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RESEARCH ARTICLE

Montreal cognitive assessment in Brazilian adults with sickle cell disease: The burdens of poor sociocultural background

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Abstract

Sickle cell disease (SCD) patients are at higher risk of developing silent cerebral infarcts and overt stroke, which may reflect cognitive impairment, functional limitations, and worse quality of life. The cognitive function of Brazilian adult SCD patients ($n = 124$; 19–70 years; 56 men; 79 SS, 28 SC, 10 S/β^0, 7 S/β^+) was screened through Montreal Cognitive Assessment (MoCA) and correlated the results with possible predictive factors for test performance, including sociocultural, clinical, laboratory data and brain imaging. The Median MoCA score was 23 (8–30); 70% had a 25-or-less score, suggesting some level of cognitive impairment. There were no significant associations between MoCA results and any clinical or laboratory data in SS and SC patients; however, a significant correlation ($P = 0.03$) with stroke was found in HbS/β-thalassemic patients. Correlations were further detected according to sociodemographic conditions, such as age ($r = -0.316$; $P < 0.001$), age at first job ($r = 0.221$; $P = 0.018$), personal ($r = 0.23$; $P = 0.012$) and *per capita* familiar incomes ($r = 0.303$; $P = 0.001$), personal ($r = 0.61$; $P = 0$), maternal ($r = 0.536$; $P = 0$), and paternal educational status ($r = 0.441$; $P = 0$). We further sought independent predictors of performance using multivariable regressions and increased education was an independent predictor of better scores in MoCA (0.8099, 95% confidence interval [CI]: 0.509–1.111). Brain imaging analysis showed significant and progressive atrophy in important cerebral areas related to memory, learning, and executive function. These data point to the high prevalence and impact of cognitive decline in adult SCD patients, mirrored in brain atrophic areas. It is also possible to observe the influence of sociodemographic conditions on patients' cognitive performances and the need for creating focused therapeutic plans that address these deficiencies. Moreover, the absence of a significant correlation of MoCA values with stroke in the SS and SC groups may be related to the worst sociocultural and economic conditions of the Brazilian African descent population, in which the

impact of low educational stimulation on cognitive function can outweigh even the anatomical damage caused by the disease.

KEYWORDS
cognitive impairment, MoCA, sickle cell disease, silent cerebral infarcts

1 | INTRODUCTION

Sickle cell diseases (SCD) are a group of hemoglobinopathies caused by a mutation in the β-globin gene and represent the most prevalent monogenic disorder in the world, affecting mainly African descendants [1–3]. This fact is especially significant in Brazil, where 60% of the population carry African native genes, resulting in the diagnosis of some type of hemoglobinopathy in approximately 4% of the population [4, 5]. An estimated three hundred thousand children are born with SCD worldwide each year, and this number is projected to rise: by 2050, four hundred thousand children may be born with this disease [6]. Increasing cases point to the importance of SCD investigations and the development of focused therapeutic plans.

In SCD patients, ischemic and hemorrhagic cerebral lesions have been frequent complications since childhood [7]. When not resulting in death, they can cause long-term morbidities and permanent neurological injury [8, 9]. The most common type is silent cerebral infarcts (SCIs), which do not present with acute symptoms and occur in approximately 53% of young adult patients [10]. Interestingly, 90% of SCIs occur in white matter border zone regions, where cerebral blood flow is at its lowest nadir, suggesting a high association between SCIs, hemodynamic factors, and tissue oxygenation [11].

However, despite being the most common cause of neurological complications in SCD, there are limited studies regarding the impact of SCI on adults, including the absence of primary or secondary preventive therapies that could attenuate the impacts on cognitive function. Thus, screening cognitive function in this group of patients and searching for associations with laboratory, clinical, or sociocultural data could add to developing specific therapeutics and reducing progressive cognitive impairment [12].

