Neurocognitive functioning in children with sickle cell anemia and history of abnormal transcranial toppler ultrasonography

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Abstract

Background: Transcranial doppler (TCD) ultrasonography can be used to identify stroke risk in children with sickle cell anemia. Previous studies have reported mixed findings on neurocognitive outcomes in children with elevated TCD. This study examined associations between TCD velocity and neurocognitive outcomes in children and adolescents without prior history of stroke.

Procedure: Participants were selected from the Sickle Cell Clinical Research Intervention Program cohort. The highest recorded mean maximum TCD velocity was selected for analysis, along with participant's most recent data from serial neurocognitive surveillance.

Results: A total of 200 children with sickle cell anemia completed neurocognitive testing (109 males, 91 females; mean age 12.7 years [SD=3.56]). Most participants were prescribed hydroxyurea (72%) at the time of neurocognitive testing and nearly 16% had a history of chronic transfusions prior to neurocognitive evaluation. Mean age at time of highest TCD value was 6.6 years (SD=2.5) and 13.5% of screenings were abnormal (200 cm/sec). Mean interval between TCD and most recent neurocognitive evaluation was 6.1 years (±3.5). There were no significant differences in the interval between TCD and neurocognitive testing across normal, conditional, and abnormal groups. Maximum TCD velocity was not significantly associated with neurocognitive outcomes in multivariate models.

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Conclusions: History of elevated TCD in the absence of overt stroke should not be considered a risk factor for poor neurocognitive outcomes in children and adolescents with sickle cell anemia on modern disease-modifying therapy.

Keywords

sickle cell disease; neurocognitive; transcranial doppler; children

Introduction

Sickle cell disease (SCD) is an inherited hemoglobin disorder that disrupts delivery of oxygen throughout the body including the brain. Silent cerebral infarct and overt ischemic stroke are the leading neurological complications of SCD.[1] The risk of overt stroke is 200–400 times greater for untreated children with SCD compared to the general population.[2] Ischemic events occur more often than hemorrhagic stroke and are most likely to occur between the ages of two and five years old in children with the HbSS genotype.[3,4]

Transcranial doppler (TCD) ultrasonography measures blood flow velocity through major cerebral arteries and has become a core component of primary stroke management.[5] The *Stroke Prevention Trial in Sickle Cell Anemia* study demonstrated that TCD ultrasonography was effective in identifying patients at risk for a primary stroke and that red blood cell transfusions were effective interventions for stroke prevention.[6] These findings prompted development of guidelines by the National Heart, Lung, and Blood Institute (NHLBI)[7,8], which recommend annual TCD ultrasonography for children with HbSS beginning at age 2 years. The incidence rate for abnormal TCDs is 6–10 % and they are more prevalent in children younger than 12 years old.[5,9]

Previous studies of associations between TCD and neurocognitive functioning have yielded inconsistent results. Importantly, these studies took place before established guidelines from the NHLBI on hydroxyurea use in children.[7] The largest study on TCD and neurocognitive outcomes (n=156; 7.7% receiving chronic transfusion, 17.4% on hydroxyurea) reported that abnormal TCD velocity was associated with poor nonverbal intelligence during a moderate latency period (<1.5 years); however, this relationship was no longer significant when participants with history of stroke were excluded.[9] A smaller study (n=60; 33% on chronic transfusion) reported abnormal TCD was associated with lower verbal intelligence compared to the conditional group, whereas the conditional group exhibited worse sustained attention and executive functioning compared to the abnormal TCD group.[10] These findings appeared to reflect variability in duration of time between TCD and neurocognitive testing for those in the conditional (6 months) and abnormal (5 years) groups, with the latter group potentially demonstrating neurocognitive decline in verbal skills that is typically associated with SCD. Studies with shorter latency periods between TCD and neurocognitive testing (i.e., medians of 63 and 150 days) failed to find associations between TCD and neurocognitive functioning.[11,12] Only verbal memory was associated with TCD results during an extended interval between ultrasonography and testing (i.e., 5 years) (n=27; 48.1% on chronic transfusion).[13]

