Cultural Diversity in Neuropsychological Assessment
Developing Understanding through Global Case Studies
Farzin Irani, Desiree Byrd

Diagnostic Challenges in Remote Communities from Colombia

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Section I: Background Information

Terminology and Perspective

People from Colombia are referred to as Colombian, while Colombians who were born and raised in the Departments of Antioquia, Caldas, and Quindío are called Paisas. We will use the words Paisa and Colombian throughout to describe cultural, social, and historical perspectives of the Paisa culture and their relationships to clinical neuropsychology in the region of Antioquia in Colombia.

The first and senior authors are Paisa neuropsychologists trained in Colombia and the United States. The first author currently conducts clinical research and neuropsychological assessments of patients with neurodegenerative diseases at the Group of Neuroscience of Antioquia (GNA) in Colombia. The senior author leads a longitudinal biomarker study of paisa families with familial Alzheimer’s disease in Boston, Massachusetts.

In this chapter, we will share the story of Roberto, originally from the mountains of Antioquia, Colombia. He first showed behavioral changes at age 40 including loss of motivation and sadness. He referred to himself as “a plague” to express feelings of inferiority and low self-esteem in the context of neuropsychiatric symptoms for which he was diagnosed with bipolar disorder (BD). After five years into treatment for those behavioral and mood changes, Roberto and his wife did not observe significant improvements and the differential diagnosis began to include multiple sclerosis (MS). Ultimately, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) was diagnosed. Through Roberto’s case, we will highlight the link between relevant clinical/cognitive and cultural/historic aspects uniquely inherent in the Antiochian culture, which can make a difference in the approach used to determine accurate differential diagnoses.

Geography

The Republic of Colombia is a northwestern South American country. It is bordered by Panama, Venezuela, Brazil, Ecuador, and Peru. The Department of Antioquia is located in northwestern Colombia, in South America, with coastal areas stretching to both the Atlantic and Pacific Oceans. Its landscape is characterized by a mix of valleys and mountains, with altitudes reaching up to 4,000 meters. The territory of Antioquia presents a great diversity of ecosystems, from coastal plains, dry and deep forests, and Andean forests, to the high mountains of the central and Western mountain ranges. A network of rivers irrigates these ecosystems connecting the highlands and lowlands. The geological changes implicated in the evolution of the Antioquia ecosystem led to a concentration

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of gold. The geographical features of Antioquia’s territory are deeply connected to the mining tradition and social, economic, and cultural aspects. Antioquia encompasses both urban and rural communities, with nearly a quarter of the population living in rural or remote areas.

**History**

The term “Paisa culture” has been widely used in Colombia to refer to the values, customs, and history of Antioqueños. Colombia is a diverse country with each region and sub-region within the country having different customs, ethnicities, accents, and cultural anchors. The characteristic diversity of Colombia is rooted in its history of Spanish colonizing missions. These were decisive in the socio-geographic divisions of the country and because of them some sub-regions experienced stronger racial segregation while others had greater ethnic and racial admixture with subsequently different processes of socioeconomic development. Specifically, during the first decade of the XVI century, Antioquia faced invasive colonization by Spanish conquerors and during the 16th and 17th centuries, the Antioquia population grew by the admixture of Antioquia natives and Spanish colonists. Since its population is mainly expanded by internal growth, Antioquia is considered genetically isolated and presents a relatively high prevalence of genetic diseases. In addition, since the Antioquia population especially experienced greater isolation and a movement toward internal colonization, this also impacted the configuration of the political and economic history of the entire country. The ethnic segregation that happened during the colonization helps to understand the highly genetically based components of neuropsychiatric clinical conditions prevalent in Antioquia and highlights the importance of paying attention to family history and genealogy in clinical conditions in those from Antioquia.

**People**

When evaluating behavioral and emotional changes among Colombians, Paisas, and Latinos is always important to account for unique cultural backgrounds. Frequently, behavioral scales are designed from Western cultural standards, which might not fit into Latin American socially accepted behaviors. Even more, it is not possible to have a homogenous cultural code or standard among Colombians due to each geographic region in the country having unique cultural parameters and characteristics.