Nowadays, the Montreal Cognitive Assessment (MoCA) is one of the most useful methods (in specificity, sensitivity, accessibility, and applicability) for screening mild cognitive impairment. This tool analyses commonly affected—and more easily screened—cognitive domains: short-term memory, visual-spatial and executive functions, attention, concentration, executive memory, language, and orientation. A score below the limits of normality (25 or fewer points in a 30-point score) suggests the presence of cognitive impairment [13]. These tests have been previously used in SCD patients by an American study which found that MoCA performed well in psychometric analyses and identified deficits in executive function that were described in other studies, although not extensively validated in those patients. Furthermore, approximately 50% had a score below the cut-off for mild cognitive impairment. The authors searched for possible predictive factors for test performance and found correlations with increased education, hydroxyurea therapy (predictors of higher scores), chronic kidney disease, cerebrovascular accidents, and increased aspartate transaminase (predictors of decreased scores) [14]. The version adapted for Portuguese was developed by a Brazilian group and is available at www.mocatest.org. This version was proven to maintain its suitability for the identification of cognitive impairment among Brazilians with at least 4 years of education (92.75% of our patients), due to its high internal consistency (0.75), sensitivity (81%), and specificity (77%) [15].

Thus, this study aimed to screen the cognitive function of Brazilian adult SCD patients through the MoCA, examining the psychometric properties in this specific sample and correlating the results with possible predictive factors for test performance, including clinical, laboratory and sociocultural data and anatomical findings of brain imaging.

2 | METHODS

2.1 | Subjects

A minimum of 112 patients were to be included in the study. We calculated this sample number using the sample size formula and considered a 95% confidence level, an alpha confidence level of 0.5 and an average of one hundred and fifty-six SCD patients who regularly attended the UNICAMP Blood Centre. This cross-sectional study enrolled 124 adult SCD patients followed at a specialized Haematology Centre in southeastern Brazil between 2018 and 2021. All patients were adults (>18 years old) and had a confirmed SCD diagnosis (sickle cell anaemia or haemoglobin SC disease or Sβ thalassemia), confirmed, in all patients, by clinical features, blood counts, haemoglobin (Hgb) electrophoresis or HPLC; family members were evaluated when possible). All patients who were regularly followed at the centre during the last six months and who had had routine exams carried out and analysed were eligible for the study and were invited to participate during routine consultations. Patients who refused to take part in the study, who did not attend their routine appointments, or who had a hemoglobinopathy diagnosis different from the ones studied were not analysed.

2.2 | Data correlation

MoCA was administered to patients attending routine outpatient appointments at the centre, by two of the authors (Silva PJF and

TABLE 1 Educational profile of patients and their parents (divided into groups based on years of study: Unschooled; primary education; secondary education and higher education).

	Patient	Father	Mother
Unschooled (0 years)	3 (2.42%)	49 (48.51%)	46 (41.82%)
Primary education (<5 years)	19 (15.32%)	30 (29.7%)	31 (28.18%)
Secondary education ($5 \leq x < 10$ years)	36 (29.03%)	11 (10.89%)	19 (17.27%)
Higher education (≥10 years)	66 (53.23%)	11 (10.89%)	14 (12.73%)

Benites BD). These patients were approached during their consultation and received a full explanation as to how the tests worked and their objectives and those patients who agreed were included in the study. Later, possible associations between MoCA and other variables were tested: age sex; diagnosis (sickle cell anaemia, haemoglobin SC disease, Sβ thalassemia); educational status; age at first job; personal incomes; family per capita income; paternal educational status; maternal educational status; blood transfusion load throughout life; hydroxyurea use; clinical complications (retinopathy; strokes; bone necrosis; leg ulcers; chronic kidney disease; acute chest syndrome and priapism); laboratorial data (Hgb levels, cell counts, haemolysis/inflammation markers and body mass index).

Laboratory and clinical data were obtained through the Hospital's database (restricted to six months before and after the application of the MoCA), whilst sociocultural data were obtained through a questionnaire given to the patients along with the MoCA. As no patient was recruited for the cognitive tests exclusively, these were administered during their routine appointments, and, as not all the laboratory tests studied were necessarily carried out during each appointment, we used an interval (6 months after and before the MoCA application) to ensure that the samples were compatible and that most patients had feasible data for the analysis. We considered that, when using this interval, the difference between the patient's clinical state during the performance tool and when the exams were carried out would be minimal.