This study addresses inconsistencies in the literature regarding the relationship between abnormal TCD examinations and neurocognitive functioning in children with sickle cell anemia (HbSS and HbSβ[0]-thalassemia). We aimed to overcome limitations of previous studies, including variability in latency periods between neurocognitive testing and TCD examinations, inclusion of children with a history of stroke, limited neuropsychological measures, and small sample size. Our results provide insight into risk for long-term neurocognitive deficits among children with a history of conditional or abnormal TCD.

Methods

This research was approved by the Internal Review Board at St. Jude Children's Research Hospital. Written informed consent was obtained from legal guardians since all participants were minors. Adolescents gave assent according to the study requirements.

Participants

Participants in the Sickle Cell Clinical Research Intervention Program (SCCRIP) cohort, aged 8–17 years, and with HbSS or HbSβ[0]-thalassemia, were eligible for this analysis. The SCCRIP study is a longitudinal lifetime cohort that collects data on children, adolescents, and adults with SCD, including clinical, neurocognitive, psychosocial, and health outcomes.[14] TCD ultrasonography was provided as standard of care for patients with sickle cell anemia beginning at age 2 years. Neurocognitive assessments were provided every four years beginning at age 8 years. Timepoints for testing were school-age (8–9 years), early adolescence (12–13 years), and late adolescence (16–17 years). These serial evaluations were provided as standard clinical care for patients with SCD and were not associated with clinical referrals, history of neurological complications, or disease severity. Children and adolescents had access to an academic advocacy coordinator who was available to help establish educational supports (i.e., Section 504 Plan or individual education plan [IEP]) to support identified neurocognitive deficits and/or accommodations for disease management.

Of the 730 SCCRIP participants, 440 had the HbSS or HbSβ[0]-thalassemia genotype and 415 received at least one TCD screening. Over half (52%) of the 415 participants also completed neurocognitive testing (n=217). Potential reasons for participants not completing neurocognitive testing include missing a scheduled appointment or being referred for a clinical neuropsychological evaluation. We excluded patients with a history of confirmed or suspected intellectual disability (FSIQ   70; n=11) and stroke (n=6) leaving 200 eligible participants for the analysis. See Fig. 1 for further details on participant selection. Group differences between participants who did and did not complete neurocognitive testing were minimal (Supplemental Table S1).

200 participants gave 80% statistical power to detect a linear correlation coefficient of 0.2 at a significance level of 0.05 based on a two-sided correlation test. In addition, out of 200 eligible participants, there were 27 participants with abnormal TCD (>200cm/sec). Based on the published data, [9] the effect size to compare neurocognitive function between abnormal TCD and normal TCD (<200cm/sec) was approximately 0.55. 200 participants (27

participants with abnormal TCD plus 173 participants with normal TCD) gave 75% power to detect the effect size of 0.55 at a significance level of 0.05 based on a two-sided t-test.

Demographic, medical, and treatment variables

Demographic, medical, and treatment variables were extracted from the SCCRIP database. Mean maximum TCD values were calculated from available data for the left and right distal internal carotid, carotid bifurcation, and anterior, middle, and posterior arteries. The highest time-averaged mean velocity (TAMV) TCD value on record preceding neurocognitive testing was selected for analysis. There was no latency cutoff between TCD and neurocognitive testing. TAMV values were categorized as normal (< 170 cm/sec), conditional (170–199 cm/sec), and abnormal (> 200 cm/sec). Follow-up TCD ultrasonography was completed for children with conditional or abnormal findings. Packed red blood cell transfusion was initiated for participants with abnormal TCD findings. Transfusion was provided monthly and hemoglobin values were monitored regularly. Most non-transfused participants received hydroxyurea in accordance with guidelines from the NHLBI.[7] Hematological measures including hemoglobin, fetal hemoglobin, white blood cell count, and platelet count were performed at steady state on the day of neurocognitive testing or were the average value of measurements within three months prior to neurocognitive testing.