In our case, we will observe how Roberto initially started to present himself as someone very concerned about cleaning and became quieter and more reluctant to socially share. These behaviors can be concerning for someone who used to be socially engaged and belongs to a cultural region generally known for being very social, open, talkative, and welcoming. This highlights the importance of performing deep clinical interviews together with administering behavioral scales to compare personality changes against pre-morbid personality traits and in the context of generally accepted social standards.

**Language and Communication**

Colombians have Spanish as the main and official language. The remaining indigenous communities in Colombia are bilingual and can communicate fluently in both Spanish and their dialect. It is worth knowing that Colombia is known for its extensive diversity of idioms according to the geographical region. Thus, it is necessary for a neuropsychologist evaluating Colombians to be aware that there are many different words available to name things. For example, when patients perform semantic fluency tests (fruits and animal), it is suggested to perform an exhaustive search using a
thESAURUS to ensure correct scoring. Rural patients, in particular, are likely to use frequent expositions to elements of nature and produce lots of names of animals and fruits that may be unknown to an urban neuropsychologist.\textsuperscript{8,9} Similarly, it is important to pay attention to the need to allow a range of words on naming tests due to the large number of different words that can be used to name objects across regions in Colombia.\textsuperscript{10} On the other hand, when evaluating phonemic fluency using F, A, S letters, it is important to consider that this may introduce bias among Spanish-speaking populations since those particular letters are based on the frequency of words in English.\textsuperscript{11}

\textbf{Education and Socioeconomic Status}

The Colombian education system includes elementary, secondary (including high school), and graduate schooling. Elementary education consists of five years, and secondary education takes an additional six years.\textsuperscript{12} When someone from Colombia completes basic education (elementary and secondary), that person has a total of 11 years of education. Regarding economics, Colombia is classified as an upper-middle-income country. However, a considerable proportion (i.e., 14\%) of Antioquia’s population lives below the poverty line and reports unsatisfied basic needs. Most of the underserved people in Antioquia live in rural areas or segregated areas of urban centers.\textsuperscript{13} Education and socioeconomic background are important considerations for cognitive evaluations and behavioral analysis. The clinical case we are sharing was evaluated using norms according to the patient’s education, and exploration of his neuropsychiatric symptoms was oriented to his socio-cultural background. These are important considerations when evaluating people from Colombia since socially accepted behaviors, habits, and customs may change according to socioeconomic influences.

\textbf{Health Status}

Patients in Antioquia face significant geopolitical and socioeconomic barriers to the diagnosis and treatment of neurological and neurocognitive disorders. This includes reduced access to differentiated healthcare services, long wait times, limited follow-ups, incomplete medical records, unreliable disease coding systems, and others.\textsuperscript{14} We will see those conditions reflected in Roberto’s case since he spent several years without an accurate diagnosis and received suboptimal medical treatment.

As noted, Antioquia has a genetic kindred of neurodegenerative and psychiatrist diseases including the biggest family groups in the world with early-onset Alzheimer’s disease,\textsuperscript{15} a family group with CADASIL,\textsuperscript{16} a family cluster of BD\textsuperscript{17} and attention deficit hyperactivity disorder.\textsuperscript{18} Therefore, within the context of Antioquia’s history, it is very important to perform a complete genealogy when a patient complains about cognitive, behavioral, and emotional disturbances. We will show later in the case how the family history of our patient was key to elucidate the differential diagnosis.

\textbf{Approach to Neuropsychological Evaluations}

The neuropsychological evaluation of Paisas comes with its challenges. Spanish translations of neuropsychological tests are not always available or adapted to the linguistic and cultural characteristics of Antioquia’s population. Due to socioeconomic constraints and scarce resources for funding, it has been widely difficult in Latin American to conduct research to validate and culturally adapt cognitive tools. The scarcity of normative data and validated cognitive tools in Latin America often leads researchers to use normative data derived from other Spanish-speaking countries. However, this may not appropriately reflect the sociodemographic features of specific regions, including different levels of educational and occupational attainment.
Recognizing the importance of culturally appropriate cognitive assessment, our group has engaged in efforts to adapt and validate common neuropsychological tests for the evaluation of neurocognitive disorders in Antioquia’s patient population. This has included tests from the Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) neuropsychological battery and the Face-Name Associative Memory Exam (FNAME). We also recently published comprehensive population-based normative data stratified by age and education for specific use in Colombian patients, thereby significantly improving our abilities to interpret results from neuropsychological tests in patients from Colombia.