For the educational analysis, the patients and their parents were divided into different categories: unschooled (0 years of schooling); primary education (less than 5 years of schooling); secondary education (between 5 and 10 years of schooling), and higher education (more than 10 years of schooling) and can be observed in Table 1. The division was set due to the possibility of a direct relationship between the educational level of patients and their parents and their sociocultural and economic status, which could influence the patient's neurodevelopment and, therefore, the results of the MoCA.

2.3 | Magnetic resonance imaging with voxel-based morphometric analysis

Morphometric images of the grey matter of 28 patients in this cohort were compared to 50 healthy controls to search for possible macrostructure lesions related to SCD. In addition, nine of these patients had a one-year-later analysis. All images were analysed by the Neuroimaging Laboratory at the Department of Neurology of the University of Campinas.

2.4 | Statistical analysis

All statistical analyses were performed using the software R Core Team Program Version 4.1.3. (https://www.R-project.org/). Correlations were sought using Spearman coefficients for quantitative variables. Mann–Whitney Wilcoxon test with continuity correction was used to find associations with qualitative binary variables and the Kruskal-Wallis rank sum test, with qualitative non-binary variables. Only *P*-values (P) < 0.05 were considered statistically significant. Finally, after bivariate analysis, we used multivariable robust linear regression to detect independent predictors of test performance. Age, sex, genotype, educational status, familiar incomes, hydroxyurea use, and blood transfusion load throughout life were the variables analysed.

3 | RESULTS

This study enrolled 124 patients with a median age of 44 years old (19–70). 68 patients (54.8%) were female, while 56 (45.2%) were male. Furthermore, the genotype distribution was: 79 (64.7%) SS, 28 (22.6%) SC, 10 (8%) S/β^0 and 7 (5.7%) S/β^+.

The median MoCA score was 23 points (8–30) and the score distribution can be observed in the chart below (Figure 1), where a 25 or less score suggests some level of cognitive impairment. SC, S/β, and SS patients had, respectively, the following median scores and ranges: 20 (9–30); 24 (14–30), and 23 (8–30).

The characteristics of clinical, laboratory and sociocultural data gathered are described in Table 2, (Supporting information Tables S1 and Table S2)

Regarding the sociocultural variables, the personal income median was US 212.84 (0.00–1160.97), whereas the family income median, was US 388.54 (0.00–4856.72). Furthermore, the nuclear family median was 3 persons (1–10)—including all those depending on or contributing to the family income—and the *per capita* family income was US 169.31 (0.00–1618.91).

The educational status median was 10.5 years (0–18) and maternal and paternal educational status were, respectively, 3 (0–15) and 1 (0–20) years. Finally, the median age at first job was 17 years old (7–39).

As for the patient's ages, a negative correlation was found (the older the patient, the worse the MoCA's performance; $r = -0.316$; $P < 0.001$). Positive correlations were evidenced with age at first job (years; $r = 0.221$; $P = 0.018$); personal (US; $r = 0.23$; $P = 0.012$) and familiar incomes (US; $r = 0.303$; $P = 0.001$); family per capita incomes (US; $r = 0.24$; $P = 0.009$); educational status (schooling in years; $r = 0.61$; $P = 0$), maternal (schooling in years; $r = 0.536$, $P = 0$), and paternal educational status (schooling in years; $r = 0.441$; $P = 0$). The sociocultural variable's characteristics can be observed in

