speed have often been described as the earliest and most prominent cognitive symptom in CADASIL.^{5,6} However, there is evidence for heterogeneity, with previous reports also highlighting significant deficits in language, visuospatial processing, praxis, and memory.^{5,6}

Here we present the case of an early-stage middle-aged CADASIL patient with a predominant decline in memory, in the absence of clinical or imaging evidence of previous hemorrhagic or ischemic stroke. This case shed light on the variability of cognitive symptoms associated with cerebral small vessel disease.

2. Case Description

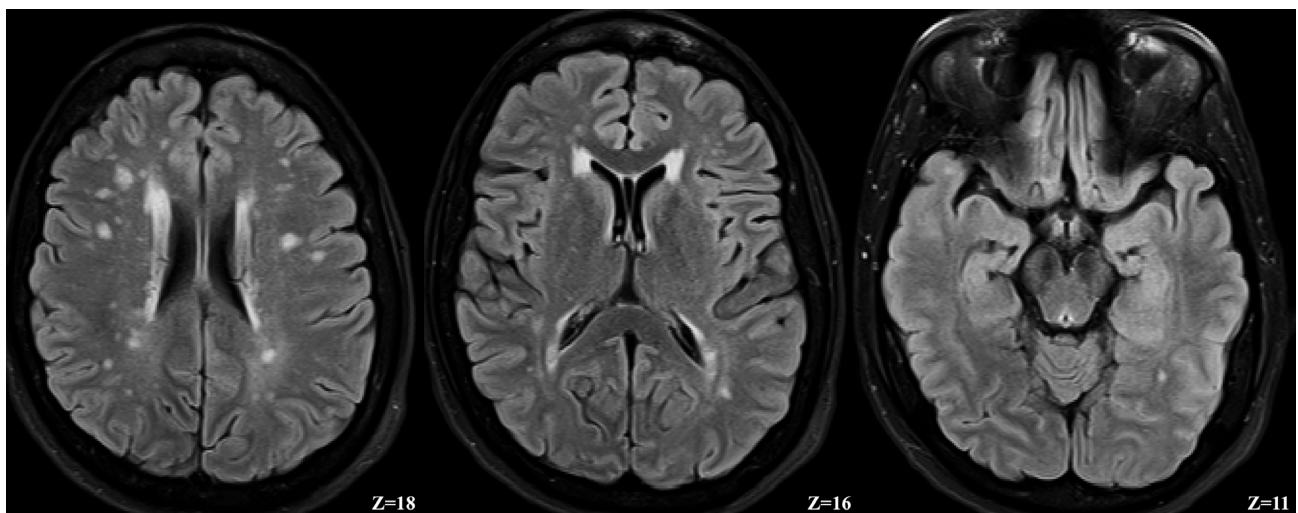
We completed a four-year neuropsychological follow-up of a right-handed 42-year-old woman with CADASIL, from the region of Antioquia in Colombia. The diagnosis was confirmed via evidence of an R1031C mutation on the NOTCH3 gene upon genotyping. At baseline, the patient underwent extensive clinical, neurological and neuropsychological examination, together with a 3-Tesla Magnetic Resonance Imaging (MRI) scan. After a period of four years, the patient was seen again and completed the same neuropsychological evaluation battery.

The patient completed 4 years of formal education, with no evidence of learning difficulties, and currently works as a salesperson. She was initially referred for a neurological consultation at the Neuroscience Group of the University of Antioquia for frequent migraines and repeated episodes of loss of consciousness. Past medical history is significant for chronic sinusitis, hypotension, chronic venous insufficiency, lumbar disc disease, gastritis, and carpal tunnel syndrome. She has a positive family history of CADASIL (the patient's father), and both her father and aunts suffered from cerebrovascular accident (unspecified). Since the age of 17, the patient suffers from frequent migraine-type headaches, occurring 4 to 5 times a month. These migraines last up to 24 hours and are sometimes accompanied by nausea. There is no report of aura preceding migraine episodes. The patient experienced a major depressive episode in her twenties, during which she endured periods of anhedonia. These symptoms occurred in the context of a grieving process but eventually resolved. The patient never had a traumatic brain injury, and her developmental history is unremarkable.