Neurocognitive battery

We selected the participant's most recent neurocognitive assessment data for analysis. Neurocognitive evaluations were supervised by a licensed psychologist. Neurocognitive variables associated with lateralized skills and localized anatomical regions were selected for analysis. The Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II) provided an estimated Full-Scale Intelligence Quotient (4-subtest; FSIQ) and measurement of verbal comprehension and visual-spatial reasoning.[15] Depending on the participant's age, attention and working memory were measured with Digit Span subtests from the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) or Wechsler Intelligence Scale for Children, Fourth and Fifth Editions (WISC-IV and WISC-V).[16,17] The Wide Range Assessment of Memory and Learning, Second Edition (WRAML-2) was used to measure verbal memory via the Story Memory subtest.[18] The Beery-Buktenica Visual Motor Integration Test, Sixth Edition (VMI) was used to assess visual-motor integration.[19] Fine motor dexterity and speed were measured with the Grooved Pegboard Test.[20]

Statistical Analysis

Summaries and comparisons of patient characteristics, labs, treatments, TCD values, and neurocognitive variables were stratified by age group and TCD category. For two-group comparisons, continuous variables were compared by either the Wilcoxon-Mann-Whitney test or t-test. For three-group comparisons, continuous variables were compared by either the Kruskal-Wallis test or analysis of variance. Shapiro-Wilk's test was used to test whether continuous data followed a normal distribution. For categorical variables, either the Pearson's chi-square or Fisher's exact test was used to compare their distributions among different groups. Linear regression models were used to assess the associations of neurocognitive outcomes with categorical and continuous TCD. The TCD variable was

forced into the model. Other candidate predictors were eliminated using backwards selection until remaining *p*-values were less than 0.10. All models were fit in SAS version 9.4.

Results

Clinical and Demographic Characteristics

Table 1 displays clinical and demographic characteristics of the sample. Males accounted for 54.5% of the sample. The frequency of conditional TCDs was 25.5% and 13.5% of participants had abnormal TCD results. Mean age at time of highest TAMV was 6.6 years (SD=2.5) and there were no statistically significant differences in age at TCD ultrasonography between normal, conditional, and abnormal groups (p>0.05). Mean age at time of neurocognitive testing was 12.7 years (SD=3.56). Mean interval between TCD screening and most recent neurocognitive assessment was 6.1 years (SD= 3.5 years). There were no statistically significant differences in the interval between TCD and neurocognitive testing across normal, conditional, and abnormal groups. The majority of participants were prescribed hydroxyurea (72%) at the time of neurocognitive testing and nearly 16% had a history of chronic transfusions prior to neurocognitive evaluation.

Univariate associations between TCD velocities and neurocognitive functioning

Univariate models were used to examine TCD as a covariate with neurocognitive performance as the outcome variable (Table 2). When analyzed as a continuous variable, TCD was associated with visual-motor integration (estimate = −0.082, standard error [SE] = 0.04, p=.043). TCD was also analyzed categorically according to 1) binary categories of normal (<200 cm/sec) and abnormal (200 cm/sec), and 2) normal, conditional, and abnormal. When TCD velocity was collapsed into binary categories (normal and abnormal), statistically significant differences were found in vocabulary (estimate = −1.431, SE = 0.636, p=.026), working memory (estimate = −1.158, SE = .555, p=.038), and visual-motor integration (estimate = −8.543, SE = 3.751, p=.024) (Table 2). Neurocognitive outcomes did not vary significantly between TCD groups when analyzed according to normal, conditional, or abnormal classifications, except for vocabulary skills (p=.046) (Supplemental Table S2).

