Distribution of sickle cell disease and assessment of risk factors based on transcranial Doppler values in the Gulf region

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ABSTRACT

Background/Objective: Stroke is a potentially fatal complication of sickle cell disease (SCD). Transcranial Doppler (TCD) is useful at identifying increased risk of stroke in children with SCD and vasospasm after subarachnoid hemorrhage. The main aim of this study was to determine the proportion of patients with SCD in the Gulf region who are at a high risk of stroke, as determined by TCD.

Methods: This multicenter (Oman, Qatar, and UAE), descriptive, cross-sectional study in patients (aged 2–16 years) with SCD included a baseline visit, 1 follow-up visit for patients with conditional TCD, and 3-year retrospective data analysis for all patients.

Results: Of the 410 eligible patients (Oman, 86.5%; Qatar, 8.2%; UAE, 5.1%), most had a TCD finding (left side, 91.7%; right side, 92.0%) of normal velocity (<155 cm/s) at baseline. For 6 of 7 patients with conditional velocity (155–179 cm/s) and 1 patient with high velocity (≥180 cm/s), baseline TCD results were not confirmed at follow-up. As per bivariate linear regression, age, race, transfusion type, and transfusion frequency were significant predictors of the TCD velocities. Multivariate logistic regressions revealed that TCD velocities were significantly correlated with sex, race, and type of transfusion. No patients reported any adverse events at follow-up. No deaths occurred during the study.

Discussion/Conclusions: The study results show that far fewer patients with SCD in the Gulf have abnormal TCD findings than the internationally reported. Larger studies are needed to to identify the factors underlying this observation.

KEYWORDS:

Cerebro-vascular accident; Gulf region; multi-center; primary prevention; sickle cell disease; transfusion; transcranial Doppler ultrasound; vaso-occlusive crises

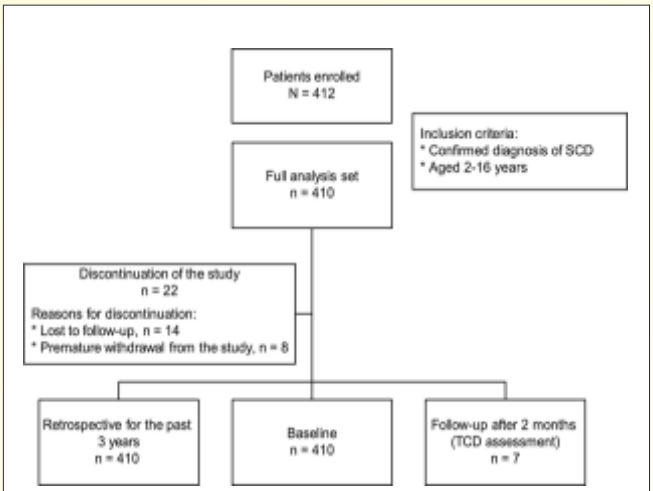

Figure 1. Patient disposition. SCD, sickle cell disease; TCD, transcranial Doppler.