In addition, for more than 30 years, the Group of Neuroscience of Antioquia (GNA) has followed large extended families with genetic mutations leading to neurodegenerative diseases. The GNA is a multidisciplinary team that includes neurologists, psychiatrists, family medicine physicians, nurses, gerontologists, speech therapists, clinical psychologists, and neuropsychologists. From the beginning, the GNA has sent clinical and research teams to rural areas in Antioquia to facilitate access to evaluation, diagnosis, and research participation for individuals living in remote areas.

Over the years, the GNA has established a registry of these extended families with genetic mutations leading to neurodegenerative diseases. Our registry regroups individuals presenting with and without cognitive or neurological symptoms. Upon enrollment, every patient completes a comprehensive evaluation of their family history. The investigation of family history and family trees is especially relevant in this context to assist with the identification of possible inheritance patterns among relatives across generations. Patients also undergo comprehensive neurological and neuropsychological evaluations. After the initial evaluation, members of our team meet to discuss findings, propose a probable diagnosis, and establish a treatment plan. The longitudinal follow-up of patients enrolled in the registry is another important aspect of the GNA’s framework. This allows the careful monitoring of disease progression and appropriate adjustment of the clinical management plan. In addition to building a rich dataset for clinical research, enrollment in this program provides families with access to annual medical and cognitive evaluations. Since most members of these families live in rural areas of Antioquia, these services would otherwise often not be available to them.

One of the cohorts we have been following at the GNA includes individuals from large families with mutations in the NOTCH3 gene leading to a neurodegenerative condition known as CADASIL. We have identified and enrolled over 200 subjects with CADASIL, due to R1031C, C455R, and R141C mutations in the NOTCH3 gene, in our registry. Individuals with CADASIL develop cerebral small vessel disease at a young age and are prone to suffer from recurrent ischemic strokes and vascular dementia at a young age. CADASIL is a low prevalence syndrome and a rare disease, leading to frequent misdiagnosis, especially in non-specialized settings.

Section II: Case Study — “When the Clinical History Is Bewildering, the Family History Enlightens”

Roberto was a 49-year-old man who was born and raised in Antioquia, Colombia. He was married with no children and lived with his wife in the city of Medellin-Antioquia. He completed 11 years of formal education, which is the equivalent of a high school degree in Colombia. His developmental history was unremarkable, and he showed no evidence of learning difficulties. He held different occupations throughout his life, such as taxi driver, security guard, and bicycle mechanic, but had been retired since 2015. In Colombia, the typical retirement age is 57 for women and 62 for men. However, a person that is disabled due to a job injury or a chronic medical condition can qualify for retirement at a younger age.

Roberto was first seen at the GNA in 2017, accompanied by his wife, because of a history of progressing behavioral changes. He was seen again approximately two years later, in early 2020,
for a follow-up neuropsychological evaluation. Since the GNA follows the population for several years, it is often possible to have a detailed history of disease evolution from baseline until the last outcomes. However, this is not true more broadly in Colombia or Latin America, where due to difficulties accessing health care and specialized medical providers, it is hard for patients to receive longer-term follow-ups.

**History of Presenting Symptoms**

A detailed interview with Roberto and his wife, together with a review of his medical chart, suggested that initial behavioral changes occurred approximately eight years ago (2009) when he was 41, and consisted mainly of significant mood disturbances. He started presenting with emotional lability (uncontrollable crying), auditory hallucinations (hearing voices encouraging him to hit someone or throw himself off the window), increased irritability, and aggressiveness toward himself and others. His wife further reported compulsion with cleaning and explained that he cleans the house up to three times a day. She described an episode during which her husband was found cleaning the bathroom at a friend’s house during a visit. These symptoms were a marked departure from his pre-morbid status. After consulting with a private psychiatrist, he was diagnosed with BD and started to receive treatment with a mood stabilizer (Lithium) and antidepressants (sertraline, and later escitalopram).

