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Effect of chronic transfusion therapy on progression of neurovascular pathology in pediatric patients with sickle cell anemia

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ABSTRACT

Background: Chronic blood transfusion (CBT) is currently the standard of care for primary and secondary stroke prevention in children with sickle cell anemia (SCA). However, the effect of CBT on cerebrovascular pathology is not well known.
Methods: We reviewed children with SCA receiving CBT for abnormal transcranial Doppler (TCD) [n = 12] or cerebrovascular accident (CVA) [n = 22]. Baseline cerebral magnetic resonance imaging (MRI) and magnetic resonance angiogram (MRA) were compared with the most recent scans available for each patient and independently scored by a neuroradiologist.
Results: Thirty-four patients with a mean age of 6.5 years at the time of baseline MRI/MRA were studied. Average elapsed time from baseline to most recent scans was 7.3 years. Overall, patients experienced worsening vasculopathy, as measured by mean increases in their baseline MRI and MRA scores of +0.76 and +1.03. There was a significant difference in the mean change of MRI/MRA scores between patients who had CVA and abnormal TCD (MRI; +1.23 vs. −0.08, p = 0.001 and MRA; +1.54 vs. +0.08, p = 0.02). Patients with abnormal baseline MRA had worsening scores compared to those with normal baseline MRA (54% vs. 9.5%, p = 0.01). Also, patients who had CVA were more likely to have an abnormal baseline MRA and worsening scores compared to abnormal TCD patients.
Conclusion: We show that children with CVA experience progression of cerebral vasculopathy despite CBT. In contrast, CBT for abnormal TCD confers protection against the development and/or progression of cerebral vasculopathy. This effect appears to be real given our large cohort of patients with longer follow up as compared to previous studies.

Introduction

One of the most feared complications of sickle cell anemia (SCA) is stroke. Children with SCA are 221 times more likely to experience stroke when compared to their peers [1–3]. Stroke occurs in 11% of sickle cell patients by the age of 20 and in 15% by age 30. The vast majority of strokes occurring before age 20 are found to be ischemic, whereas those occurring after age 20 are mostly hemorrhagic [4].

The current standard of care for patients with overt cerebrovascular accident (CVA) is immediate initiation of chronic blood transfusion (CBT) therapy. CBT is thought to increase oxygen saturation, and therefore reduce red blood cell sickling. The recurrence rate of stroke in sickle cell patients is around 70% without treatment where as CBT decreases this risk to as low as 0–13% [2]. In 1998, the STOP trial led by Dr. Adams found that CBT therapy in patients with an abnormal transcranial Doppler (TCD) exam (defined as a timed average mean maximum velocity ≥ 200 cm/s) conferred a 92% reduction in primary stroke risk [5]. It was also found that stopping the treatment even after normalization of TCD velocity could result in the reversal of the benefit of chronic transfusion therapy [6]. Since that time, CBT has been widely used as a method of primary stroke prevention in patients with abnormal TCD.

Although there have been many studies of clinical stroke risk and prevention in SCA, little is known about the effect of chronic transfusion therapy on radiographically observed cerebrovascular pathology. Previous studies have reported that CBT has been effective in arresting the progression of stenosis of cerebral blood vessels in most sickle cell children after stroke but failed to prevent progression in patients with large vessel disease such as Moyamoya syndrome [7,8]. We sought to determine the effect of chronic blood transfusion

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on the progression of cerebral vasculopathy in our pediatric cohort with sickle cell anemia.

Material and methods

We retrospectively reviewed the electronic medical records of pediatric sickle cell patients at our institution who were on chronic transfusion therapy. We abstracted clinical, laboratory, and transfusion history data from each patient. Each of these patients had baseline MRI and MRA scans performed around the time of the CVA or abnormal TCD as well as every few years after starting the chronic transfusion therapy. The baseline and most recent scans available were retrospectively assessed by an experienced Neuroradiologist with no access to each patient's demographic and clinical information. A total of 136 MRIs and MRAs, all performed as 1.5 T (Philips-Intera and Siemens-Avanto) scans, were evaluated. The MRI studies included non-contrasted sagittal T1-weighted images (TR: 400–500, TE: 12.5–14, slice thickness: 5 mm), axial T2-weighted images (TR: 4000–5000, TE: 90–140, slice thickness: 5 mm), and axial fluid-attenuated inversion recover images [FLAIR] (TR: 4150–8000, TE: 144–100, IT: 1800–2220, slice thickness: 5 mm). Fifty-one of the 68 MRI studies, all of which were performed after 1998 also had Diffusion-weighted images and apparent diffusion coefficient (ADC) maps. MRAs were performed in conjunction with MRIs and focused on the circle of Willis using time-of-flight sequence with 3-D reconstructions. Findings of patients' scans including abnormal white matter bright T2 signal, infarct, atrophy, arterial narrowing and occlusion, or Moyamoya phenomena, were systematically scored (Table 1) with a modified semi-quantitative scale based on prior reports [5,8]. The scoring system assigned distinct constant factor values for each finding according to severity.