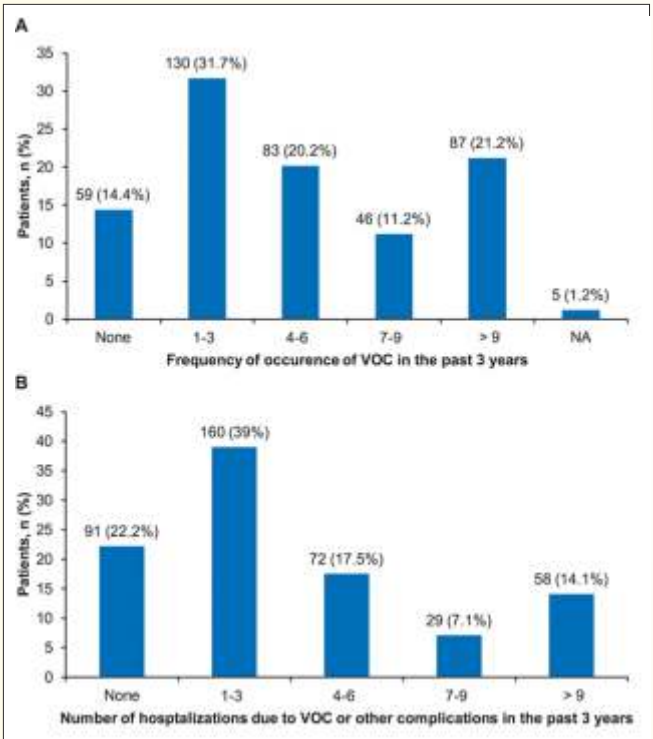

Figure 2. (A) Frequency of VOC in the past 3 years and (B) Hospitalization due to VOC or other complications in the past 3 years. NA, not available; VOC, vaso-occlusive crisis.

Introduction

Sickle cell disease (SCD) is an autosomal recessive, monogenic, a multi-organ disorder associated with high morbidity, mortality, and poor quality of life [1]. It is characterized by inefficient sickle-shaped red blood cells, produced due to a mutation in the hemoglobin gene (sickle hemoglobin, HbS) [2,3]. SCD is prevalent worldwide but is most common among people from the sub-Saharan African, Spanish-speaking regions (including South and Central America), India, Middle Eastern, and other Mediterranean countries [4]. The distribution of homozygous SCD in different Middle-East Arab countries of Gulf cooperation council was reported in available literature from Qatar (3.9%), Oman (3.8%), Bahrain (2.1%), United Arab Emirates (UAE; 1.9%) Yemen (0.95%) and Saudi-Arabia (0.01%–0.10%) [5–9]. Malarial endemicity, high rates of immigration, large family size, tribe/clan endogamy, and consanguinity in Arab communities over the decades have led to a genetic drift toward abnormal HbS, increasing frequency of SCD in the Gulf region [4]. Almost two-thirds of patients with SCD carry a homozygous HbSS genotype (sickle cell anemia) and are severely affected [10]. Patients who carry a heterozygous HbS and normal β-globin (sickle cell trait) are clinically asymptomatic. Other patients carry a compound heterozygote with 1 copy of the HbS and a β-globin gene variant (HbSC, HbSD, HbSE, HbSO Arab) or β-thalassemia variant (sickle beta plus thalassemia [HbSβ+] or sickle beta zero thalassemia [HbSβ0],). HbSβ0 is