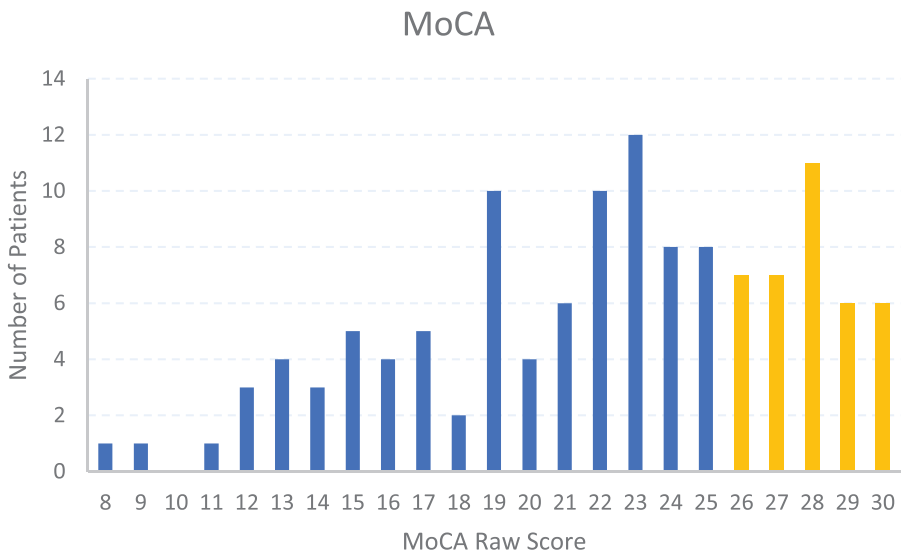

FIGURE 1 MoCA score distribution among patients. In blue, scores are considered indicative of cognitive decline; in yellow, scores are considered as indicative of typical cognitive function.

TABLE 2 Characteristics of sociocultural numeric variables (in parenthesis, minimum and maximum values obtained in the database).

	Median	Mean	Standard deviations	Spearman's rank correlation coefficient (*r*)	*P*-value
Age (years)	44.5 (19–70)	44.3	11.9	−0.316	<0.001
Educational status (years)	10.5 (0–18)	8.94	3.81	0.61	<0.001
Age at first job (years)	17 (7–39)	16.9	4.9	0.221	0.018
Personal income (USD)	212.84 (0–1160.97)	272.29	221.69	0.23	0.012
Family income (USD)	388.54 (0–4856.72)	558.35	648.65	0.303	0.001
Family per capita income (USD)	169.31 (0–1618.91)	209.26	219.19	0.24	0.009
Patient educational status (years)	1 (0–20)	3.05	4.07	0.536	<0.001

Note: In the fourth and fifth columns, there are, respectively, the correlation coefficient and the *P*-value for correlations between these variables and MoCA's results.

TABLE 3 Patients were studied gathered and divided by genotype for correlations with stroke and MoCA results.

	Overt stroke episodes (SS, S/β and SC)	Overt stroke episodes (S/β)	Overt stroke episodes (SS)	Overt stroke episodes (SC)
Number of patients	11	2	7	2
Median MoCA score	22	15.5	25	14.5
Wilcoxon rank sum test with continuity correction	$P = 0.444$	$P = 0.03$	$P = 0.311$	$P = 0.08$

Note: Statistical analysis using the Wilcoxon rank sum test with continuity correction showed significant correlations only for S/β patients.

Table 2 and the educational profile of patients and their parents in Table 1.

Another important variable to study was the impact of overt strokes on patient's MoCA results (Table 3). Eleven patients had had one overt stroke episode (median MoCA score of 22 points), whereas a hundred and eleven had not had an episode recorded (median MoCA score of 23 points). The correlation between MoCA score and overt stroke was not statistically significant ($P = 0.444$) using the Wilcoxon rank sum test with continuity correction when all were patients analysed. However, when divided by genotype, a significant correlation ($P = 0.03$) was found for S/β patients, whereas for SC and SS patients the correlation was, respectively, $P = 0.08$ and 0.311.

Regarding multivariable analysis, educational status appears as an independent predictor for increased test performance ($P < 0.0001$), associated with a 0.8099-point rise (95% CI, 0.509–1.111). The other variables showed no statistically significant associations (Table 4).

TABLE 4 Multivariable analysis and possible independent predictors for MoCA test performance.