Table 1
Modified semi-quantitative scale of neuroradiological findings in our cohort.

	Points	
MRI		
I. White matter signal abnormalities	Absent	0
	Mild	1
	Moderate	2
	Severe	3
II. Junctional infarctions	Absent	0
	One	2
	Two	4
	Three	6
III. Territory infarctions	Absent	0
	One	2
	Two	4
	Three	6
IV. Atrophy	Absent	0
	Mild	1
	Moderate	2
	Severe	2
MRA		
I. Lesions with less than 50% stenosis	Absent	0
	One	1
	Two	2
	Three	3
II. Lesions with more than 50% stenosis	Absent	0
	One	2
	Two	4
	Three	6
III. Lesions with total occlusion	Absent	0
	One	3
	Two	6
	Three	9
IV. Moyamoya disease	Absent	0
	Present	4

Statistics

The values obtained from each scan finding, as shown in Table 1, were added to produce the patient's final scores. These scores and other demographic information were compiled for each patient. The baseline and current scores were compared to determine if patients improved, stabilized, or worsened. Two-tailed Paired *T* Test was used to compare the mean MRI/MRA scores between groups with significant p values set ≤ 0.05. Fisher's Exact test was used to compare the impact of baseline MRA between groups with significant p values set ≤ 0.05.

Results

A total of 34 patients (53% male) with a mean age of 6.5 years at the time of baseline MRI/MRA were studied. Thirty- three patients had Hb SS phenotype and one patient had Hb Sβ° thalassemia. These patients were receiving chronic transfusions due to CVA ($n=22$) or abnormal TCD ($n=12$). The median elapsed time from baseline MRI/MRA to the current scans was 7 years (range 2–13 years).

Overall, patients had a mean change from the baseline MRI score of +0.76 and a mean change in MRA score of +1.03 indicating worsening vasculopathy (Table 1). However, there was a significant difference in the mean change of MRI score between patients started on transfusion for a CVA compared to patients with abnormal TCD (+1.23 vs. −0.08, respectively: $p=0.001$) (Table 2). There was also a significant difference in the mean change of MRA score between CVA and abnormal TCD patients (+1.54 vs. 0.08, respectively: $p=0.02$) (Table 2). This data suggests that patients in the CVA group have more progression (worsening) of pathology than those in the abnormal TCD group. Furthermore, patients with CVA were more likely to start with abnormal baseline MRA (mean baseline MRA score in CVA patients was 2.82 vs. a score of 0 in abnormal TCD patients) (Table 2).

Only 1 of 12 patients started on transfusion for an abnormal TCD showed worsening in MRA score. In contrast, 8 of 22 (36%) of CVA patients had worsening scores. CVA patients appeared more likely to have worsening scores when compared to abnormal TCD patients (Fig. 1). In addition, patients who had abnormal baseline MRA scores were more likely than those with normal baseline scores to have worsening cerebral vasculopathy (54% of baseline abnormal patients worsened vs. 9.5% of baseline normal patients) (Fig. 1). There was no significant difference in average age or average hemoglobin S (HbS) level between those who worsened and those who improved or stabilized (Table 3).

Discussion

The data from our study suggests that chronic blood transfusion in pediatric sickle-cell patients with abnormal TCDs prevents the progression of cerebral vasculopathy seen on MRI and MRA. This sheds new light on a topic for which there was previously little literature available.