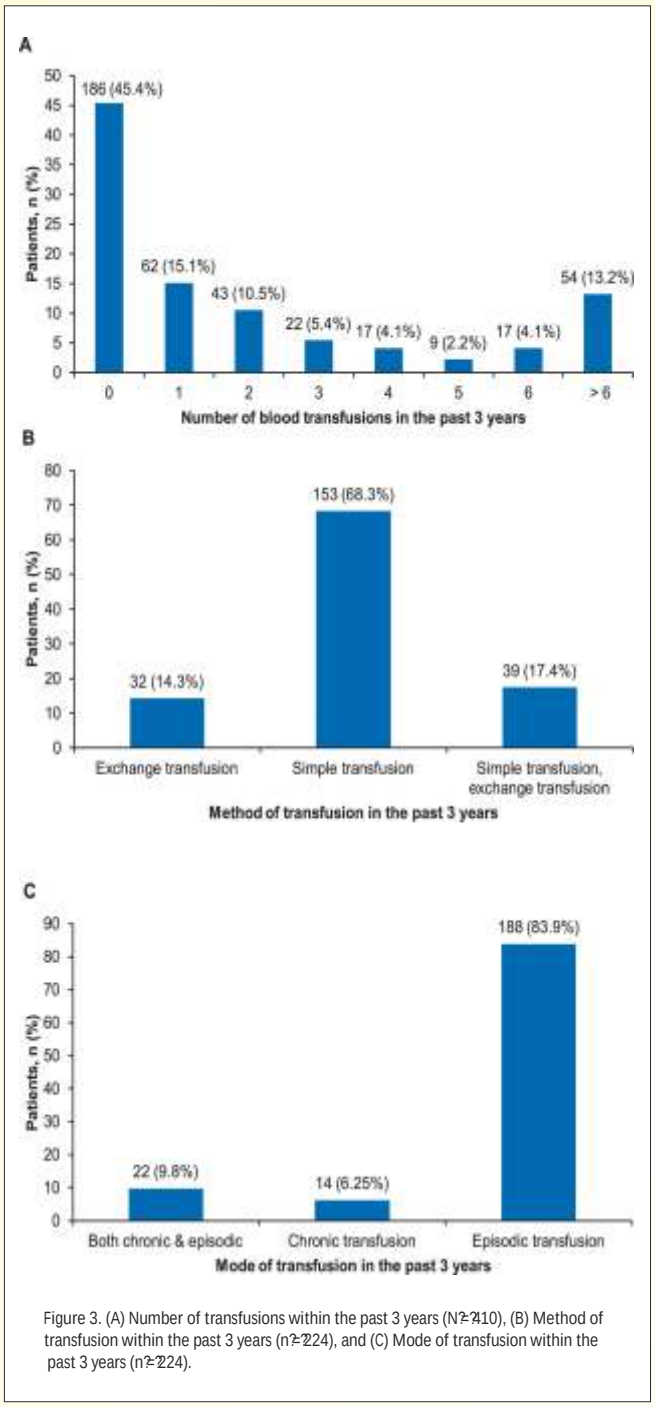

Figure 3. (A) Number of transfusions within the past 3 years (N=410), (B) Method of transfusion within the past 3 years (n=224), and (C) Mode of transfusion within the past 3 years (n=224).

usually as severe as HbSS, while other genotypes vary from mild to moderate in severity [10–12].

Morbidity and mortality in SCD patients primarily occur due to vaso-occlusive crises (VOC) and cerebrovascular events that follow obstructed blood flow [13]. Other common complications include severe anemia, acute chest syndrome, and splenic and renal dysfunction [13]. SCD usually manifests clinically within the first 6 months of life, but the clinical presentation and severity varies considerably [13,14]. For instance, the frequency of neurologic complications of SCD varies with age: silent brain infarcts occur in 39% by age 18; ischemic stroke, in 1% and 11% of children with and without effective screening and prophylaxis, respectively; and hemorrhagic stroke, in 3% of children and 10% of adults [13]. The risk of clinically apparent stroke in SCD is lowest among children aged <2 years, is 1.02% per year between the ages 2 and 5 years, and increases to 11% and 24% by the age of 20 and 45 years, respectively [13]. The overall incidence of stroke in children is 0.5% to 1% per year, suggesting that > 100 children/year need a blood transfusion to prevent a stroke [15]. The risk of recurrent stroke without transfusion is 46% to 90% [16,17].

Transcranial Doppler (TCD) is a well-established predictor of the risk of ischemic stroke. TCD measures the time- averaged maximal mean velocity (TAMMX) in distal intracranial portions of the internal carotid artery and the proximal middle cerebral artery (MCA) [16]. In children with abnormal cerebral blood flow velocities (TAMMX values $\geq$200 cm/s), indefinite monthly blood transfusion is the optimal choice

Table 1. TCD imaging velocities of patients (TAMMX).

TCD imaging velocity	Baseline N = 410		Follow-up n = 7	
	Left n (%)	Right n (%)	Left n (%)	Right n (%)
I-Normal velocity (<155 cm/s)	376 (91.7)	377 (92.0)	7 (100)	6 (85.7)
I-Conditional velocity (155–179 cm/s)	4 (1)	5 (1.2)	0 (0)	1 (14.3)
I-High velocity (≥180 cm/s)	0 (0)	1 (0.2)	0 (0)	0 (0)
I-inadequate velocity	3 (0.7)	3 (0.7)	0 (0)	0 (0)
Missing	27 (6.6)	24 (5.9)	0 (0)	0 (0)

Abbreviations: TAMMX, time-averaged maximal mean velocities; TCD, transcranial Doppler.

of therapy. Chronic blood transfusion reduces the risk of stroke by 90% as it maintains the level of HbS at <30% and hemoglobin (Hb) at 9–10 g/dL [18,19]. In patients with acute complications such as acute chest syndrome and/or stroke with a baseline Hb of ≥9 g/dL, exchange transfusion is indicated, while in patients with Hb ≤5 g/dL, simple transfusion is considered more appropriate [18].