In 2014, despite remission of psychotic symptoms, there was no significant improvement in psychoactive symptoms, and he showed increasing irritability, impulsivity, and anhedonia. His wife also noticed that he was experiencing difficulties in handling financial transactions and was becoming increasingly forgetful. She described her husband as forgetting to pay bills and important dates. Examination by a private neurologist, together with an MRI showed signs of white matter lesions which led to an additional diagnosis of MS. Treatment with betaferon (interferon beta-1b) was initiated in early 2015. The patient’s wife explained that no improvements were observed with this new medication over the following two years. Instead, she noticed a progression of symptoms, including the onset of ptosis, loss of sensation in his limbs, loss of strength in lower limbs, unusual lip/mouth movements considered to be Bell’s palsy, frequent falls, and sensory hallucinations (i.e., the patient would say that he has “animals in his face and ears”). However, because of limitations associated with Roberto’s medical insurance, he had irregular access to medical follow-up with his psychiatrist and neurologist, and no further medical investigations were pursued at the time.

**Initial Clinical Interview**

During the initial medical interview at the GNA, Roberto came accompanied by his wife and was cooperative. He reported a sedentary lifestyle and denied smoking tobacco, drinking alcohol, or taking recreational drugs. At the time of the interview, he complained about a heavy global oppressive headache and a global sense of fatigue. He further endorsed current symptoms of depression, including a sense of worthlessness and passive suicidal ideation. Sleep disturbances and a lack of appetite were also reported. He however felt that the sleep disorder was likely a consequence of intermittent sleep patterns he had to adapt over the last two decades because of his prior work as a security guard and taxi driver. He reported taking quetiapine nightly for management of sleep difficulties. The clinical interview further highlighted memory and word-finding difficulties, as well as disorientation to time and space.

At the beginning of symptoms, Roberto presented irritability, motor restlessness, aggressiveness, auditory hallucinations, and obsession with cleaning. At the clinical interview, his wife said that they stopped visiting friends and engaging socially due to his husband’s behavioral changes, she explained that they felt embarrassed for the situation and experienced loneliness and isolation.
This situation is not exceptional since, in Antioquia, it is still needed to raise awareness about mental disease stigma and education in the community to improve social support for people with mental diseases. Roberto and his wife were advised by the GNA psychologist about strategies to cope with mood disturbance and to improve their socialization.

The medical history further highlighted the frequent occurrence of pulsatile, insidious frontal region headaches, without aura, for the past three years, which usually improved with acetaminophen. He did not have a history of hypertension, diabetes, or dyslipidemia. Examination of his family history revealed that his father had a history of dementia, his brother and niece had a history of stroke (age 39 and 22, respectively), and his half-sister had been diagnosed with CADASIL. Taking this information into consideration, suspicion for a potential diagnosis of CADASIL was raised by the GNA neurologist, and genotyping for NOTCH3 mutations known to be present in the region of Antioquia was recommended. A neuropsychological evaluation was also performed to characterize the nature and severity of cognitive symptoms.

**Baseline Neuropsychological Evaluation**

The baseline neuropsychological evaluation was administered by a neuropsychologist at the GNA. Since Roberto is Spanish monolingual and does not speak any indigenous language, the evaluation was administered in Spanish using questionnaires and cognitive measures previously adapted and validated for use in patients from Antioquia. Since Roberto had completed secondary school, we used normative data for 11 years of education. In concordance with the clinical interview, the patient’s score on a depression questionnaire revealed the presence of moderate to severe depressive symptoms. His score on a Global Deterioration Scale confirmed the presence of cognitive deficits and suggested a significant decline in cognition from his estimated pre-morbid level of functioning. However, he was still able to perform most Instrumental Activities of Daily Living (IADL) independently. To obtain an objective and unbiased estimation of Roberto’s cognitive performance, his scores were standardized based on normative data recently published by our group and derived from 2,673 cognitively unimpaired individuals from Colombia. The standardized neuropsychological test data for his baseline and follow-up evaluation data are summarized in Table 30.1.

The results of this evaluation highlighted a significant impairment in global cognitive status, with an MMSE score of 22/30. While performance on a confrontational naming task was in the superior range, his performance in semantic fluency (i.e., animal naming) was in the borderline range. Performance on verbal free and cued delayed recall was in the borderline range, suggesting difficulties with verbal episodic memory. Performance on visual free delayed recall was less affected and in the low average range. Performance on tasks assessing processing speed and attention was in the low average range. Finally, performance on tasks assessing executive function and visuoconstructional praxis were unaffected and in the average range. In summary, the initial neuropsychological evaluation revealed a wide range of performance across cognitive domains, ranging from superior to extremely low, with predominant impairments observed on tasks of semantic fluency and memory, tasks commonly linked to dysfunction of temporal lobes systems.

