Repeat transcranial Doppler ultrasound imaging in Kuwaiti children with sickle cell disease after a 10-year interval

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Abstract

Objectives: Transcranial Doppler imaging (TCDI) of the cerebral arteries is the method of choice to predict patients with sickle cell disease (SCD) at risk for stroke. The present study reports TCDI follow-up of cerebral blood flow in Kuwaiti children with SCD after a 10-year interval. **Methods:** Twenty-one pediatric patients with SCD, aged 16.0 ± 1.6 years were initially studied when they were aged 6.5 ± 1.2 years. TCDI scanning was carried out using a phased-array transducer of 1-3 MHz through the trans-temporal window. Peak systolic velocity (PSV), end diastolic velocity (EDV), time-averaged mean of the maximum velocity (TAMMV), resistive index (RI), and pulsatility index (PI) were obtained in the anterior and posterior Circle of Willis vessels. **Results:** The follow-up indices were mostly lower than in the initial study although they remained within the normal range in all the arteries. TAMMV was less than 170 cm/s, and PSV did not exceed 200 cm/s in all vessels. The initial and follow-up TAMMV were: 77.3 ± 20.9 and 71.6 ± 9.9 in the terminal internal carotid artery, 94.3 ± 25.8 and 82 ± 18.2 in the middle cerebral artery, 76.6 ± 25.6 and 70.6 ± 10.7 in the anterior cerebral artery, and 59.1 ± 15.8 and 63.9 ± 8.5 in the posterior cerebral artery respectively. The differences between the old and follow-up data for PSV, RI, and PI were statistically significant ($P<0.05$). **Conclusions:** Kuwaiti patients with SCD appear to be largely protected from cerebral artery vasculopathy in childhood.

Introduction

Although a monogenic blood disorder, sickle cell disease (SCD) presents with a progressive vasculopathy triggered by free heme, which causes activation of endothelial cells, reticulocytes, neutrophils and platelets[1,2]. Consequent nitric oxide depletion leads to vasoconstriction, upregulation of adhesion molecules and endothelial intima proliferation[3,4]. As a direct consequence of this, SCD patients are prone to several complications including chronic lung disease, leg ulcers and stroke[5]. The latter is the most devastating of the complications and it is ischemic in affected children, in whom it occurs in about 11% before the age of 20 years if no specific intervention is instituted[6]. Arterial stenosis usually occurs in the large vessels of the Circle of Willis, especially the internal carotid, the middle and anterior cerebral arteries.

Stroke tends to be recurrent in SCD; therefore, there is a need for primary and secondary prevention by identifying patients at risk[6]. Transcranial Doppler ultrasound imaging (TCDI) is used for screening children with SCD and the STOP guidelines call for patients with abnormal time-averaged mean of the maximum velocity (TAMMV) of >200 cm/s to start prophylactic blood transfusions to reduce the concentration of HbS[7]. Hydroxyurea has also been shown to be effective for primary stroke prevention, especially in resource-poor populations[8].

Kuwaiti patients with SCD uniformly carry the Arab/India (A/I) haplotype and have elevated HbF levels[9,10].

Stroke is relatively rare in these patients, just as has been reported for other Arab Gulf patients with SCD[11]. A previous TCDI study carried out in Kuwait about 10 years ago did not identify any patients with abnormal or conditional TAMMV in any of the cerebral arteries[12]. The present study was therefore designed to repeat TCDI as a follow up on the same patients to see if or how their parameters have changed in the intervening years. Would the TAMMV values remain in the normal range or would the effects of cumulative vasculopathy be evident in elevated velocities? Or will the effects of age produce lower velocities than in the initial study?

Patients and Methods

Patients

Efforts were made to recall as many of the patients in the previous observational study [12] as possible, using the parents' phone numbers. The study was conducted between September 2021 and May 2022. The patients were attending the pediatric and adult hematology clinics of Mubarak Al-Kabeer Hospital in Kuwait. They were studied in steady state i.e., no acute illness, crisis or blood transfusion within 3 months of the study. The study was approved by the Human Ethics Committee of the Health Science Centre and the Kuwait Ministry of Health. An informed, signed consent was obtained from the parents and/or patients as appropriate.

Laboratory Examinations Ethylenediaminetetraacetic acid (EDTA) tubes were used to collect blood through venipuncture. Complete blood count (CBC) was carried out using ABX Pentra 120 cell counter. Cation-exchange high performance liquid chromatography (HPLC) was used to confirm the hemoglobin (Hb) genotype and the hemoglobin F (HbF) concentration. Serum lactate dehydrogenase (LDH, IU/L), and bilirubin (μmol/L) were measured using routine techniques.

Transcranial Doppler Imaging (TCDI)

TCDI was performed through the temporal window using the GE, Vivid 3, USA ultrasound machine with a 1-3 MHz phased-array transducer, equipped with both color and power Doppler capabilities. With the patient lying in a supine position on the ultrasound table at room temperature (22 ± 2°C), terminal internal carotid artery (t-ICA-C_5), middle cerebral artery (MCA-1), anterior cerebral artery (ACA-1), posterior cerebral artery (PCA-1), and basilar artery were respectively insonated. No angle correction was used. An envelope outlining the peak velocity throughout 3 to 5 cardiac cycles was taken. The envelope of the waveform was traced electronically or manually, depending on the quality of the waveform.

The highest cerebral blood flow velocities with an insonation sample gate diameter of 4-6 mm was recorded. Flow direction, PSV (peak systolic velocity), EDV (end diastolic velocity), TAMMV (time-averaged mean maximum velocity), RI (resistivity index), and PI (pulsatility index) were stored on the ultrasound machine memory and recorded on the scan template for later analysis. RI was calculated automatically by the PSV-EDV/PSV formula and PI was calculated from the Doppler trace by PSV-EDV/MV(mean velocity) formula. The TCDI was performed by one experienced vascular sonographer (AA), who was blinded to the previous data at the time of follow-up.