The aim of this study was to evaluate the disease characteristics and treatment profile of patients with SCD in the Gulf region and determine the proportion of patients with a high risk of stroke, as determined using TCD.

Methods

Study overview

This multicenter, regional, descriptive, cross-sectional study was conducted in 3 treatment centers of the Gulf region, one each in Oman, Qatar, and United Arab Emirates (UAE). Patients aged 2–16

years with a confirmed diagnosis of SCD were eligible. The study was conducted according to the ethical principles of the Declaration of Helsinki, and informed consent was obtained from all parents/legal guardians of enrolled patients. The study included a baseline visit, 1 followup visit (after 2 months) for patients with conditional velocity on TCD, and data from past 3 years was analyzed retrospectively for all patients. The primary objective of the study was to determine the proportion of patients with SCD who were at a high risk of stroke with abnormal TCD results, and were eligible for transfusion therapy. The secondary objectives were to assess the characteristics, disease and treatment profile, and distribution of patients with SCD in the Gulf region.

Assessments

Demographics, HbS genotype pattern, history of acute pain crises, hospitalizations in the past 3 years, frequency of blood transfusions and other treatments in the past 3 years, and history of diseases other than SCD were recorded at baseline. HbS genotype pattern was studied using high-performance liquid chromatography. All patients with a conditional velocity at baseline were required to undergo a confirmatory TCD at a follow-up visit scheduled after 2 months. A single ultrasound operator performed TCD imaging at both baseline and follow-up visits for each patient using PHILIPS IU 22 machine, 2 MHz TCD ultrasound transducer. The sonographer placed the transducer over the temporal area just above the zygomatic arch, in front of the tragus of the ear and oriented the transducer slightly upwards, anteriorly. The probe is placed so that the power motion Doppler screen is filled with color signals between 30 and 80 mm depth. A red color signal (towards the probe) between 40 and 65 mm represents the flow in the ipsilateral MCA, while the blue signal between 65 and 80 mm represents the flow from the ipsilateral anterior cerebral artery. Concomitant treatments and clinical adverse events (AEs) were recorded at baseline and at the follow-up visit for all patients with conditional velocity recorded at baseline. As per the study protocol, AEs may be related to medical procedures, including TCD, or other concomitant treatments in the study.

Statistical methods

About 500 patients were to be enrolled

and their data analyzed; no formal sample size calculation was performed. The study data were analyzed using descriptive epidemiological statistical methods. Risk of stroke was analyzed in 2 ways: (1) as a categorical outcome (using logistic regression models): normal velocity vs conditional/high velocity and (2) as a continuous outcome, the continuous TAMMX score, (using linear regression models). Risk of stroke yielded by TCD was categorized (by TAMMX) as low risk: normal velocity <155 cm/s, moderate risk: conditional velocity = 155–179 cm/s and high risk: high velocity ≥180 cm/s [20]. Difference in TCD imaging results from baseline to follow-up for patients who scored conditional velocity at baseline was determined using the McNemar test (cross tabulation). Correlation of age, sex, race, HbS genotype pattern, transfusion type and frequency with the risk of stroke was analyzed using bivariate logistic regression models and bivariate/ multivariate linear regression models. Significance for all statistical procedures was considered at $P < 0.05$. All statistical analyses were performed using IBM SPSS software version 22. Clinical AEs were recorded at baseline and follow-up visits for all patients with a conditional velocity at baseline.

Results

Patient disposition

Overall, 412 patients were recruited in the study between February 23, 2014, and August 24, 2016. In total, 410 patients (male, 222 [54.1%]; female, 187 [45.6%]) who met the age inclusion criteria (2–16 years) were analyzed at baseline. Eight patients with conditional velocity were requested to attend the follow-up 2 months after their baseline visit. Followup data were collected from 7 patients. Overall, 384 patients (93.66%) completed the study. Twenty-two patients either lost follow-up or prematurely withdrew from the study (Figure 1).