Independent variables	Coefficient (95% CI)	*P*-value
Educational status	0.8099 (0.509–1.111)	<0.0001
Age	0.0164 (−0.073 to 0.105)	0.715
Sex	0.9991 (−0.707 to 2.705)	0.248
Genotype	−0.7029 (−2.005 to 0.599)	0.286
Familiar Incomes	0.0001 (0.000 to 0.000)	0.576
Hydroxyurea use	0.2798 (−1.746 to 2.306)	0.784
Blood transfusion load throughout life	0.0185 (−0.227 to 0.264)	0.882

Concerning neuroimaging findings, magnetic resonance imaging (MRI) with voxel-based morphometric (VBM) analysis showed significant atrophic areas in 28 patients studied (27 SS and 1 S/β^0) and compared with a healthy control group. Those areas were observed especially in the cerebellum, left frontal lobe and occipital and temporal lobes (Figure 2). In addition, the 1-year-after exam of the nine analysed patients (SS) showed progression of this atrophy, especially in the right temporal lobe, left frontal lobe and basal ganglia (Figure 3).

4 | DISCUSSION

The results of this study show that more than 70% of SCD adult patients in our centre had a MoCA test score below the limits of normality (a score of 25 or less), evidencing some level of cognitive impairment and pointing to the probable contribution of patients' sociocultural background on this impairment. To our knowledge, this is the first study to evaluate the cognition status specifically in the SCD Brazilian population which has a particular ethnic background.

Both bivariate and multivariable models used led to the importance of educational status as the main predictor for MoCA performance and highlighted the need for early target and aggressive educational interventions for better cognitive development in those patients. These results mirrored another American study that analysed 49 adults with SCD and revealed not only cognitive impairment in 53% of them after MoCA's application but also associations with higher educational attainment ($P = 0.001$), overt stroke ($P = 0.03$; associated with median MoCA score) and WRAT-4 Reading and S-TOFHLA subtests scores ($P = 0.001$ and 0.002, respectively), which are validated tests of health literacy and general literacy. As education influences on cognitive performance, sensitive cognitive tests are likely to be associated with educational attainment. Yet, patients with high educational attainment remain vulnerable to cognitive impairment and also demand sociocultural and/or pharmacological interventions [16].

It is also important to mention that, while the MoCA was designed to diminish the impact of educational status on test performance, the tool does not eliminate its influence. Therefore, the search for screening tests that are more educationally independent and their validation remains an important requirement in SCD patient care and screening.

In our study, we observed a lack of correlation between any clinical or laboratory variables with MoCA results, except for overt stroke in S/β thalassemic patients. It is also important to highlight the lack of correlation between MoCA scores and the occurrence of overt stroke episodes (Table 3 and Supporting information Table S1) in SS and SC patients. In this scenario, associated with the fact that MRI with VBM analysis showed significantly progressive atrophic areas in the patients studied and compared with a healthy control group (proving real damage in brain tissue of these patients), we can infer that silent cerebral infarcts can be more relevant for cognitive impairment than symptomatic strokes.