Multivariate associations between TCD velocities and neurocognitive functioning

In multivariate models, TCD values were not significantly associated with visual-motor integration, vocabulary, or working memory skills when analyzed as a continuous or categorical variable (Table 3) after controlling for demographic and treatment factors. After reducing the full models using backward selection (p<0.10), TCD values (continuous or binary) continued to demonstrate no significant associations with visual-motor integration, vocabulary, or working memory.

Discussion

Findings from the largest study to-date on TCD and neurocognitive outcomes provide little evidence to suggest that neurodevelopmental trajectory is associated with the results of prior TCD examinations. In our study, the average duration between TCD screening and neurocognitive testing was 6.1 years, which represents the longest reported follow-up of

TCD outcomes. Our results indicate that highest recorded TAMV was not significantly associated with future neurocognitive performances in a sample with high rates of hydroxyurea use and school support services (e.g., 504 Plan or IEP). Consistent with our prior work, aging and treatment factors (i.e., hydroxyurea and chronic transfusions) were significant predictors of visual-motor integration, vocabulary, and working memory skills.[21]

In contrast to previous studies, we did not find evidence that TCD predicted outcomes in areas of nonverbal intelligence, language, working memory/executive functioning, or memory.[10,13,22] Our study excluded children with overt stroke, thus confirming the findings reported by Bernaudin and colleagues when stroke patients were removed from their analysis.[9] Previous studies identifying differences in language and working memory/ executive functioning between TCD groups have been limited by variability in duration of time between TCD and testing (for example, 6 months vs. 5 years for conditional and abnormal groups, respectively).[10] In our study, there were no statistically significant differences in duration between TCD groups and neurocognitive testing, allowing us to overcome this limitation.

Differences in design methodology likely account for the contrast in our results and previously reported findings. Our study represents the most robust sample of participants with TCD and neurocognitive testing and includes the most comprehensive assessment of neurocognitive abilities to date. We opted to select participant's highest recorded TAMV in order to capture the most significant marker of risk for neurological injury. Our decision to select participant's most recent neurocognitive test data allowed us to examine future neurocognitive risk, thus providing a better understanding of the long-term impact of TCD on neurocognitive development.

This study has several limitations. MRI was not available for all participants, and we are unable to consider the impact of silent infarcts on neurocognitive outcomes. Although the highest-recorded TAMV on record was not associated with most neurocognitive outcomes, future studies may consider examining multiple TAMV timepoints. Academic measures were not included in our analysis, thus this study did not assess the potential impact of TCD on learning skills. While our sample is representative of the sickle cell anemia population in the southern United States, our study lacked diversity with regard to other racial and ethnic groups who experience sickle cell anemia worldwide.

In summary, these results indicate that elevated TCD velocities have minimal influence on long-term neurocognitive outcomes in children without history of stroke who receive modern disease-modifying therapies, such as hydroxyurea and chronic transfusion. Elevated TCD velocity in the absence of stroke should not be considered a risk-factor for future neurocognitive outcomes for children on disease modifying therapy. Other measures of cerebral blood flow, such as functional magnetic resonance imaging, that demonstrate concordance with neurocognitive performance may be better predictors of neurocognitive outcomes for children and adolescents with sickle cell anemia.[23] Additionally, emerging research with single-and multi-inflow time arterial spin labeling sequences in sickle cell anemia suggests that this technique may be better equipped to identify hemodynamic stress

and associations with cognition, including overall intellectual functioning, processing speed, and executive functioning. [24,25]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Data Availability Statement

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

Abbreviations

FSIQ	Full scale intellectual quotient
NHLBI	National Heart, Lung, Blood Institute
SCCRIP	Sickle Cell Clinical Research and Intervention Program
SCD	Sickle cell disease
TAMV	Time-averaged mean velocity
TCD	Transcranial doppler
VMI	Beery-Buktenica Visual Motor Integration Test, Sixth Edition
WAIS-IV	Wechsler Adult Intelligence Scale, Fourth Edition
WASI-II	Wechsler Abbreviated Scale of Intelligence, Second Edition
WISC-IV and WISC-V	Wechsler Intelligence Scale for Children, Fourth and Fifth Editions
WRAML-2	Wide Range Assessment of Memory and Learning, Second Edition