Demographics and other baseline characteristics

Of the 410 patients (Caucasians [58.8%]; African Americans [12.9%]; Arabs [28.3%]), 86.6% were recruited from Oman, 8.3% from Qatar, and 5.1% from the UAE. Overall, 79.8% (327 of 410) had a family history of SCD, with most being first-degree relatives (84.4% [275 of 326] followed by second-degree relatives, 14.7% [48 of 326] and both first-and second-degree

relatives, 0.9%) (Supplementary Table S1).

History of SCD

Hbs genotype pattern

The most common HbS genotype was HbSS (217 [52.9%]), followed by HbSβ0 thalassemia (106 [25.9%]), and HbSβ+ thalassemia (74 [18.0%]). Few patients (3.2% [13 of 410]) reported other HbS genotype patterns including sickle cell hemoglobin D (HbSD), sickle cell hemoglobin E (HbSE) and HbS codon-71 (Supplementary Table S1).

Clinical manifestations

The most common type of the first presentation (related to the history of SCD) was VOC (237 [57.8%]), followed by anemia (98 [23.9%]). VOC with anemia was reported in an additional 10 patients (2.4%), while 12 patients (2.9%) were asymptomatic. Of the 410 patients with SCD, 59 (14.4%) did not report any VOC, and 346 (84.4%) reported having a VOC at least once in the past 3 years (Figure 2A). Other clinical manifestations of SCD were reported in 222 patients (54.1%) within the past 3 years. The most common clinical manifestations (> 25%) included splenic sequestration crisis (40.5%), acute chest syndrome (33.3%), and hemolytic crisis (25.2%). Aplastic crisis was reported in 3.6% (8 of 222) of patients, stroke was reported in 1.8% (4 of 222), and silent stroke in another 1.8% (4 of 222) of patients.

Hospitalization

Of 410 patients, 319 (77.8%) required hospitalization at least once in the past 3 years owing to VOC or other complications (Figure 2B).

Treatment history of SCD

Overall, 400 of 410 patients (97. 6%) at baseline received prior treatment, all 400 patients received folic acid, 291 (72.8%) received prior blood transfusion therapy, 22 (5.5%; deferasirox [n = 15], deferiprone [n = 6]) received iron chelation therapy, and 184 (46%) received hydroxyurea.

History of blood transfusion therapy in the past 3 years

Of the 410 patients, 224 (54.6%) received ≥1 blood transfusion in the past 3 years (Figure 3A). Simple transfusion (153 patients [68.3%]) was the most common method

of transfusion (Figure 3B), and episodic transfusion (188 patients [83.9%]) was the most common mode of transfusion (Figure 3C).

Transcranial Doppler imaging

Of 410 patients, 376 (91.7%) and 377 (92.0%) reported normal velocity (<155 cm/s), and 4 (1%) and 5 (1.2%) reported conditional velocity (155–179 cm/s) on their left and right sides, respectively, at baseline. Only 1 patient (0.2%) had a high velocity (≥180 cm/s) on the right side (TAMMX = 181 cm/s) at baseline (Table 1).

Seven patients with the conditional velocity at baseline underwent repeat TCD at the follow-up visit after 2 months. Of the 7 patients, one had a conditional velocity of 155 cm/s in the right TCD. Of the 7 patients, 6 (85.7%) had normal TCD velocities at follow-up, in contrast to their baseline conditional velocity. Left TCD imaging for all 7 patients (100%) reported normal velocities (<155 cm/s) at follow-up. Based on the McNemar test, the changes in TCD findings from baseline to follow-up in these 7 patients were non-significant (P = 1.000).

Although it was not part of the study protocol, in Oman, 29 patients with low TCD values (<70 cm/s velocity) were followed up for a repeat TCD imaging after 2 months. Patients with persistently low values were further assessed by magnetic resonance imaging, magnetic resonance angiography, and magnetic resonance venography. Seven of these patients were found to have abnormalities in cerebral circulations. Three had a severe form of Moyamoya disease, 2 had aneurysm of the MCA, 1 had tortuosity of the left MCA, and 1 had findings consistent with multiple cavernomas in the cerebellar hemispheres.