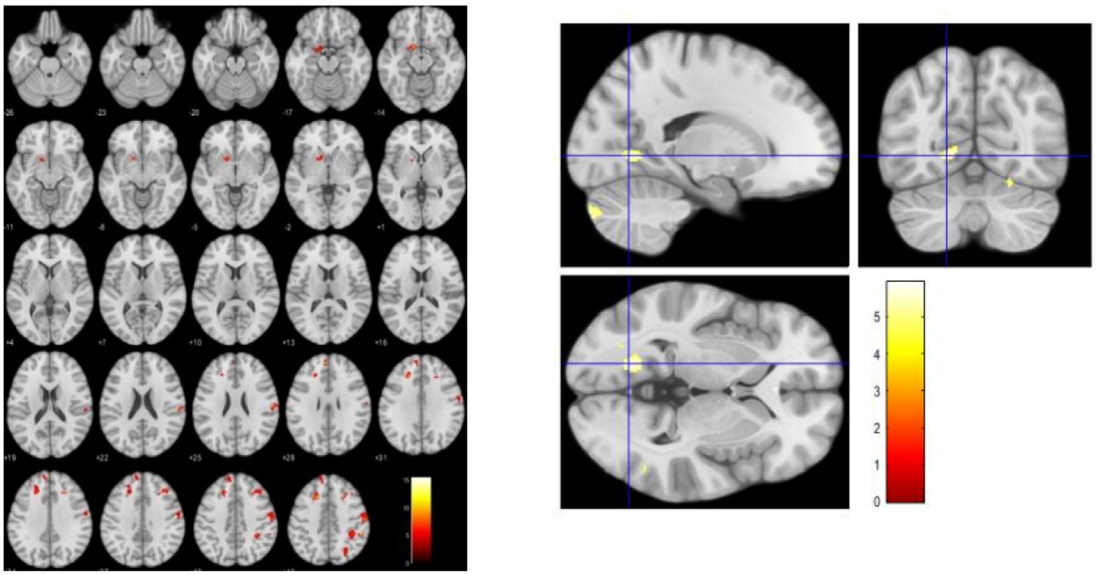

FIGURE 2 Morphometric images of the grey matter of 28 SCD patients compared to 50 healthy controls Significant atrophic areas were found in cerebellum, left frontal lobe, occipital lobe and temporal lobes (colored areas) of patients in comparison to healthy subjects.

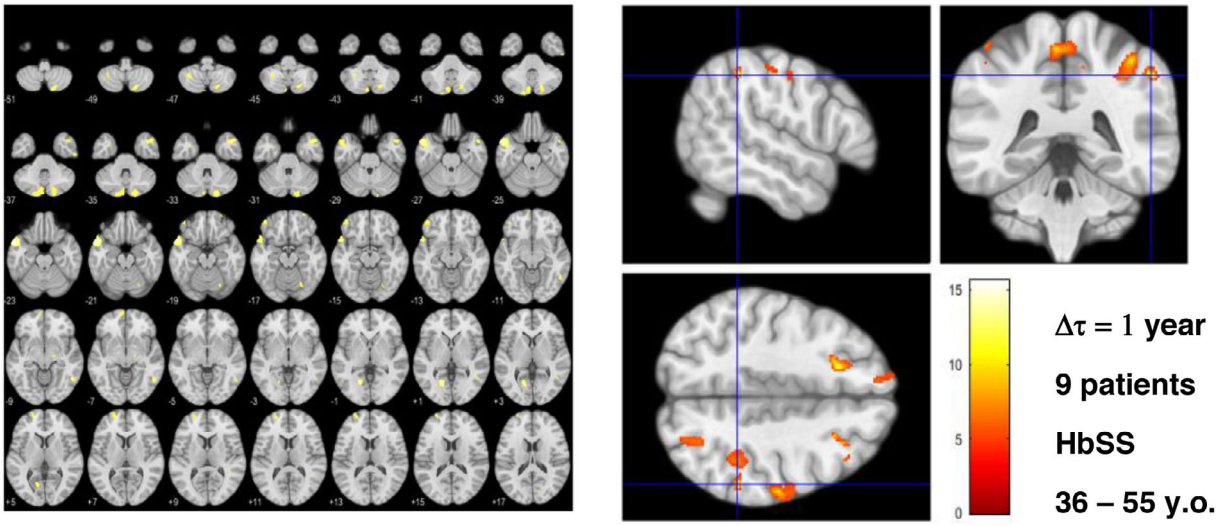

FIGURE 3 In nine SS patients, morphometric analysis after 1 year of the first MRI revealed progressive atrophy, especially in the right temporal lobe, frontal lobes and basal ganglia (colored areas). All patients had a sickle cell anemia diagnosis (SS).

Our study was unable to differentiate the impact of a single event and the recurrence of stroke events on patients' cognitive functions. However, Couette et al. [17] showed that, although the occurrence of stroke episodes did not affect global cognition, the time of the first stroke did: SCD patients with childhood stroke seem to be at increased risk of a global cognitive deficit profile. Furthermore, MoCA scores mirrored the severity of the cognitive deficits. The paediatric group also had lower educational attainment, which could be explained in part by the disruption of the patient's schooling due to childhood strokes [17].