**Initial Clinical Impressions**

The review of the family history by the GNA's neurologist was key in this case, as it shed light on a family history of CADASIL, strokes at an early age, and dementia. The occurrence of frequent headaches, the presence of cognitive impairment, and the family history led to initial suspicions for an alternative diagnosis of CADASIL and a referral to genetic analysis of the NOTCH3 gene. Genotyping was performed shortly after the initial clinical interview at the GNA and confirmed
the presence of an R141C mutation on the NOTCH3 gene. After an interdisciplinary team meeting including neurologist experts in demyelinating diseases, a comorbid diagnosis of MS was judged unlikely. Roberto was given a diagnosis of CADASIL and treatment with betaferon was discontinued. Roberto and his family were invited to follow-up evaluations to characterize the progression of his clinical and cognitive symptoms.

Follow-Up Neuropsychological Evaluation

Roberto, now diagnosed with CADASIL, was seen again by the GNA team after two years. His wife described increasing memory difficulties and spatial disorientation in familiar settings. He reported a lack of appetite and weight loss. There was new onset of slurred speech, which appeared approximately four months before the evaluation. He also complained of numbness in his right arm and weakness in his inferior limbs. He reported mood disturbance, characterized by a general feeling of sadness, frequent unmotivated crying episodes, and passive suicidal ideation. His score on the GDS-15 corroborated the presence of moderate to severe depressive symptoms. He described feeling like a burden to his wife and being worried that she was going to leave him. He also reported auditory hallucinations in the form of “voices telling him to do bad things.”

Table 30.1 Summary of cognitive performance

<table>
<thead>
<tr>
<th></th>
<th>Baseline Z-score (qualitative range)</th>
<th>Follow-up Z-score (qualitative range)</th>
<th>Changes in performance Δ Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Global Cognitive Functioning</strong>&lt;sup&gt;19,28&lt;/sup&gt;</td>
<td>MMSE –3.66 (extremely low) –3.66 (extremely low)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CERAD Total Score –1.46 (borderline) –1.56 (borderline)</td>
<td>–0.10</td>
<td></td>
</tr>
<tr>
<td><strong>Language/Semantics</strong>&lt;sup&gt;19,28&lt;/sup&gt;</td>
<td>Boston Naming Test—15 items 1.37 (superior) 1.37 (superior)</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Semantic Fluency (Animals) –1.45 (borderline) –1.83 (borderline)</td>
<td>–0.38</td>
<td></td>
</tr>
<tr>
<td><strong>Memory</strong>&lt;sup&gt;19,28,29,30&lt;/sup&gt;</td>
<td>Word List Learning—Total –2.04 (borderline) –1.27 (low average)</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immediate Recall –1.85 (borderline) –1.27 (low average)</td>
<td>0.58</td>
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<tr>
<td></td>
<td>Delayed Recall –1.52 (borderline) –0.50 (average)</td>
<td>1.02</td>
<td></td>
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<tr>
<td></td>
<td>Word List Learning—Recall –0.78 (low average) –1.52 (borderline)</td>
<td>–0.74</td>
<td></td>
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<tr>
<td></td>
<td>Constructional Praxis—Recall –0.77 (low average) –1.05 (low average)</td>
<td>–0.38</td>
<td></td>
</tr>
<tr>
<td><strong>Processing Speed/Attention</strong>&lt;sup&gt;10,31&lt;/sup&gt;</td>
<td>Trail Making Test A –1.22 (low average) –2.58 (extremely low)</td>
<td>–1.36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Digit-Symbol Coding (WAIS-III) –1.30 (low average) –1.54 (borderline)</td>
<td>–0.24</td>
<td></td>
</tr>
<tr>
<td><strong>Executive Function</strong>&lt;sup&gt;12,33&lt;/sup&gt;</td>
<td>Phonemic Fluency (F-A-S) 2.64 (very superior) 3.07 (very superior)</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WCST—Perseveration 0.35 (average) –0.06 (average)</td>
<td>–0.41</td>
<td></td>
</tr>
<tr>
<td><strong>Visuoconstructual Praxis</strong>&lt;sup&gt;19,29,30&lt;/sup&gt;</td>
<td>Constructional Praxis—Copy 0.75 (average) –1.09 (low average)</td>
<td>–1.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ROCFT—Copy –0.21 (average) –2.57 (extremely low)</td>
<td>–2.36</td>
<td></td>
</tr>
</tbody>
</table>