Correlations of predictor variables and risk of stroke

Bivariate and multivariate regressions were conducted between the predictor variables (age, sex, race, HbS genotype pattern, transfusion type, and frequency of transfusions) and risk of stroke. Based on the bivariate logistic regression model, race was the only predictor for the risk of stroke (conditional/high velocity ≥ 155 cm/s) (Supplementary Table S2). Caucasians were at a lower risk of stroke than African Americans (odds ratio [OR], 0.145; P = 0.003). No other predictors were significantly correlated to the risk of stroke and none had a P value of ≤0.2 to allow inclusion in the

multivariate regression model. Based on the bivariate linear regression model, age, race, type of transfusion, and frequency of transfusion were all significant predictors of TCD velocity (Supplementary Table S2). Older patients with SCD had significantly lower TCD velocities (B: -0.789; P < 0.0001). Caucasian or Arab patients also had significantly lower TCD velocities (B: -6.599; P < 0.0001). Patients with exchange transfusion had lower TCD velocities than those with simple transfusion, and those with both exchange and simple transfusions had the lowest TCD velocities (B: -5.902; P < 0.0001). Patients with higher transfusion frequencies had higher TCD velocities (B: 0.798; P = 0.016). Based on the multivariate linear regression model, sex, race, and transfusion type were significantly associated with TCD velocities (Supplementary Table S2). Females had a higher TCD velocity than males (B: 5.53; P = 0.017). Caucasians had a TCD velocity lower than patients with an African American descent by 4.68 points, and patients with an Arab descent had a TCD velocity lower than Caucasians by another 4.68 cm/s (B: -4.68; P = 0.012). Patients with an exchange transfusion had a TCD velocity lower than that of patients with a simple transfusion by 4.97 cm/s, and patients with both simple and exchange transfusions had a TCD velocity lower than that with an exchange transfusion by another 4.97 cm/s.

Adverse events

Thirty-eight AEs were reported by patients during the study, and most were mild (76.3%) in severity. The most common AEs (reported in >1 patient) included VOC (n = 7; moderate [n = 4], mild [n = 3]), abdominal pain (n = 3; moderate [n = 1], mild [n = 2]), upper respiratory tract infection (n = 5; all mild), back pain (n = 2; moderate [n = 1], mild [n = 1]), and vomiting (n = 2; all mild). No patient with conditional velocity reported any AEs at follow-up visit after 2 months. No deaths occurred during the study.

Discussion

This multicenter, cross-sectional study reported the characteristics, disease and treatment profile, and distribution of SCD in children (aged 2–16 years) from the Gulf region (Oman, Qatar and UAE).

All patients included in the study were aged 2–16 years, in line with the recommended age for screening to

identify high risk of stroke by TCD in the Stroke Prevention Trial in Sickle Cell Anemia (STOP) study [21]. Gujjar AR et al demonstrated that adults and children >15 years old in Oman (n = 18) had significantly lower TCD velocities than younger children (P < 0.03) [22]. Similarly, in the present study, results from the bivariate linear regression model analysis revealed that older children with SCD had significantly lower TCD velocities (B: -0.789; P < 0.0001). These results were consistent to those of the first incidence of cerebrovascular accident (per 100 patient-years) in patients with SCD by age group: <2 years, 0.08; 2–5 years, 0.75; 6–9 years, 0.55; 10–19 years, 0.30 [23].

Most patients (79.8%) in this study who had a family history of SCD reported so mainly in their first-degree relatives (84.4%). The high incidence was believed to be due to genetic inheritance linked with malaria endemicity, high rate of consanguinity, large family size, and tribe /clan endogamy in Arab communities [4,24,25]. Ashley-Koch et al stated that individuals of African descent exhibited the highest frequency of at-risk genotypes associated with HbS [11]. In this study, race was identified as a significant predictor for the risk of stroke determined by TCD velocities; African-Americans were at a high risk of stroke, followed by Caucasians and Arabs. In our cohort, females had higher TCD velocities (B: 5.53; P = 0.017) than males. Karl MC et al. showed that female children were significantly more in the conditional and abnormal velocity diagnostic groups (χ^2 =6.24; P < 0.05) [26]. Saraf SL et al suggested that VOC, stroke, acute chest syndrome, and early mortality were higher with HbSS or HbSβ0 thalassemia than with HbSC or HbSβ+ thalassemia [27]. Ashley-Koch et al. showed that the US incidence of median survival by genotype was higher in females than in males with SCD [11]. However, Adekile A et al showed, no consistent differences in TCD velocity between male and female patients or in patients with different HbS genotypes [28]. In the current study, the correlation of HbS genotypes with TCD velocities, which in turn correlate with risk of cerebrovascular events, was not significant. Fewer genotypes other than HbSS might explain this finding. The incidence of stroke in SCD was reported as 0.61, 0.17, 0.11, and 0.10 per 100 patient-years among HbSS, HbSC, HbSβ+ thalassemia, and HbSβ0 thalassemia genotypes, respectively [23]. In this study,