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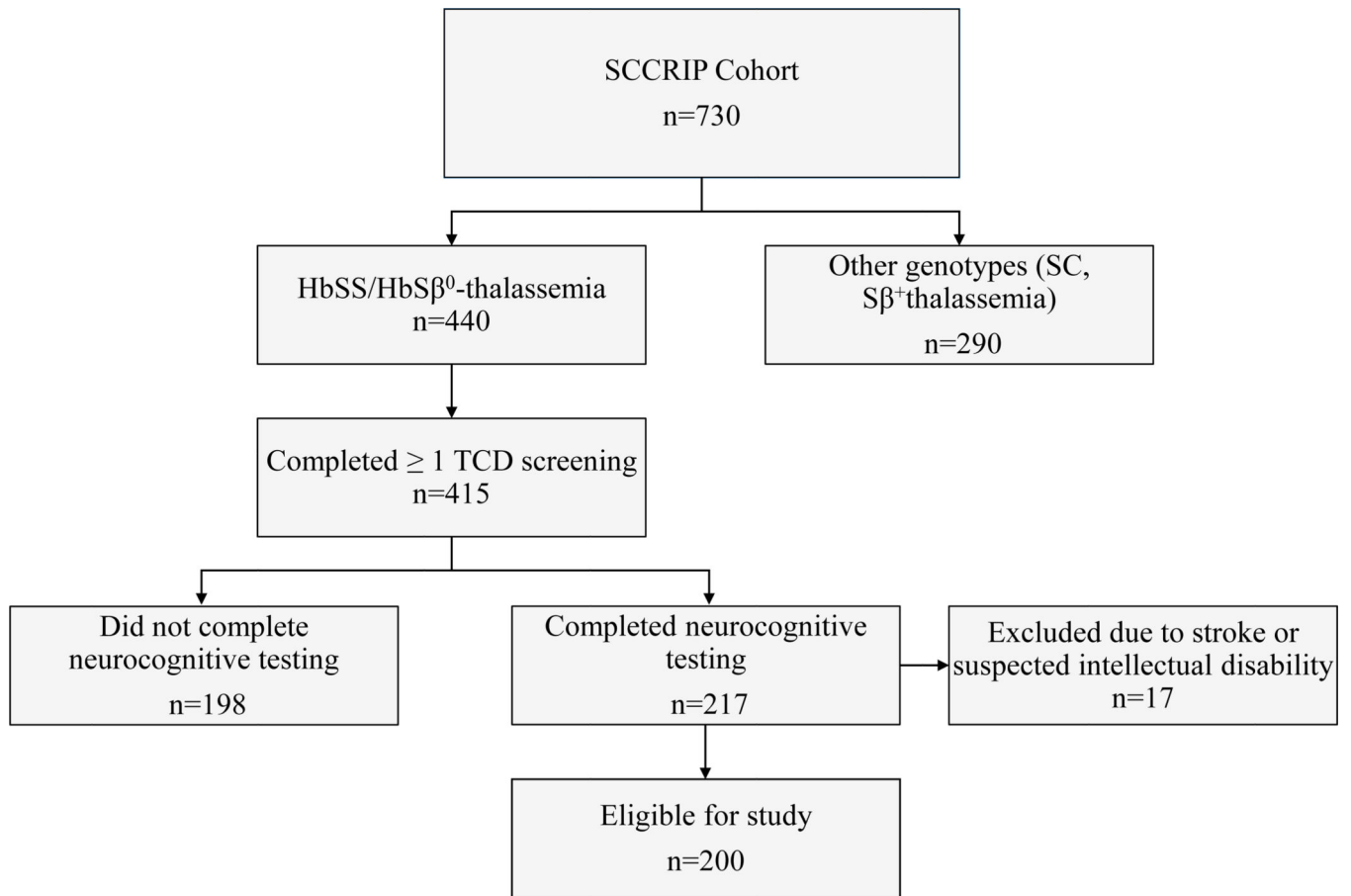
FIGURE 1.