2.1 Neuroimaging Presentation

An MRI scan was performed at the Hospital Pablo Tobón Uribe (Colombia) within one month of the baseline neuropsychological evaluation. The patient presented significant areas of white matter hyperintensity in periventricular regions, as well as in the cerebral white matter (see Figure 1). There was no evidence of cerebral microbleeds, lacunes, microinfarcts, or chronic ischemic or hemorrhagic lesions suggestive of previous strokes. Visual examination of MRI images did not reveal significant ventricular or sulcal enlargement indicative of atrophy.

Figure 1. White Matter Hyperintensity on Fluid-Attenuated Inversion Recovery. Presence of white matter hyperintensity in the CADASIL case, visualized on a fluid-attenuated inversion recovery (FLAIR) in the semioval centers, corona radiata, and some small ones in the temporal poles. Coordinates in the Montreal Neurological Institute (MNI) space are presented on the bottom right corner of each slice.



2.2 Neuropsychological Evaluation Results

Neuropsychological evaluations were administered by a neuropsychologist at the University of Antioquia. Tests were administered in Spanish, using previously validated translations. Raw scores on individual tests were transformed into Z-scores adjusted for age and education, based on published normative data.⁷ This data transformation adjusts the values to work with a standard normal distribution, where the mean is zero and ± 1 standard deviation. To obtain domain-specific composite scores, Z-scores were averaged across tests primarily assessing a specific cognitive function, as displayed in Table 1. To further characterize the pattern of cognitive decline in this patient, we plotted her scores against those obtained in thirteen non-carrier subjects (9 females, 4 males; Figure 2-A) that were also followed for a duration of four years (mean: 4.2 years, SD: 0.4), and presented similar sociodemographic features (mean age: 44.5, SD: 10.3; mean education: 7.8, SD: 4.2).

At baseline, the patient's physical and neurological examinations were unremarkable. She did not report sleep or appetite disturbances. The level of depressive symptoms, assessed via questionnaires, was in the normal range. She was not taking any medication, except for the occasional use of acetaminophen. She denied smoking, consuming alcohol, or taking psychoactive drugs. She complained of memory difficulties, such as not remembering the content of books, but specified that this did not interfere with her daily life activities. The patient presented globally preserved cognitive abilities, with performances across most neuropsychological tests falling in the Average range (Table 1). Her lowest scores were found on tasks of semantic fluency (animal naming) and set shifting (perseveration errors). It is, however, difficult to interpret the clinical relevance of these findings: We did not have an accurate estimate of her premorbid functioning, and factors associated with the patient's background could have influenced these results.

At the follow-up evaluation, the patient complained of increasing memory difficulties. She perceived a decrease of around 20% in her memory abilities. Still, she was able to manage daily life activities independently. She did not notice problems concentrating, no behavioral changes, or difficulty planning a task. Her family also reported an increase in memory difficulties.

No significant medical events, or changes in medication, were reported between baseline and follow-up. The level of depressive symptoms remained low and in the normal range. While performance on tasks assessing global cognition was in the Average range, the patient lost three points on the MMSE (-1 on Attention and Calculation, and -2 on Language), with a raw score of 27/30. Consistently with the baseline evaluation, the patient's performance remained in the Average range across most cognitive domains, including language, processing speed/attention (evaluated with Trail Making Test A, Digit-Symbol Coding (WAIS-III)), executive function (evaluated with Phonemic Fluency (F-A-S), WCST – Perseveration), and visuoconstructional praxis. However, her performance on the memory domain was more variable, with some scores now falling in the Borderline and Extremely Low range. The patient appeared aware of cognitive deficits, with an increase in both informant- and self-ratings of subjective memory decline (Figure 2-B), suggesting an absence of anosognosia sometimes accompanying cognitive impairment.