Bader-Meunier et al. had also analyzed the efficacy of chronic blood transfusion in 24 patients with SCA [9]. Seventeen patients were receiving CBT for abnormal TCD and 7 patients for CVA. The mean follow up time was 29 months. The authors concluded that the course of cerebrovasculopathy in these patients was heterogeneous. There was a trend that patients who had CVA showed minimal improvement in their cerebrovascular pathology compared to those with abnormal TCD. However, this did not attain statistical significance due to a small sample size and limited follow up. In another report, Brousse et al. studied 18 sickle cell patients receiving chronic blood transfusions [10]. The median follow up time for the abnormal TCD group ($n=9$) was 14.3 months and the median follow up time for the CVA ($n=9$) group was 59.6 months. The authors showed that optimized transfusion treatment did not prevent progression of cerebral vasculopathy in the CVA group. They also observed that the absence of disease progression in the

Table 2
Effect of chronic blood transfusion therapy on cerebral vasculopathy in children with sickle cell anemia.

Group	Duration of transfusion	No of patients	MRI scores			MRA scores		
			Baseline (mean)	Current (mean)	Change	Baseline (mean)	Current (mean)	Change
All patients	10–13 years	9	2.33	3.67	1.22	2.33	3.89	1.55
	5–10 years	16	2.5	3.31	0.81	1.31	2.25	0.94
	2–5 years	9	3.11	3.22	0.11	1.22	2.89	1.78
	All	34	2.62	3.38	0.76	1.82	2.85	1.03
CVA	10–13 years	6	3.5	5.33	1.83	3.5	5.83	2.33
	5–10 years	10	3.4	5	1.6	2.1	3.6	1.5
	2–5 years	6	4.67	4.67	0	3.33	4.17	0.83
	All	22	3.77[a]	5[a]	1.23	2.82[a]	4.36[a]	1.54
Abnormal TCD	10–13 years	3	0	0.33	0.33	0	0	0
	5–10 years	6	1	0.5	−0.05	0	0	0
	2–5 years	3	0	0.33	0.33	0	0.33	0.33
	All	12	0.5[a]	0.42[a]	−0.08	0[a]	0.08[a]	0.08

MRI, magnetic resonant imaging; MRA, magnetic resonant angiography; CVA, cerebrovascular accident; TCD, Transcranial Doppler.
[a] p value<0.000001 when comparing CVA vs. abnormal TCD (changes in mean levels analyzed using two-tailed Paired *T* Test with significant $p \leq 0.05$).

abnormal TCD group, however this could be related to the short follow-up time in these patients. We feel that given our extended follow up, our study clearly demonstrates that transfusion therapy leads to the prevention of progression of cerebrovascular pathology in patients with abnormal TCD.

Chronic transfusion therapy does prevent overt stroke recurrence. However, chronic blood transfusions failed to protect the progression of cerebrovascular pathology in our cohort of patients with CVA which is consistent with previously reported studies [9,10]. As one would suspect, the baseline MRI and MRA scores of those patients in the CVA group were markedly worse than those in the abnormal TCD group. As previously mentioned, patients who started out with abnormal baseline scores are more likely to worsen despite chronic transfusion therapy. This suggests that once a vessel has crossed a certain threshold of pathology, chronic transfusion therapy is no longer able to prevent further damage. Thus, other treatment options must be considered in addition to CBT to prevent overt stroke in these at-risk patients.

One approach would be optimizing pretransfusion HbS level in these chronically transfused patients. Traditionally, pretransfusion HbS level is closely monitored with a goal of 30–50% in patients with stroke or abnormal TCD. This is based on a study by Cohen et al. suggesting that increasing target pretransfusion HbS level from 30 to 50% significantly decreased blood requirements and iron overload without affecting the clinical outcome in the prevention of recurrent stroke in SCA [11]. However, neuroradiological findings and the course of cerebral vasculopathy were not reported in that study. In our study, maintaining pretransfusion HbS level between 30 and 50% did not seem to affect the neurovascular progression. Future studies are needed to evaluate whether HbS% should be maintained at an even lower level to prevent progression of neuropathology in the most high risk patients.