Eligibility criteria for participant selection. SCCRIP= sickle cell clinical research intervention program; TCD= transcranial doppler.

TABLE 1

Summary of descriptive statistics for demographic, medical, and clinical variables

	Total	TCD Normal	TCD Conditional	TCD Abnormal	*P*
	N (%):	N (%):	N (%):	N (%):	
Sex					0.24
Female	91 (45.5%)	50 (41.0%)	28 (54.9%)	13 (48.1%)	.
Male	109 (54.5%)	72 (59.0%)	23 (45.1%)	14 (51.9%)	.
Genotype					-
HbSS/HbSβ0–	200 (100%)	122 (100%)	51 (100%)	27 (100.0%)	.
Race					.
Black	199 (99.5%)	121 (99.2%)	51 (100%).	27 (100%)	1
Other	1 (0.5%)	.1 (0.8%)	.	.	.
Maximum TCD Classification	200	122 (61%)	51 (25.5%)	27 (13.5%)	.
Taking HU					0.094
No	56 (28.0%)	33 (27.0%)	11 (21.6%)	12 (44.4%)	.
Yes	144 (72.0%)	89 (73.0%)	40 (78.4%)	15 (55.6%)	.
Chronic transfusions prior to evaluation					<.001
No	169 (84.5%)	116 (95.1%)	47 (92.2%)	6 (22.2%)	.
Yes	31 (15.5%)	6 (4.9%)	4 (7.8%)	21 (77.8%)	.
Chronic transfusions prior to TCD					0.009
No	185 (92.5%)	117 (95.9%)	47 (92.2%)	21 (77.8%)	.
Yes	15 (7.5%)	5 (4.1%)	4 (7.8%)	6 (22.2%)	.
Receiving school services[a]					0.687
No	60 (31.1%)	40 (33.3%)	13 (27.7%)	7 (26.9%)	
Yes	133 (68.9%)	80 (66.7%)	34 (72.3%)	19 (73.1%)	

	Total	TCD Normal	TCD Conditional	TCD Abnormal	*P*
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Social Vulnerability Ranking[b]	0.66 (0.25)	0.67 (0.25)	0.64 (0.24)	0.67 (0.28)	0.535
Max TCD	163.8 (30.0)	144.1 (15.4)	183.4 (8.6)	216.1 (14.7)	<.001
Age at TCD, years	6.67 (2.50)	6.42 (2.51)	6.90 (2.40)	7.36 (2.59)	0.182
Age at evaluation, years	12.75 (3.56)	12.37 (3.52)	12.98 (3.51)	14.02 (3.61)	0.065
Interval between TCD and evaluation[c]	2220 (1266)	2173 (1214)	2218 (1297)	2432 (1454)	0.670
Total days on HU	2187 (1418)	2195 (1360)	2166 (1476)	2189 (1686)	0.950
Fetal Hemoglobin, %	15.68(9.52)	17.28 (9.24)	15.01 (8.02)	9.76(11.08)	<.001
Hemoglobin, g/dL	9.18 (1.23)	9.31 (1.26)	8.85 (1.13)	9.23 (1.15)	0.080
Platelet count, $\times 10^9$/L	398.8 (173.3)	392.7 (184.5)	395.2 (154.5)	433.4 (155.8)	0.386
White blood cell $\times 10^9$/L	9.94 (4.26)	9.60 (4.04)	9.52 (3.84)	12.28 (5.30)	0.019

Note. Values are presented as mean (standard deviation) or frequency (group %) unless otherwise noted. HU = hydroxyurea; TCD = transcranial doppler. *P* values based on chi-square or Fisher's Exact test for categorical variables and Kruskal-Wallis for continuous variables.