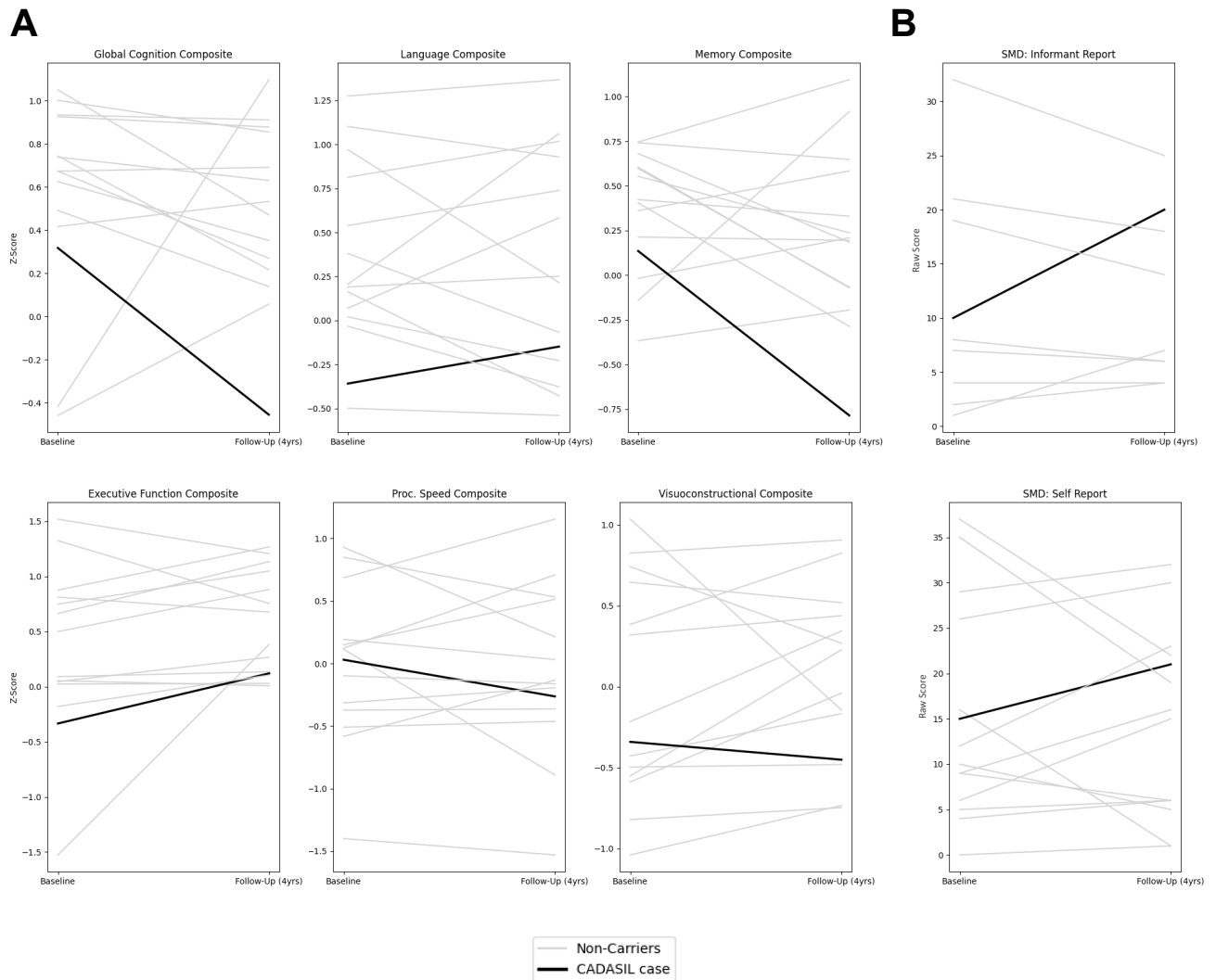


Figure 2. Longitudinal Progression of Cognitive Symptoms. Plots representing the longitudinal progression of cognitive symptoms over four years across A) cognitive domains, and B) Self- and informant- ratings of subjective memory decline (SMD) in the CADASIL case (black) and in non-carrier individuals (grey).