On the other hand, our results show significant correlations between MoCA scores and most sociocultural variables, including age, age at first job, personal and family income, family per capita income and personal, maternal and paternal educational status. Socioeconomic and environmental factors (social determinants of health) seem to have at least the same impact on cognition as the pathophysiology of SCD. Our results mirror a study that showed children with SCD who lived in a household in which the head of household had a lower educational level (less than a college education) had a six-point decrease in full-scale intelligence quotient (FSIQ), and every $1000 increase in family income per capita was associated with a 0.3-point increase in the scale [18]. Furthermore, parental education and occupation status have frequently been documented as predictors of neurocognitive and academic performance in SCD patients, as well as neighbourhood-level metrics of socioeconomic status [18–22].

Indeed, we can speculate that the impact of the unfavourable socioeconomic environment to which these patients are exposed is so impressive that it strongly overshadows the effects of other potential determinants of the occurrence of cognitive deficits, such as stroke history, inflammatory/haemolytic blood markers and others. Another consideration to be made when analysing the data is the identification of possible limitations of the MoCA test itself when used in this specific population, as the outcome can be influenced by the patient's educational level. Therefore, the need for new studies to identify the best tools for assessing cognitive decline in these patients, considering replicability, ease of use and patient understanding, that leave no doubt as to the potential biases related to cultural and educational background remains.

Studies show that literacy and health literacy are decreased in SCD, which leads to poor adherence to health-promoting behaviours and difficulties with instrumental activity of daily living skills that rely on those abilities [16, 23]. Disruptions to household activities and social relationships were the most frequent concerns and the fact that these patients have an unemployment rate (17%) nearly three times higher compared with the population and a two-times higher disability status (24%) illustrates the impacts on patients daily lives [24–26].

Our study further shows the importance of the development of strategies that mitigate the patients' outcomes, not only pharmacological but multidisciplinary. A study taking place in Cincinnati Children's Hospital Medical Center compared the cognitive status of thirty children with SCD who initiated hydroxyurea before the age of five years to an unaffected, matched healthy control cohort and found that they had similar cognitive performance (school-aged children with the disease normally scores an average of ten points lower on FSIQ than the unaffected ones) [27]. Other studies also reported improvements in FSIQ and reading comprehension after one year of hydroxyurea use, suggesting that this drug may slacken neurocognitive decline and provide some neuroprotective effects [28, 29]. However, as all our patients were adults, we could not analyse the neuroprotective function of the ones on this medication therapy.

Nonpharmacological interventions remain limited. Early, home-based parent education and computer-based cognitive interventions using Cogmed have demonstrated improvements in SCD children's cognitive domains and could be used in Brazilian public clinical practice [30–32]. The introduction of neuropsychology services into patient care (such as cognitive screening and targeted and comprehensive neuropsychological evaluation) could also help patients by identifying

and managing cognitive impairment. Some benefits of this introduction would include increased access to community-based services, assistance with the transition from paediatric to adult care and treatment planning [23].

5 | CONCLUSION

These results demonstrate the high prevalence and impact of cognitive decline in Brazilian adult SCD patients and the expressive influence of sociocultural conditions on cognitive performance, such as lower educational status, worse family income, and the need to start working earlier. We believe the study results highlight the need for early screening of vascular instability in those patients and the influence of sociocultural conditions on cognitive impairment, which leads to the urge to develop public health strategies to reduce the impacts of these risk factors. Proactive strategies for managing cognitive and functional challenges should be integrated into childhood care plans, starting at an early age.

AUTHOR CONTRIBUTIONS

Bruno Deltreggia Benites, Sara Teresinha Olalla Saad and Fernando Cendes participated in study design. Bruno Deltreggia Benites, Pedro Junqueira Fleury Silva, Caroline Martins Silva, Brunno Machado de Campos, José Vitor Coimbra Trindade, Paula de Melo Campos, Samuel de Souza Medina and Andreza Lamonica participated in data collection and all authors participated in data analysis and manuscript writing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The ethical and methodological aspects of this project were reviewed and approved by the Research Ethics Committee from the University of Campinas (protocol number: 50496421.3.0000.5404) and patients were included only after signing the Informed Consent Form.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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