

Hematopoietic Stem Cell Transplantation Stabilizes Cerebral Vasculopathy in High-Risk Pediatric Sickle Cell Disease Patients: Evidence From a Referral Transplant Center

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Abstract

Background: Severe sickle cell disease (SCD) can present with different vaso-occlusive manifestations with cerebral vasculopathy (CV) as one of the most serious complications. Hematopoietic stem cell transplant (HSCT) is the ultimate therapy for this complication. The aim of this study was to assess the outcome and impact of HSCT on severe SCD patients with CV complications.

Methods: Twenty-five consecutive transplants-naive pediatric SCD patients with CV complications underwent HSCT at our institution between 1993 and 2015, using bone marrow as stem cells source from fully match related donors were included. Neurologic evaluation was done both clinically and radiologically before transplantation and regularly following the HSCT.

Results: With a median follow-up of 52.2 ± 5.8 months, the cumulative probability of overall survival (OS) at 3 years was 92.0% and event-free survival (EFS) was 88%. Significant neurologic improvements were observed in most of the patients clinically. Different neurologic complications were assessed. The neurologic manifestations before and after HSCT were hemiparesis (11, 1), seizures (13, 8), focal neurologic deficit (4, 2), loss of conscious (2, 1) headache (6, 1), and psychological symptoms (5, 2). Post-HSCT radiological imaging was done in 15 patients, which showed stabilization of CV among all.

Conclusions: Allogeneic HSCT in patients with severe SCD presenting with CV complications including moyamoya vasculopathy showed favorable outcome with significant clinical neurologic improvement and stabilization of the disease. None of the patients with severe vasculopathy underwent neurological vascular by-pass surgery prior to HSCT.

Keywords: Stem cell transplantation; Pediatric sickle cell disease; Cerebral vasculopathy; Overt stroke; Neurologic deficit; Convulsions

Introduction

Sickle cell disease (SCD) is a major health challenge in Saudi Arabia. The prevalence of SCD in Saudi Arabia varies significantly in different parts of the country, with the highest prevalence in the Eastern Province, followed by the Southwestern Province. The reported prevalence for sickle-cell trait ranges from 2% to 27% [1-4]. Overt stroke occurs in 7-13% of children with SCD and can lead to motor disability, neuropsychological impairment and death [5, 6]. Reports on the incidence of stroke in SCD in Saudi Arabia are limited. From a hospital-based study of SCD in the western part of Saudi Arabia, the incidence of overt stroke in children was reported to be 9.4% in a predominantly African (severe) haplotype [7-9]. While in Eastern Province this statistic is around 6% [10]. It is expected to be lower considering its less severe phenotype due to the high hemoglobin F percentage (Arab-Indian haplotype) compared to the severe African type seen in the Southwestern region, which all of our patient cohort represents [7]. SCD patients can present with serious complications, such as cerebral vasculopathy (CV), leading to stroke and other neurologic deficit [6, 8, 11, 12]. Such clinical manifestation can be elicited by magnetic resonance imaging/angiogram (MRI/MRA) that can show spectrum of radiological abnormalities indicative of infarction, ischemia and atrophy (Fig. 1) [13, 14].

About 5% to 17% of SCD patients can develop stroke during childhood and adolescence [15]. The recurrence rate of infarction without regular monthly transfusion in patients who have had a prior clinical stroke can be as high as 67% [16, 17]. Hematopoietic stem cell transplant (HSCT) had shown a remarkable potential cure for SCD [18-21]. For patients with CV, studies have shown improvement in neurological deficit as well as vascular improvement after HSCT [20, 22-29]. We conducted an observational study to review and describe the outcome of HSCT in pediatric SCD patients presenting with CV at our institution.