[a]Includes parent report of unspecified school services, 504 Plan, or Individual Education Plan (IEP).

[b]Classifies individuals based on social vulnerabilities at the neighborhood level (e.g., housing data, poverty, and education); higher values indicate higher social vulnerability.

[c]interval based on number of days.

TABLE 2

Univariate TCD models with continuous and binary categorical analysis

Outcome / Dependent variable	Continuous TCD[1]			Binary TCD[2]		
	Estimate	SE	*P*	Estimate	SE	*P*
FSIQ[a]	−0.028	0.035	0.416	−5.178	3.521	0.144
Block Design[a]	−0.008	0.007	0.242	−0.390	0.555	0.483
Matrix Reasoning[a]	0.002	0.007	0.731	−0.563	0.603	0.352
Vocabulary[a]	−0.008	0.007	0.260	−1.431	0.636	**0.026**
Similarities[a]	−0.006	0.009	0.521	−1.155	0.883	0.193
Digit Span Forward[b]	−0.003	0.007	0.714	−0.442	0.610	0.470
Digit Span Backward[b]	−0.008	0.006	0.240	−1.158	0.555	**0.038**
Story Memory Recognition[c]	0.014	0.007	0.059	0.085	0.748	0.910
Motor Dominant Hand[d]	0.003	0.005	0.598	0.367	0.470	0.436
Motor Non-dominant Hand[d]	0.004	0.004	0.333	0.222	0.431	0.607
Visual-Motor Integration[e]	−0.082	0.040	**0.043**	−8.543	3.751	**0.024**

Abbreviations. TCD = transcranial doppler; SE = standard error.

[1] Maximum TCD velocity

[2] Normal (< 200 cm/sec) and Abnormal (200 cm/sec).

[a] Wechsler Abbreviated Scale of Intelligence, Second Edition (scaled score)

[b] Wechsler Intelligence Scale for Children, Fourth and Fifth Editions and Wechsler Adult Intelligence Scale, Fourth Edition (scaled score)

[c] The Wide Range Assessment of Memory and Learning, Second Edition (scaled score)

[d] The Grooved pegboard Test (z score)

[e] Beery-Buktenica Visual Motor Integration Test, Sixth Edition (standard score)

TABLE 3

Multivariable models for TCD and neurocognitive functioning

| | Continuous TCD Models | | | | | | Categorical TCD Models | | | | | |
| | Full model | | | Reduced Model | | | Full model | | | Reduced Model | | |
	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P
Visual-Motor Integration [a]												
Intercept	109.3	12.4	<.0001	111.7	7.5	<.0001	101.5	9.7	<.0001	100.6	4.8	<.0001
TCD	−0.046	0.045	0.310	−0.070	0.040	0.086						
Normal [+]							0.000	.	.	0.000	.	.
Conditional							−0.637	2.597	0.807	−0.653	2.504	0.795
Abnormal							−2.586	5.152	0.617	−6.378	3.981	0.111
Age, years	−0.733	0.356	**0.041**	−0.612	0.300	**0.043**	−0.742	0.362	**0.042**	−0.588	0.305	0.056
Female	−0.346	2.178	0.874				−0.469	2.191	0.831			
Chronic transfusions	−5.444	3.962	0.172				−5.731	4.607	0.216			
Using HU	−1.095	3.481	0.754				−1.138	3.527	0.747			
Time on HU, years	0.315	0.371	0.396				0.322	0.375	0.392			
Socioeconomic Vulnerability [c]	−8.750	4.193	**0.039**	−9.234	4.072	**0.025**	−8.548	4.253	**0.046**	−8.699	4.106	**0.036**
Hemoglobin, g/dL	0.198	1.003	0.844				0.281	1.013	0.782			
Fetal Hemoglobin, %	−0.103	0.136	0.451				−0.102	0.137	0.458			
Vocabulary [b]												
Intercept	9.60	2.35	<.0001	10.88	1.52	<.0001	11.08	1.83	<.0001	11.93	0.96	<.0001
TCD	0.008	0.008	0.323	0.007	0.008	0.410						
Normal [+]							0.000	.	.	0.000	.	.
Conditional							−0.024	0.485	0.961	−0.076	0.470	0.871
Abnormal							0.500	0.922	0.588	0.386	0.904	0.670
Age, years	−0.222	0.067	**0.001**	−0.248	0.064	**0.000**	−0.220	0.068	0.001	−0.246	0.065	**0.0002**
Female	−0.246	0.413	0.553				−0.196	0.414	0.636			
Chronic transfusions	−1.284	0.709	0.072	−1.434	0.666	**0.033**	−1.268	0.843	0.135	−1.430	0.807	**0.078**