Statistical analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 27 for Windows (SPSS Inc., Chicago, IL, USA). Independent t-test was used to test for statistical significance of differences in the mean values between the old and follow-up data in SCD patients. Paired t-test was used to test for any significant differences between both sides for all vessels between. Pearson's correlation coefficient was used to test the correlation between TAMMV and the other vascular parameters for each vessel. A p value of <0.05 was considered statistically significant.

Results

Twenty-one (11 HbSS, 9 HbSβ^0 Thal, and 1 HbSD) out of the 43 patients in the original study were successfully recalled and studied. Of the other 22 patients who could not be studied, 11 were away in college, 6 had changed their phone numbers, and 5 did not give consent. The mean age of the 21 patients at the time of the initial TCDI was 6.5±1.2 and at the time of the follow-up scan the mean was 16.0 ± 1.6

years. The mean follow-up was 10.1 ± 3.1 years (range, 7 - 10 years). There was a predominance of girls (62%) over males (38%). All the patients were on hydroxyurea (HU) between 2012 and 2022.

The patients presented significantly lower mean total Hb, hematocrit, and bilirubin but significantly higher HbF, platelets, and ANC counts than in the initial study. The mean LDH, WBC, and reticulocyte count showed no significant differences. Subjects' characteristics are summarized in Table1.

There were significant differences ($p<0.05$) between old and follow-up data for all vascular parameters in all vessels. In general, follow-up SCD patients showed lower values than the old data although the values were within the normal range in all the cerebral arteries. All TAMMV values were less than 170 cm/s, and no PSV value exceeded 200 cm/s in any vessel. Normal values of PI (0.5-1.2) and RI (0.5-0.7) were observed in both old and follow-up studies. The mean ± SD of TAMMV for old and follow-up data for t-ICA, MCA, ACA, and PCA were 77.3±20.9, 71.6±9.9; 94.3±25.8, 82±18.2; 76.6±25.6, 70.6±10.7; and 59.1±15.8, 63.9±8.5, respectively. There was positive statistically significant difference for PSV and significant negative differences for RI and PI ($P<0.05$). There was no statistically significant difference for EDV and TAMMV ($P>0.05$). There were no statistically significant inter-hemispheric differences ($p<0.05$) in both groups for all parameters. Results are summarized in Table 2.

Discussion

Several studies are bearing out the relative rarity of neurological events among patients with SCD in the Arabian Gulf. This is particularly true of patients with the AI haplotype and increased HbF level, where the prevalence of stroke is <1.0%[11,13,14]. Moreover, it has been shown consistently that cerebral blood flow is hardly impeded, with very low prevalence of abnormal or conditional TAMMV in studies from Kuwait and other Gulf[15,16]countries. This suggests low progression of cerebral vasculopathy among these patients. Interestingly, however, this sparing of the cerebral vessels is not only limited to patients with the AI haplotype, as reports from Oman[17,18], Iran[15] and Iraq[16,19], where this haplotype is not particularly common, also report relatively normal TCDI indices. Therefore, there may be other obscure factors in this population that protect them from neurological events.

There are not many prospective studies of TCD among SCD patients in the literature. We therefore thought it was intriguing to investigate what would happen over time to cerebral blood flow velocities among our Kuwaiti patients. Hence we recalled patients who were studied about 10 years ago as relatively young children. We wanted to see if the effects of vasculopathy would now be evident as increased TAMMV values or if, indeed they would remain static or, in fact, decrease. It was interesting that uniformly, the TAMMV and other indices showed significant decreases compared to the values in the initial study.

Even, in the normal population, TAMMV decreases with age[19] and in our previous study[12], we found a negative correlation between the 2 variables. It was therefore not surprising that TAMMV decreased over the 10-year interval in the patients in whom we succeeded in repeating the study. It also indicates that there has been no significant vasculopathy that would produce stenosis and associated increased TAMMV. The other possible factor is the effect of hydroxyurea, which has been associated with decreasing TAMMV and useful in preventing primary stroke as an alternative to chronic transfusion therapy[20-22]. Moreover, the significant increase in the HbF level between the 2 studies, could be attributed to hydroxyurea effect.

Our previous studies[12,23] also showed that silent brain infarcts (SBI) are uncommon in our patients under the age of 12 years, although among adult Kuwait patients, the prevalence is ˜20%[24]. This is the reverse of what has been reported among American patients in whom SBI is common in early childhood and rare after 16 years. We have interpreted this as effective protection from cerebral vasculopathy, that is provided by elevated HbF levels at the critical period of 2 - 3 years of age, when vasculopathy is established, hence the peak incidence of ischemic stroke in susceptible patients is between the ages of 7 and 10 years[6]. However, before the age of 3 years, most of our patients have HbF levels of 20 - >30%[25], thus inhibiting the development of significant vasculopathy. There is still ongoing low-level chronic inflammation, hence the relative severity of SCD among our adult patients and the increased prevalence of SBI[13,24,26].

The major limitation of this study is the small sample size. Larger prospective studies are required to investigate long-term effects of SCD on cerebral vasculopathy in patients with elevated HbF. It is also important to correlate TCDI indices with MRI/MRA findings, as well as neurological and psychological examination results especially in patients with very low TAMMV since we do not have many patients with abnormally elevated values.

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Conflict of Interest Statement : The authors have no conflict to report

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`Table 2 LT.docx` available at https://authorea.com/users/514268/articles/590124-repeat-transcranial-doppler-ultrasound-imaging-in-kuwaiti-children-with-sickle-cell-disease-after-a-10-year-interval