Manuscript submitted November 4, 2021, accepted December 28, 2021
Published online February 26, 2022

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doi: <https://doi.org/10.14740/jh949>

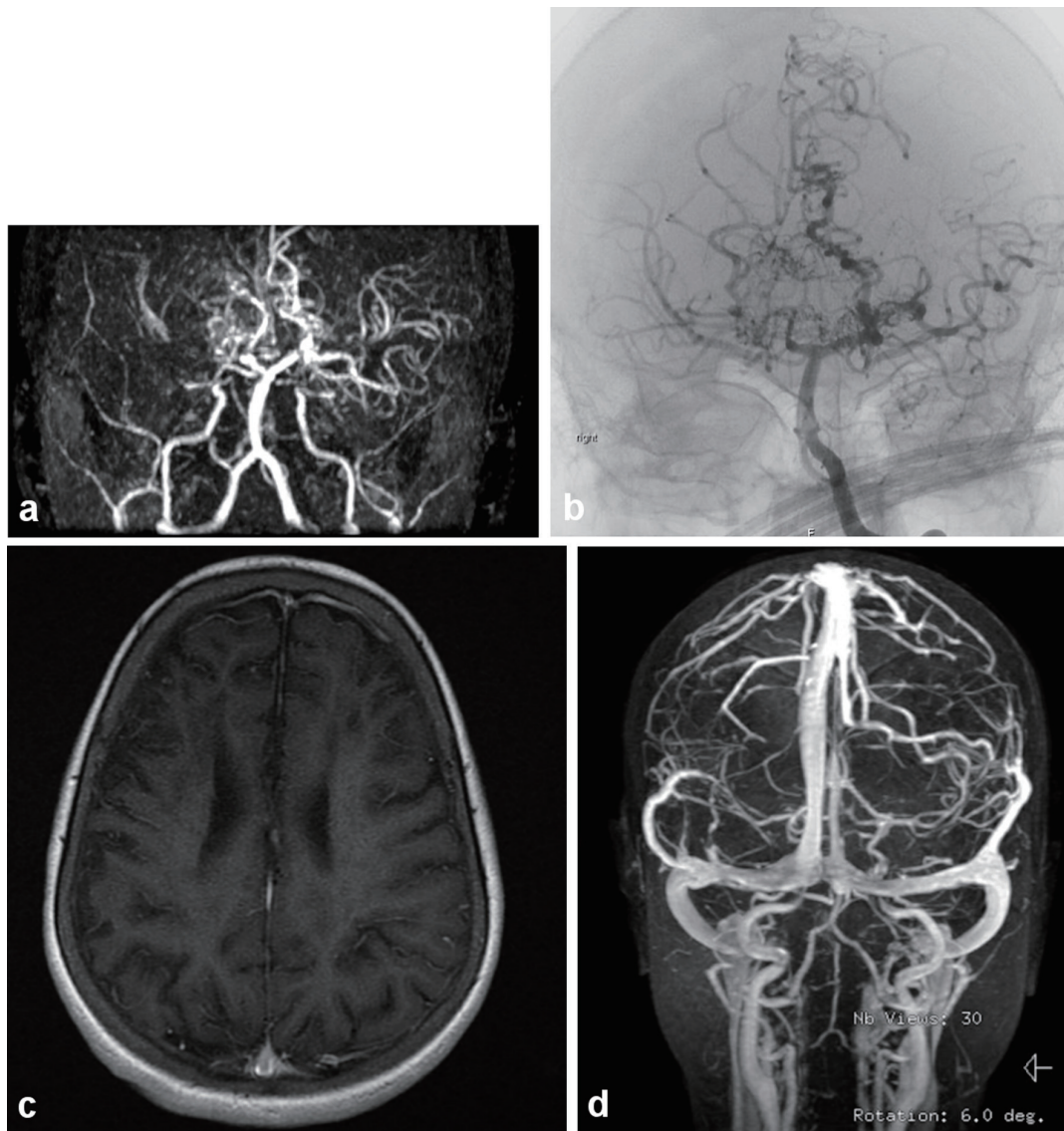


Figure 1. (a) The magnetic resonance (MR) angiography of the intracranial circulation showed significant prominent collateral vessels in the posterior cerebral artery territory with evidence for probable retrograde filling of middle cerebral artery territory from the posterior circulation. Significant collateral vessel prominence especially in the perforator branches in the thalamic region is detected. The findings are consistent with moyamoya disease with major thinning and attenuation in the supraclinoid internal carotid artery, and associated multiple watershed zone infarctions (before HSCT: March, 2009). (b) Evidence of narrowing at the distal internal carotid artery in the supraophthalmic segment bilaterally with the development of significant amount of small perforators giving puff of smoke appearance characteristic of moyamoya disease (same patient after HSCT in July, 2011). (c) Significant cortical and subcortical encephalomalacia diffusely along supratentorial brain parenchyma, significant within right frontal lobe with evidence of hemodynamic ischemic changes along the bilateral centrum semiovale. (d) Magnetic resonance imaging (MRI) with normal vascular distribution with moderately severe sickle cell disease.

Materials and Methods

Study design

From January, 1993 to December, 2015, 36 pediatric SCD patients (age ≤ 14 years) were referred to us for possible HSCT. Twenty-five patients had full matched human leukocyte antigens (HLA) identical related donors and underwent HSCT,

which are the focus of this study. This is a retrospective account of their transplant outcome. Data on clinical, radiologic, transplant-related parameters including donor HLA type, post-transplant chimerism, engraftment, incidence of graft-versus-host disease (GVHD), infectious and non-infectious toxicity and outcome were downloaded from institutional databases, being populated prospectively. All parents and/or guardians signed institutional review board-approved parental informed consent prior to the transplant.

Patients

All patients were transplant-naive and were evaluated clinically for CV. MRI/MRA was the radiological method of evaluating patients with neurologic abnormality. None of the patients had undergone cerebral re-vascularization surgery like encephaloduroarteriosynangiosis (EDAS) or encephalomyoarteriosynangiosis (EMAS) prior to the transplant [30]. All recipients had normal renal and cardiac function at the time of transplant.