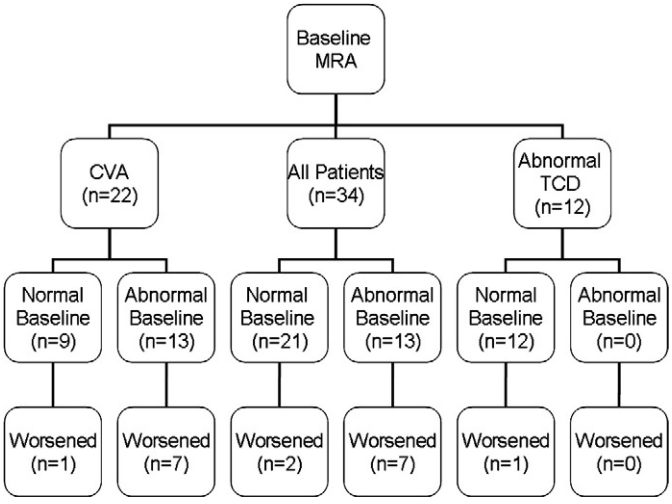

Fig. 1. Impact of baseline MRA on the progression of cerebral vasculopathy. [MRA, magnetic resonant angiography; CVA, cerebrovascular accident; TCD, Transcranial Doppler. *54% of abnormal baselines vs. 9.5% of normal baselines had worsening scores ($p = 0.01$)].

In a retrospective cohort study of children with SCA and strokes, Hulbert et al. reported that patients who received exchange blood transfusion both acutely and on a chronic basis had significantly fewer overt strokes compared to patients who received simple transfusions [12]. The efficacy of exchange transfusion in stabilizing and/or preventing the neurovascular progression could not be determined as MRI and MRA data were not reported in that study. It is possible that exchange rather than simple transfusions will be beneficial in arresting cerebrovasculopathy because they are more effective in reducing the blood viscosity and in improving oxygen transport [3]. However, routine implementation of exchange transfusion may be challenging because of technical difficulties and the requirement of more blood units.

Alternatively, different therapies such as allogeneic hematopoietic stem cell transplantation (AHSCT) or hydroxyurea (HU) could be considered in this patient population given the additional disadvantages of chronic blood transfusions such as iron overload, allo-immunization and catheter infections. Walters et al. recently reported the neurological outcomes of 29 sickle cell children with CVA who underwent AHSCT [13]. One patient had overt ischemic stroke and another had subarachnoid hemorrhage after AHSCT. Both of these events occurred when these patients experienced graft rejection. They also reported that 27 out of 28 patients who had neuroimaging showed stable or improved MRI with a median follow up of 3.2 years after AHSCT. MRA data was not reported in that study. Though this is encouraging, the availability of matched sibling donor is the major limitation for AHSCT in SCA. Results of an ongoing trial of unrelated donor stem cell transplantation in children with SCA may increase the feasibility of this option in the future.

Hydroxyurea (HU) with phelobotomy is another promising alternative therapy for sickle cell patients with CVA, however the data is limited [14–16]. Results of the ongoing SWiTCH *(Stroke with Transfusions Changing to Hydroxyurea)* study will help determine the efficacy of HU on the cerebrovascular pathology. The SWiTCH study may also address another important question which is the clinical significance of these neuroradiological changes in patients with CVA despite chronic blood transfusions. We were unable to answer this question in our cohort as neuropsychological testing is not routinely performed in these patients outside of a clinical trial.

In summary, we demonstrate that patients with SCA with a baseline CVA or abnormal MRA experience progression of cerebral vasculopathy

Table 3
Comparison of pediatric SCA patients whose cerebral vasculopathy improved/stabilized vs. those whose worsened while receiving chronic blood transfusions.

Variables	Improved/stabilized MRI (n = 19)	Worsened MRI (n = 15)	p	Improved/stabilized MRA (n = 25)	Worsened MRA (n = 9)	p
Median age (years) at baseline MRA	7.4	5.8	0.41	6.2	6.8	0.28
Number of patients with CVA at baseline (%)	10 (53)	12 (80)		14 (56)	8 (89)	
Median elapsed time (years) from baseline MRI/MRA to most current	5	9	0.05	7	9	0.06
Mean baseline MRI score	2.42	2.87	<.05	–	–	
Mean baseline MRA score (SD)	–	–		1.32 (2.9)	3.22 (2.73)	0.05
Mean HbS% value	30.7	33.6	0.21	32.3	31.1	0.39
Number of patients with severe stenosis or occlusion of cerebral arteries at baseline (%)	4 (21)	6 (40)		5 (20)	5 (56)	
Number of patients with Moyamoya at baseline (%)	2 (11)	3 (20)		3 (12)	2 (22)	
Number of patients with multiple stenosis of cerebral arteries at baseline (%)	3 (16)	1 (7)		3 (12)	1 (11)	

despite chronic blood transfusion therapy. Further studies are needed to determine the effects of transfusions and the clinical significance of these radiographic findings.

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