Table 1. Summary of cognitive performance of the CADASIL case

	Baseline	4-Year Follow-Up
	Z-score (qualitative range)	Z-score (qualitative range)
Global Cognitive Functioning		
MMSE	0.73 (High Average)	-0.58 (Average)
CERAD Total Score	-0.10 (Average)	-0.33 (Average)
Language/Semantics		
Boston Naming Test – 15 items	0.11 (Average)	0.11 (Average)
Semantic Fluency (Animals)	-0.83 (Low Average)	-0.41 (Average)
Memory		
Word List Learning - Total Learning	0.67 (Average)	-0.11 (Average)
Word List Learning – Delayed Recall	-0.08 (Average)	-0.55 (Average)
Word List Learning – Recognition	0.46 (Average)	0.46 (Average)
Constructional Praxis - Recall	0.43 (Average)	-1.02 (Low Average)
MIS – Total Free Recall	-0.47 (Average)	-1.79 (Borderline)
MIS – Total Free & Cued Recall	-0.38 (Average)	-3.38 (Extremely Low)
Processing Speed/Attention		
Trail Making Test A	0.52 (Average)	-0.12 (Average)
Digit-Symbol Coding (WAIS-III)	-0.46 (Average)	-0.41 (Average)
Executive Function		
Phonemic Fluency (F-A-S)	0.12 (Average)	0.03 (Average)
WCST - Perseveration	-0.78 (Low Average)	0.21 (Average)
Visuoconstructional Praxis		
Constructional Praxis - Copy	-0.41 (Average)	-0.41 (Average)
ROCFT - Copy	-0.27 (Average)	-0.49 (Average)

Presented values are Z-scores normalized for age and education (qualitative range of performance), using previously published normative data. MMSE – Mini Mental State Examination; CERAD – Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery; MIS – Memory Impairment Screen; WAIS-III – Third Edition of the Wechsler Adult Intelligence Scale; WCST – Wisconsin Card Sorting Test; ROCFT – Rey-Osterrieth Complex Figure Test. Qualitative range of performance was determined as such: ≤ 1 Percentile Rank = Extremely Low; 2-9 Percentile rank = Borderline; 9-24 Percentile Rank = Low average; 25-74 Percentile Rank = Average; 75-90 Percentile rank = High average; 91-97 Percentile Rank = Superior; ≥ 98 Percentile Rank = Very Superior.

3. Discussion

This case report describes the longitudinal progression of cognitive symptoms in a 42-year-old Hispanic woman from Colombia, who is a carrier of the R1031C NOTCH3 mutation, with an extensive family background of CADASIL.

The R1031C mutation in NOTCH3 affects the 26th EGF-like repeat. Carriers of this mutation have an age of first stroke around 51 years and an age of the onset of dementia around 54.7 years, similar to those reported in other CADASIL patients.^{3,8} At her early age, she was in an early stage of the disease, with a personal history of migraine without aura but no clinical or imaging evidence of stroke, however, showed a predominant memory decline over a period of four years.

Based on available information, the selective memory decline did not seem driven by the onset of strokes, nor by underlying psychiatric or medical co-morbidities. Impairments in memory did not seem secondary to executive function or attentional deficits, as performance on tasks assessing these functions remained relatively unaffected. Additionally, there was no use of medications that could affect test performance.

Depression is a common psychiatric symptom in CADASIL that can mediate cognitive presentation. However, the patient did not report mood disturbances at the baseline or follow-up evaluation.

Patients with migraine often report subjective cognitive complaints, and predominant deficits in neuropsychological tests are typically observed in the domains of language and general cognition.⁹ Profiles characterized primarily by a pure progressive amnesic decline, as in this patient, are rarely found.

This patient did not have any other risk factors for secondary cognitive decline, such as sleep disorders, sleep apnea, hearing impairment, chronic alcohol consumption, psychoactive substance use, or previous traumatic brain injuries. Despite being overweight, the patient did not have other cardiovascular risk factors such as high blood pressure, diabetes, dyslipidemia, or smoking. Although there was no new neuroimaging available during follow-up, she did not report symptoms, nor were any signs found to suggest an acute symptomatic stroke during the physical examination.

Because of the young age of the patient, it is also highly unlikely that the memory decline is related to underlying neurodegenerative pathologies, such as Alzheimer's disease. These findings suggest that the observed memory decline is secondary to the presence and progression of CADASIL.