Transplant procedure

Patients were conditioned with myeloablative regimen, which consisted of busulfan, cyclophosphamide and anti-thymocyte globulin (ATG) in 19 (76.0%) patients, while ATG was not a part of the conditioning regimen for the remaining six (24.0%) cases. GVHD prophylaxis was in the form of short methotrexate and cyclosporine. Bone marrow was the source of stem cells in all cases.

Patients were hospitalized in single rooms with high-efficiency particulate air filtration with positive pressure until neutrophil recovery. Patients received acyclovir prophylaxis if they were seropositive for herpes simplex virus and/or cytomegalovirus (CMV). Oral trimethoprim-sulfamethoxazole was given for Pneumocystis prophylaxis after engraftment for 1 year. Broad-spectrum intravenous (IV) antibacterial and antifungal and/or antiviral antimicrobials were administered for fevers as indicated. All patients received granulocyte colony-stimulating factor 5 µg/kg per day subcutaneously, from the day after transplant until neutrophil recovery. CMV reactivation was monitored weekly until at least day 100 following transplant and preemptively treated with ganciclovir or foscarnet. No prophylactic rituximab was given.

End point definitions

Time to neutrophil recovery was the first of 3 consecutive days on which the absolute neutrophil count (ANC) was $\geq 0.5 \times 10^9/L$. Primary graft failure was defined as failure to achieve an ANC of $0.5 \times 10^9/L$ by day 42, and secondary graft failure as an ANC $< 0.5 \times 10^9/L$ for 3 consecutive days, or 0% donor chimerism by polymerase chain reaction (PCR) in patients who have achieved an ANC of $\geq 0.5 \times 10^9/L$. Time to platelet recovery was the first of 3 consecutive days on which the platelet count was $> 20 \times 10^9/L$ without transfusions for 7 days before the first measurement. GVHD was graded by standard criteria. Graft failure and death from all causes was considered as an event. Overall survival (OS) was taken from infusion to the expiry or the last contact date, while event-free survival (EFS: probability of survival with sustained donor cell engraftment) was taken from the day of infusion till the disease recurrence date, with death from any cause or graft failure as an event, whichever came first.