Presented values are Z-scores normalized for age and education (qualitative range of performance), using previously published normative data derived from a Colombian sample.<sup>28</sup> MMSE—Mini-Mental State Examination; CERAD—Consortium to Establish a Registry for Alzheimer’s Disease neuropsychological battery; 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.

the presence of an R141C mutation on the NOTCH3 gene. After an interdisciplinary team meeting including neurologist experts in demyelinating diseases, a comorbid diagnosis of MS was judged unlikely. Roberto was given a diagnosis of CADASIL and treatment with betaferon was discontinued. Roberto and his family were invited to follow-up evaluations to characterize the progression of his clinical and cognitive symptoms.

Follow-Up Neuropsychological Evaluation

Roberto, now diagnosed with CADASIL, was seen again by the GNA team after two years. His wife described increasing memory difficulties and spatial disorientation in familiar settings. He reported a lack of appetite and weight loss. There was new onset of slurred speech, which appeared approximately four months before the evaluation. He also complained of numbness in his right arm and weakness in his inferior limbs. He reported mood disturbance, characterized by a general feeling of sadness, frequent unmotivated crying episodes, and passive suicidal ideation. His score on the GDS-15 corroborated the presence of moderate to severe depressive symptoms. He described feeling like a burden to his wife and being worried that she was going to leave him. He also reported auditory hallucinations in the form of “voices telling him to do bad things.”
Roberto also now required assistance with instrumental activities of daily living, including selecting his clothes and dressing. He had difficulty using familiar objects, including utensils and the telephone, and needed reminders related to personal hygiene (i.e., taking a shower). His score on the Global Deterioration Scale corroborated the severity of cognitive decline, and now suggested the presence of dementia. Over the past years, there were also issues with accessing medications prescribed for the management of his affective and behavioral symptoms due to limitations associated with their insurance policy. His wife described a sense of exhaustion due to caregiver burden, which was exacerbated by a lack of social support.

To objectively characterize the pattern of cognitive decline over time, Roberto completed the same neuropsychological evaluation battery as during his initial visit (see Table 30.1). The neuropsychological evaluation revealed a mix of both preserved and declining cognitive functions over the last two years. The MMSE score remained unchanged, at 22/30. Congruently, global cognitive functioning estimated with the CERAD total score was stable and in the borderline range. Performance on tests assessing language/semantics and executive function also remained relatively stable when compared to performance at the baseline evaluation. In contrast, a decline in performance was noted on tasks involving visuoconstructional praxis. Performance on both the copy of the Rey-Osterrieth Complex Figure Test (ROCT) and the CERAD Constructional Praxis, which was in the average range at the baseline visit, now dropped to the low average to extremely low range. There was also a notable reduction in performance on the Trail Making Test A, suggesting progressive impairment in visuospatial attention and processing speed. Interestingly, scores for verbal memory improved in comparison to the previous evaluation. On the other hand, his score on nonverbal memory tasks showed a trend toward a reduction in performance, possibly secondary to impairments in visuoconstructional praxis.

**Follow-Up Clinical Impressions**

After two years, Roberto, now with a diagnosis of CADASIL, was seen by members of the GNA for a follow-up evaluation highlighting the onset of new physical symptoms, including slurred speech, weakness in inferior limbs, and numbness in the right arm. He was depressed and anxious and experienced auditory hallucinations. He was increasingly dependent on his wife for daily life activities, needed assistance to dress, and had difficulties using familiar objects, indicating a progression of dementia syndrome. On objective cognitive testing, he displayed a prominent decline in visuoconstructional abilities. The GNA team concluded that the pattern of physical and cognitive deterioration was likely associated with the progression of cerebrovascular changes linked to CADASIL, and consistent with the presence of vascular dementia. Unfortunately, because of limited resources in this setting, we did not have access to neuroimaging data to explore potential neurological correlates of this decline.