8 of 410 patients had a stroke with a prevalence of 1.95%, which is far below the reported prevalence in the literature (11% by age of 20 years) [15,29]. Younger age of the patients might explain this finding. Reported use of hydroxyurea in almost 50% of patients in our study might also explain the lower prevalence of stroke in this study.

The STOP study demonstrated that simple or exchange transfusion prevents the occurrence of stroke in patients with a prior stroke or with high TCD values [18]. In addition, a retrospective study [30] found that the recurrence of secondary stroke in SCD with exchange transfusion is lower than that with simple transfusion therapy. Consistent with published literature, [18,30,31] TCD velocities in patients with exchange transfusion were lower than that with simple transfusion by 4.97 cm/s, and TCD velocities with both simple and exchange transfusions were lower by another 4.97 cm/s than with exchange transfusion alone. A correlation between HbS genotype pattern and transfusion frequency with TCD velocities may be possible, since the P values were close to significance. According to TCD imaging results, most (>90%) patients had normal velocity (<155 cm/s) at baseline and were not followed-up as per protocol. Of the 7 patients with a baseline conditional velocity, only 1 patient confirmed a conditional velocity of 155 cm/s at follow-up. In addition, the patient who had high velocity (≥180 cm/s) at baseline had normal findings at follow-up. Thus, based on our TCD results, no conclusions can be derived with regard to confirmatory TCD findings for patients with SCD with either a conditional velocity or a high velocity. The conclusion that nonetheless can be drawn from a single TCD imaging result (especially if the result is conditional) may not be adequate. On the other hand, of 29 patients (from Oman in our study) with low TCD velocities (TAMMX <70 cm/s) who were followed up for a repeat TCD imaging after 2 months, seven were found to have abnormalities in cerebral circulations. Zetola, et al. suggests that very low TCD velocities (<70 cm/s) may be indicative of severe stenosis [32]. Thus, low TCD velocities may be truly abnormal and need further evaluation with regard to their correlation with the occurrence of cerebral vascular abnormalities. None of the AEs recorded during the study could be affirmatively related to the study procedures. Thus, this study did not impose any risks related to the safety measures.

This study had some limitations. Differences in racial and genotype distribution might have affected the correlation analysis of predictor variables and the risk of stroke. Population genetic studies have shown that patients recruited from Oman, Qatar, and UAE present wide variations in clinical features ranging from mild to moderate to severe disease, with different β-globin gene (Benin, Bantu and Saudi-Indian) haplotypes, elevated fetal hemoglobin (Hb F) levels, and associated alpha thalassemia [4]. The study did not evaluate the impact of hydroxyurea or other major modifiers of SCD genotype (beta globin haplotype, HbF levels, alpha thalassemia) on TCD velocities.

Future studies should enroll a large sample that includes more proportions of patients with SCD at a high risk/ high TCD velocity, and re-confirm the baseline TCD imaging results at a follow-up visit using same methodology.

Geolocation Information

Oman, Qatar, and United Arab Emirates (UAE).

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Disclosure statement

Yasser Wali is an employee of Sultan Qaboos University, received research grants and honoraria from Novartis and Pfizer. Mohamed A Yassin is an employee of Hamad Medical Corporation and reports received research funding and honoraria from Novartis Pharmaceuticals. Vishwanatha Kini has nothing to disclose. No other potential conflict of interest was reported by the authors.

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