Statistical considerations

All continuous data were presented as median with minimum

Table 1. Patient Characteristics and Primary Disease-Related Parameters

Age at infusion, median (range), years	10.6 (3.0 - 13.9)
Gender	
Female	20 (80.0%)
Male	5 (20.0%)
Sickle cell disease	
SS	22 (88.0%)
S β 0	3 (12.0%)
Indications for HSCT	
Cerebrovascular accident (n = 25)	
Severe with moyamoya changes	14 (56.0%)
Moderate infarction	7 (28.0%)
Silent	2 (8.0%)
Transient	2 (8.0%)
Symptoms (symptomatic = 23, 92%)	
Convulsions	13 (52.0%)
Hemiparesis	11 (44.0%)
Headache	6 (24.0%)
Psychiatric symptoms	5 (20.0%)
Focal neurological loss	4 (16.0%)
Loss of consciousness (any episode)	2 (8.0%)

Values are provided as numbers (%) unless otherwise specified. HSCT: hematopoietic stem cell transplant.

and maximum points. Kaplan-Meier curves were drawn for survival analyses. McNemar's test was used to test for the independence of differences for the number of patients for observed symptoms in the group. IBM-SPSS for Windows (version 20.0) was used for statistical analysis of the data.

Ethical considerations

This study was submitted to the Institutional Review Board of King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia before initiation, and was approved by the Research Advisory Committee through established procedures via approval number 2171164; and the study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

A total of 25 pediatric patients (age ≤ 14 years) with SCD underwent consecutive HSCT from January 1993 to December 2015 at our institution were included. Median age at HSCT was 10.6 years (range: 3.0 - 13.9 years); 20 (80.0%) were female. Median follow-up time was 52.2 ± 5.8 months (95% confidence interval: 40.7 - 63.7 months). Patients' demographics and primary disease-related parameters are presented in Table 1. Pre-HSCT MRI/MRA was done in 21 patients. More than half of them had

Table 2. Post-Transplant Primary Disease Evaluation

Outcome of interest	Pre-HSCT, n (%)	Post-HSCT, n (%)	Improvement, n (%)	P value
Clinical findings pre- and post-HSCT				
Hemiparesis	11 (44.0%)	1 (4.0%)	10 (90.9%)	0.002
Headache	6 (24.0%)	1 (4.0%)	5 (83.3%)	0.063
Psychological symptoms	5 (20.0%)	2 (8.0%)	3 (60.0%)	0.250
Focal neurological loss	4 (16.0%)	2 (8.0%)	2 (50.0%)	0.500
Loss of consciousness (any episode)	2 (8.0%)	1 (4.0%)	1 (50.0%)	1.000
Convulsions	13 (52.0%)	8 (32.0%)	5 (38.5%)	0.063
Post-HSCT radiological imaging results (n = 15)				
Stabilized CV (alive)		14 (93.3%)		
Stabilized CV (expired) ^a		1 (6.1%)		

^aThe patient died after 6.5 months post-infusion due to exacerbation of chronic GVHD of gut. HSCT: hematopoietic stem cell transplant; GVHD: graft-versus-host disease; CV: cerebral vasculopathy.

suffered ischemic stroke with moyamoya changes as depicted by MRI evaluation (n = 14, 56.0%), 13 (52.0%) had convulsions and 11 (44.0%) with hemiparesis. Records on pre-HSCT transcranial Doppler (TCD) studies were not available for all the referred patients. Nineteen (76%) patients were receiving monthly packed red blood cell (PRBC) transfusions and iron chelation prior to referral to our institution. Iron overload assessments were done including MRI T2* for those with high serum ferritin.

Donors were HLA identical sibling in 21 (84.0%) or identical parent in four (16.0%) recipients. Median cluster of differentiation (CD)34⁺ cell dose was $5.0 \times 10^6/\text{kg}$ (range: 1.1 - 11.8), whereas total nucleated cell (TNC) dose was $2.98 \times 10^8/\text{kg}$ (range: 1.3 - 45.4). All patients received one to two transfusions during the myelosuppression phase of early transplantation.