**Discussion**

CADASIL is a genetic disorder leading to the early and progressive onset of cerebral small vessel disease. Patients with CADASIL often suffer from recurrent ischemic strokes and develop vascular cognitive impairment at a young age, typically in the absence of conventional cardiovascular risk factors. CADASIL is a rare disease, with large-scale longitudinal European studies estimating a prevalence ranging from 4 to 15 cases per 100,000 individuals.34 CADASIL is still under-recognized in the medical community, with common misdiagnosis including MS (most common), dementia, encephalitis, or migraines.35

Further contributing to its diagnostic complexity, CADASIL has a highly heterogeneous clinical presentation. The age of onset, nature, severity, and progression of clinical symptoms in CADASIL is variable, even within members of the same family. The genotype, sex, and environmental factors
Remote Communities from Colombia 463

(e.g., cardiovascular risk) have been discussed as potential factors influencing the disease presentation and trajectory in CADASIL. However, factors surrounding the phenotypic heterogeneity of CADASIL are still poorly understood and require further investigation. CADASIL can be accompanied by diverse neurological symptoms, including migraines with aura, seizures, or gait disturbances. Psychiatric disturbances are also highly prevalent in CADASIL, affecting an estimated 20 to 40% of patients and having a deleterious impact on their quality of life. Some of the most prevalent psychiatric symptoms in CADASIL include major depression, mania, BDs, and apathy.

The described case is therefore not unique in its presentation, and multiple reports have described cases of CADASIL with a clinical picture consistent with BD. The occurrence of psychotic symptoms and hallucinations has also been described, albeit fewer frequently. Interestingly, it has been demonstrated that psychiatric disturbances represent the initial presenting symptom in as much as 15% of cases and that CADASIL might be underdiagnosed in late-onset psychiatric patients.

CADASIL should be considered as a possible differential diagnosis whenever the MRI confirms the presence of white matter lesion, especially when observed at a relatively young age and in the absence of cardiovascular risk factors or comorbidities. A family history suggestive of an autosomal dominant mode of inheritance, stroke, dementia, and migraine with aura would further support this hypothesis. In this case, genotypic analysis for NOTCH 3 should be considered.

This case study illustrates challenges associated with the diagnosis of complex neurological syndromes in Antioquia, Colombia. This case study is a fitting illustration, as CADASIL is a rare and under-recognized disorder with a heterogeneous clinical presentation. The patient presented in this case study was misdiagnosed for eight years and prescribed various ineffective medications that are costly, have potential side effects, and are not always available due to limitations associated with medical insurance. The restricted access to regular follow-up, specialists, and advanced diagnostic tools (e.g., MRI) in this setting are important barriers to appropriate diagnosis and clinical management, particularly when confronted with complex cases.

Section III: Lessons Learned

- It is important to carefully review family histories in clinical interviews. Family history is particularly relevant in Antioquia, a location that is associated with a relatively high frequency of hereditary diseases. In CADASIL, the investigation of family history should expand beyond premature stroke and target other cardinal features of the disease, including migraines with aura and neurocognitive impairment. An incomplete investigation of family history can lead to misdiagnosis.
- Genealogy is essential to establish since the approach to paisas patients with neuropsychiatric and motor symptoms requires remembering that this ethnic group comes from a history made up of large family groups where genetic pathologies have been identified.
- Social norms and cultural practices vary in Colombia, and it is important to evaluate behavioral and emotional changes from the perspective of the patient and the family rather than against socially accepted standards.
- It is important to consider linguistic aspects specific to the patient’s sociodemographic background when administering and scoring cognitive tests to avoid misinterpretation due to accents or prototypical use of idioms and language (e.g., number of different words used to name things in Paisa communities).
- The development of regionally relevant normative data can improve diagnostic precision in specific cultural communities that may have distinct features even within the same country.
- The use of a multidisciplinary, culturally relevant framework with longitudinal follow-up can improve the diagnostic accuracy of neurological disorders and facilitate access to medical care for underserved populations.
464  Lina Velilla-Jiménez et al.

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