Studies have often described deficits in executive function or processing speed as the chief cognitive manifestations of vascular contributions to cognitive impairment and dementia.¹⁰ Previous studies carried out in our group with participants with mutations in NOTCH3, found that in the early stages, the neurocognitive profile was characterized by a deficit in executive functions, with slowing processing speed, and low verbal fluency.⁶

Another study carried out on patients with CADASIL at different clinical stages reveals that individuals between 41.7 and 58.3 years old show a slowdown in processing speed and a decrease in cognitive flexibility. These changes become evident from the age of 25. Some patients, concomitant

to these changes, may exhibit memory failures in Total Free Recall tests with a slight decrease in sensitivity to cueing, but Delayed Total Recall remains intact. Nevertheless, in this patient, Delayed Total Recall was significantly affected compared to her baseline evaluation, which did not benefit from the use of cues and with nonsignificant compromise in other domains.¹¹

The present case report challenges previous concepts by showing that other cognitive functions can be primarily targeted and sheds light on the variability of cognitive deficits of vascular etiology. Our report is consistent with previous studies demonstrating an important overlap between the cognitive presentation of patients with Alzheimer's disease and Vascular Dementia¹² and illustrates limitations associated with the differential diagnosis of age-related neurodegenerative disorders based solely on the profile of cognitive impairment.

While previous reports have described a slow rate of cognitive decline in CADASIL,¹³ this early-stage CADASIL patient presented a significant decrease in performance on the MMSE and in the Memory domain over a period of four years. Interestingly, the decline predominantly affected memory and was not generalized across cognitive domains. This report is incongruent with the notion that measures of executive function and processing speed are the most sensitive to the presence of cerebral small vessel disease and corroborates the heterogeneity of clinical manifestations in CADASIL. Factors surrounding the phenotypic heterogeneity of CADASIL are still poorly understood and require further investigation. The genotype, sex, and environmental factors (e.g. cardiovascular risk factors) have been discussed as potential factors influencing the disease presentation and trajectory in CADASIL.^{8,14} However, additional longitudinal studies are needed to better characterize factors influencing the pattern of cognitive decline in this clinical population.

A limitation of this case report is the small number of individuals who were available for the 4-year follow-up with the same neuropsychological tests. While these findings allow us to observe trends in the performance of cognitive domains among the evaluated participants, it does not provide enough data to conduct a statistical analysis due to the limited sample size. Therefore, continued monitoring of these participants and their families over time is crucial, remaining attentive to amnesic complaints in other patients at early stages of CADASIL.

The longitudinal follow-up of this patient provided a unique opportunity to evaluate intra-individual variations in cognitive performance and to further elucidate the nature and progression of CADASIL-related cognitive impairments.

References

1. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* [Internet]. 1996 Oct 24 [cited 2016 Dec 4];383(6602):707–10. DOI: [10.1038/383707a0](https://doi.org/10.1038/383707a0)
2. Joutel A, Vahedi K, Corpechot C, Troesch A, Chabriat H, Vayssière C, et al. Strong clustering and stereotyped nature of Notch3 mutations in CADASIL patients. *The Lancet* [Internet]. 1997 Nov 22 [cited 2017 Feb 23];350(9090):1511–5. DOI: [10.1016/S0140-6736\(97\)08083-5](https://doi.org/10.1016/S0140-6736(97)08083-5)

3. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserre E, Bousser MG. CADASIL. *Lancet Neurol*. 2009 Jul;8(7):643–53. DOI: [10.1016/S1474-4422\(09\)70127-9](https://doi.org/10.1016/S1474-4422(09)70127-9)
4. Schoemaker D, Quiroz YT, Torrico-Teave H, Arboleda-Velasquez JF. Clinical and research applications of magnetic resonance imaging in the study of CADASIL. Vol. 698, *Neuroscience Letters*. Elsevier Ireland Ltd; 2019. p. 173–9. DOI: [10.1016/j.neulet.2019.01.014](https://doi.org/10.1016/j.neulet.2019.01.014)
5. Buffon F, Porcher R, Hernandez K, Kurtz A, Pointeau S, Vahedi K, et al. Cognitive profile in CADASIL. *J Neurol Neurosurg Psychiatry*. 2006 Feb;77(2):175–80. DOI: [10.1136/jnnp.2005.068726](https://doi.org/10.1136/jnnp.2005.068726)
6. Zuluaga-Castaño Y, Andrés Montoya-Arenas D, Velilla L, Ospina C, Arboleda-Velasquez JF, Quiroz YT, et al. Cognitive performance in asymptomatic carriers of mutations R1031C and R141C in CADASIL. Desempeño cognitivo en portadores asintomáticos de las mutaciones R1031C y R141C en CADASIL. *Int j psychol res*. 2018;11(2):46–55. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7110283/>
7. Torres VL, Vila-Castelar C, Bocanegra Y, Baena A, Guzmán-Vélez E, Aguirre-Acevedo DC, et al. Normative data stratified by age and education for a Spanish neuropsychological test battery: Results from the Colombian Alzheimer's prevention initiative registry. *Applied Neuropsychology:Adult*. 2021;28(2):230–44. DOI: [10.1080/23279095.2019.1627357](https://doi.org/10.1080/23279095.2019.1627357)
8. Ospina C, Arboleda-Velasquez JF, Aguirre-Acevedo DC, Zuluaga-Castaño Y, Velilla L, Garcia GP, et al. Genetic and nongenetic factors associated with CADASIL: A retrospective cohort study. *J Neurol Sci*. 2020 Dec 15;419. DOI: [10.1016/j.jns.2020.117178](https://doi.org/10.1016/j.jns.2020.117178)
9. Gu L, Wang Y, Shu H. Association between migraine and cognitive impairment. *Journal of Headache and Pain*. 2022 Dec 1;23(1). DOI: [10.1186/s10194-022-01462-4](https://doi.org/10.1186/s10194-022-01462-4)
10. O'Brien JT, Erkinjuntti T, Reisberg B, Roman G, Sawada T, Pantoni L, et al. Vascular cognitive impairment. *Lancet Neurol*. 2003 Feb 1;2(2):89–98. DOI: [10.1016/S1474-4422\(03\)00305-3](https://doi.org/10.1016/S1474-4422(03)00305-3)
11. Brice S, Reyes S, Jabouley A, MacHado C, Rogan C, Gastellier N, et al. Trajectory Pattern of Cognitive Decline in Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy. *Neurology*. 2022 Sep 6;99(10):E1019–31. DOI: [10.1212/WNL.0000000000200805](https://doi.org/10.1212/WNL.0000000000200805)
12. Reed BR, Mungas DM, Kramer JH, Ellis W, Vinters H V., Zarow C, et al. Profiles of neuropsychological impairment in autopsy-defined Alzheimer's disease and cerebrovascular disease. *Brain*. 2007;130(3):731–9. DOI: [10.1093/brain/awl385](https://doi.org/10.1093/brain/awl385)
13. Liem MK, Lesnik Oberstein SAJ, Haan J, Van Der Neut IL, Ferrari MD, Van Buchem MA, et al. MRI correlates of cognitive decline in CADASIL A 7-year follow-up study [Internet]. 2009. Available from: www.neurology.org. DOI: [10.1212/01.wnl.0000339038.65508.96](https://doi.org/10.1212/01.wnl.0000339038.65508.96)
14. Singhal S, Bevan S, Barrick T, Rich P, Markus HS. The influence of genetic and cardiovascular risk factors on the CADASIL phenotype. *Brain*. 2004 Aug 2;127(9):2031–8. DOI: [10.1093/brain/awh223](https://doi.org/10.1093/brain/awh223)

Ethics Disclosure

The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine at the University of Antioquia on September 12, 2019.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing Interests

Drs. Quiroz and Lopera serve as consultants for Biogen. All other authors declare that they have no competing interests.

Authorship Roles

- **Carolina Ospina:** Investigation, Data Curation, Data Analyses, Writing
- **Dorothee Schoemaker:** Conceptualization, Investigation, Data Curation, Data Analyses, Writing
- **Lina Marcela Velilla:** Investigation, Data Curation, Methodology, Writing (Review & Editing)
- **Yesica Zuluaga:** Investigation, Data Curation, Writing (Review & Editing)
- **Francisco Lopera:** Funding Acquisition, Resources, Supervision, Writing (Review & Editing)
- **Joseph F. Arboleda-Velasquez:** Conceptualization, Resources, Supervision, Writing (Review & Editing)
- **Yakeel T. Quiroz:** Conceptualization, Methodology, Project Administration, Resources, Supervision, Writing (Review & Editing)