Hematopoietic recovery/engraftment/chimerism

ANC recovery was observed in all cases with a median time to ANC recovery of 15 days (range: 12 - 24 days), and platelets recovery was observed in 24 patients with a median recovery time of 26.5 days (range: 16 - 100 days). Sixteen patients (64.0%) exhibited full donor chimerism (100%) in myeloid lineage on day +100 evaluation, while in the remaining recipients it varied from 68% to 96%. There was no event of primary graft failure whereas incidence of secondary graft failure was 4.0% (n = 1) in our cohort. The only patient with secondary graft failure had exhibited 96% chimerism in myeloid line on day +100. Transplanted from an HLA identical brother, the chimerism in myeloid line gradually dropped to 0% for this patient leading to a documented graft failure 14.3 months after infusion. She was on regular transfusions at her last clinical visit for her CV. At the last update to the data set, all but one surviving patients were maintaining sustained donor cells.

GVHD

Cumulative incidence of all grade overall acute GVHD was

20.0% (n = 5), whereas grade I - II acute GVHD accounted for 16% (n = 4) and severe acute GVHD (grade III, gut) was seen in only one case (4.0%). Severe chronic GVHD was seen in three (12.5%) evaluable patients, two of them succumbed to it.

Infections and transplant-related toxicity

In terms of transplant-related morbidity during the day +100, five (25%) recipients had CMV reactivation which was managed successfully using ganciclovir/foscarnet. No other viral infections including Epstein-Barr virus (EBV), adenovirus or BK virus were encountered on routine screening. One patient had hemorrhagic cystitis, and two (8.0%) had sinusoidal obstructive syndrome (SOS); all were self-limiting. None of our patients had transplant-associated thrombotic microangiopathy.

Survival, mortality and causes of death

With a mortality rate of 12.0% (n = 3), all but one of 22 (88%) survivors were hematologically and clinically asymptomatic at the last contact. The cumulative probability of 3-year OS was 92.0% (\pm 5.4%) and EFS 88.0% (\pm 6.5%). Causes of death were acute respiratory failure and septic shock due to polymicrobial pneumonia in the first case, acute exacerbation of chronic GVHD of gut in the second patient, and in the third one it was progressive worsening of chronic GVHD of lung (bronchiolitis obliterans); events of death were recorded at 1.6, 6.5, and 45.4 month post-HSCT, respectively.

Post-transplant neurologic assessment

Post-transplant parameters related to neurologic status of the cohort are described in Table 2. Clinically, patients had neurologic examination before and after HSCT regularly in the outpatient clinics and continued on anti-epileptic for 1 year, then it was tapered and discontinued if there were no evidence

of epileptic activity on electroencephalogram (EEG). Eleven patients with hemiparesis showed remarkable recovery and regained motor strength (90.9%) except one who continued to have persistent deficit ($P = 0.002$). Recurrent seizures were seen in 13 patients prior to HSCT; five (38.5%) patients resolved while eight remained to have seizure activity requiring prolonged anticonvulsant therapy. Improvement in neuropsychological abnormality was recorded in three patients and headache resolved in five out of six patients. Post-HSCT radiological imaging was done in 15 patients, which showed stabilization of CV among all. Two of eight patients who had seizures post-HSCT were due to posterior reversible encephalopathy syndrome (PRES) in early post-transplant days. All patients were clinically stable at their last follow-up appointment maintaining normal hematopoiesis, and were leading normal life with no debilitating neurologic deficit except in one who had permanent hemiplegia.

Discussion

Our results confirm that HLA-related HSCT offers a curative option and a risk-benefit balance in children who have severe SCD [18-20]. This study is one of a few studies that explored the outcome of HSCT in pediatric SCD patients with CV complications specifically [20]. The incidence of stroke in SCD patients is increased in pediatric age group, which indicates the need for early identification by screening using TCD to detect patients at risk and initiate blood transfusions or refer them for possible HSCT [6, 18, 20]. Unfortunately, most of the patients referred to our center were already symptomatic, due to established vasculopathy and were on regular transfusions. Established CV requires lifelong PRBC transfusions in an attempt to offset the disease progression. However, recurrence of stroke may occur even in patients on transfusion program [17, 22, 23]. For severe symptomatic vasculopathy (moyamoya disease) neurosurgical neo-vascularization EDAS/EMAS can be performed as therapeutic option; however, postoperative complications and recurrence of stroke are usually high [30]. Fourteen of our patients had moyamoya changes on MRI prior to transplantation; all of them stabilized post-HSCT.