| | Continuous TCD Models | | | | | | Categorical TCD Models | | | | | |
| | Full model | | | Reduced Model | | | Full model | | | Reduced Model | | |
	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P
Using HU	0.448	0.637	0.483				0.490	0.642	0.447			
Time on HU, years	0.161	0.071	**0.024**	0.211	0.052	**<.0001**	0.159	0.071	0.027	0.211	0.053	**<.0001**
Socioeconomic Vulnerability [c]	−1.497	0.811	0.067	−1.424	0.806	0.079	−1.532	0.820	0.063	−1.448	0.814	0.077
HgB	0.034	0.193	0.861				0.009	0.194	0.964			
Hgb_F	0.026	0.027	0.333				0.026	0.027	0.342			
Working Memory [d]												
Intercept	8.51	2.22	0.0002	9.16	1.36	<.0001	9.03	1.73	<.0001	9.64	0.75	<.0001
TCD	0.005	0.008	0.542	0.004	0.007	0.619						
TCD Normal [+]							0	.	.	0.000	.	.
TCD Conditional							0.461	0.456	0.313	0.436	0.436	0.319
TCD Abnormal							0.671	0.890	0.452	0.295	0.775	0.704
Age, years	−0.097	0.065	0.133	−0.090	0.054	0.098	−0.101	0.065	0.121	−0.093	0.055	0.090
Female	0.222	0.392	0.573				0.197	0.391	0.616			
Chronic transfusions	−1.556	0.657	**0.019**	−1.395	0.599	**0.021**	−1.725	0.820	**0.037**	−1.357	0.726	0.063
Using HU	1.344	0.608	**0.028**	1.034	0.417	**0.014**	1.314	0.611	**0.033**	1.010	0.421	**0.018**
Time on HU, years	−0.021	0.067	0.752				−0.018	0.067	0.789			
Socioeconomic Vulnerability [c]	0.385	0.737	0.601				0.348	0.740	0.639			
HgB	0.048	0.182	0.790				0.066	0.182	0.717			
Hgb_F	−0.022	0.027	0.421				−0.021	0.027	0.434			

Abbreviations: HU = hydroxyurea; TCD = transcranial doppler. Note: TCD was forced into the models. Neurocognitive variables selected based on statistical significance in univariate models. Candidate predictors were eliminated using backward selection until remaining p values were less than 0.10.

[+] reference group for comparison

[a] Beery-Buktenica Visual Motor Integration Test, Sixth Edition (standard score)

[b] Wechsler Abbreviated Scale of Intelligence, Second Edition Vocabulary (scaled score)

[c] Classifies individuals based on social vulnerabilities at the neighborhood level (e.g., housing data, poverty, and education); higher values indicate higher social vulnerability

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*d*Wechsler Intelligence Scale for Children, Fourth and Fifth Editions and Wechsler Adult Intelligence Scale, Fourth Edition Digit Span Backward (scaled score)