Post-HSCT risk of neurological complications has been reported to increase with incidence up to 38% in untransfused patients with prior stroke. Seizures are one of the most common neurological complications [31]. Nevertheless, we found a reduction in seizures in our cohort. Two patients had seizures due to PRES in the early post-transplantation period confirmed with CT scan of the brain. Higher incidence of PRES in SCD (22%) was reported in the literature in patients with SCD following HSCT [29].

HSCT in high-risk SCD patients before development of stroke and CV reduces the risk of subsequent neurologic complications [28]. This was shown using TCD with improved vasculopathy demonstrating low values at 1-, and 3-year follow-up [20]. Extended duration of anticonvulsant post-HSCT with intensified antihypertensive management and platelet support may diminish the frequency of seizures [1, 31]. We also found clinical improvement in our cohort of patients simi-

lar to these studies. Considering the high-risk category of our cohort, 3-year OS was 92% and EFS was 88%, still comparable to international reports [18-21]. We also looked at the post-HSCT quality of life for our patients with respect to neurological and psychological status. Our patients showed improvement in their motor and cognitive functions, which was also supported by stabilization of radiological imaging (Table 2, Fig. 1). This report from a single transplant center, will add to the existing literature as it addresses and evaluates specifically the conditions and the outcome of the patients with CV pre- and post-HSCT. Further follow-up of this cohort of patients will continue to be assessed for the long-term effect of HSCT on the neurologic status of these patients. We also have demonstrated in this report a favorable outcome of HSCT in symptomatic patients with severe vasculopathy (moyamoya) compared to those undergoing by-pass surgery EDAS/EMAS for severely narrowed vessels [30].

Limitations

Being a retrospective chart review, our study suffers from obvious limitations. One of the patients was referred to us from another country and had to be censored at 35.6 months at his last follow-up with us. Majority, but not all of the cases had pre- and post-HSCT MRI assessment, importantly, the clinical improvement was remarkable and durable. In addition, TCD studies were not available for all the referred patients prior to HSCT.

Conclusions

HSCT is a curative therapy for high-risk pediatric SCD patients having CV with a favorable outcome resulting in stabilization of brain vascularity and clinical improvement of symptoms like headache, hemiparesis, and convulsion. None of the patients had to go for neo-vascularization procedure before HSCT. Ideally, early TCD should be done to detect high-risk patients followed by early HSCT for eligible patients to avoid the development of neurological complications and to improve the outcome.

Acknowledgments

None to declare.

Financial Disclosure

All authors verify that they do not have any financial disclosure to declare.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Data of interest collected from the patients' medical records were secured as governed by the institutional policies on patient confidentiality and privacy. No informed consents were obtained since this was a retrospective study and all data items collected were already documented in medical charts as part of the patient care and disease management.

Author Contributions

Abdullah Al-Jefri conceived the idea, reviewed the results, did literature search, prepared the manuscript. Khawar Siddiqui designed the study, performed the statistical analysis of the data and wrote the results for the manuscript. Amira Al-Oraibi collected the data and assisted in literature search. Amal Al-Seraihy, Ali Al Ahmari, Ibrahim Ghemlas, Awatif Al Anazi, Hawazen Al Saedi, and Mouhab Ayas reviewed the results and approved the manuscript.

Data Availability

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

Abbreviations

SCD: sickle cell disease; HSCT: hematopoietic stem cell transplant; CV: cerebral vasculopathy; PRBC: packed red blood cell; ATG: anti-thymocyte globulin; GVHD: graft-versus-host disease; HLA: human leukocyte antigen; OS: overall survival; EFS: event-free survival; TCD: transcranial Doppler

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