Salama *et al.*
Egyptian Pediatric Association Gazette (2024) 72:6
https://doi.org/10.1186/s43054-024-00247-5

Egyptian Pediatric Association Gazette

RESEARCH

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Eligibility for hematopoietic stem cell transplantation in a cohort of children with sickle cell disease: a single-center report

Khaled Salama[1], Asmaa F. Allam[1] and Yasmeen M. M. Selim[1*]

Abstract

Background Hematopoietic stem cell transplantation (HSCT), is the only currently available curative option for SCD. Yet, the eligibility of SCD patients for HSCT is always limited by the significant associated toxicity and lack of suitable donors. At Cairo University's pediatric hematology outpatient clinic, we aimed to determine hematopoietic stem cell transplantation (HSCT) candidates among a sickle cell disease (SCD) cohort, estimate the number of possible donors, and analyze the differences between patients with and without an HSCT indication.

Methods This study was a cross-sectional analytic study including 128 SCD children. Their demographic, clinical, and laboratory profiles, total number, and number of siblings with SCD were obtained from their medical records.

Results Sixty-nine (53.9%) had at least one HSCT indication. Recurrent severe pain episodes despite hydroxyurea were the most common indication. Hemoglobin was lower, while reticulocyte count, serum ferritin, and aspartate aminotransferase were higher in HSCT candidates (p value < 0.001). Additionally, the prevalence of splenomegaly, the dose of hydroxyurea, and the number of transfusions were noticeably higher in HSCT candidates (p value = 0.013, 0.005, and < 0.0001 respectively). Among those indicated for HSCT; 75.3% had at least one healthy sibling who might be a potential donor.

Conclusion More than half were eligible for HSCT which should always be considered to provide a possible cure for the disease. Of the transplantation-eligible cases, about two-thirds had at least one healthy sibling who might potentially serve as a donor. Those meeting the requirements for HSCT eligibility should routinely undergo human leukocyte antigen (HLA) testing of their unaffected siblings.

Keywords Hematopoietic stem cell transplantation, Eligibility, Sickle cell children, Healthy siblings

Background

One of the most prevalent hemoglobinopathies with an autosomal recessive inheritance pattern is sickle cell disease (SCD). The hallmarks of the disease are chronic hemolysis and repeated vascular occlusions resulting in subsequent organ dysfunction [1]. Around 8 million individuals globally live with SCD, and more than 500,000 newborns were born with it in 2021, with more than 75% of those births taking place in sub-Saharan Africa [2]. Sickle cell patients' life expectancy has improved significantly owing to the improved supportive care including vaccination, antibiotic prophylaxis, hydroxyurea treatment, and transfusions [3]. However, SCD patients surviving into adulthood usually live with pain, disabling complications, and altered quality of life. Hematopoietic stem cell transplantation (HSCT), is the sole curative option for SCD. However, due to the severe associated

*Correspondence:
Yasmeen M. M. Selim
yasmeenselim87@gmail.com
[1] Pediatric Hematology and BMT Unit, Department of Pediatrics, Faculty of Medicine, Cairo University, El-Rashidy Street, El-Sayeda Zeinab, Cairo, Egypt

toxicity, a paucity of acceptable donors, and socioeconomic hurdles, not all SCD patients are eligible and/or fit for HSCT [4]. Hematopoietic stem cell transplantation is only indicated for those who have a severe or complicated phenotype [5]. In Egypt, since 1997, HSCT procedures have increased dramatically despite financial and administrative challenges [6]. This study aimed at identifying the number of pediatric SCD patients who are eligible for HSCT among children following at Cairo University's pediatric hematology outpatient clinic, to estimate the proportion of candidates who have siblings who could serve as potential donors for HSCT, and to analyze the differences between patients with and without an HSCT indication in terms of their demographic, clinical, and laboratory data.

Methods

Study population

The current study included 128 Egyptian sickle cell disease children ≤ 18 years of age. Patients were recruited from the New Cairo University Children's Hospital's Pediatric Hematology Outpatient Clinic. Patients' clinical, laboratory, and demographic data were obtained from their medical records. Alkaline hemoglobin electrophoresis and high-performance liquid chromatography (HPLC) were used to diagnose and phenotype SCD patients. Fifty-nine (46.1%) patients had sickle cell anemia (HbSS), and 69 (53.9%) were double heterozygous for sickle-beta-thalassemia (HbSβ).

The number of HSCT candidates was determined from the data gathered from the patient's medical records at enrollment. Sickle cell disease patients were identified as HSCT candidates if despite receiving hydroxyurea treatment, patients had at least 1 of the following: overt stroke, cerebrovascular disease, alloimmunization to red blood cells with a recognized indication for a chronic transfusion regimen, recurrent severe pain episodes (≥ 3/year), recurrent acute chest syndrome (ACS), recurrent priapism, increased transcranial doppler (TCD) velocity neither responsive to hydroxyurea nor a chronic transfusion regimen, elevated estimated systolic pulmonary artery pressure (esPAP) (measured using conventional echocardiography) ≥ 35 mmHg or detection of a tricuspid valve regurgitant jet velocity ≥ 2.7 m/s, sickle nephropathy (30–50% of estimated normal glomerular filtration rate), bone and joint affection, sickle retinopathy, or stage I or II sickle cell lung disease [7].

Patients having at least one HSCT indication were compared to patients without an HSCT indication based on their demographic, clinical, and laboratory characteristics. Both the overall number of siblings and the number of siblings that had SCD were obtained for each participant at the time of cohort enrollment. Based on this, we identified the number of healthy siblings, who were negative for SCD, to determine the number of potential HSCT donors for the enrolled subjects.

The Research Ethics Committee of the Department of Pediatrics at the Faculty of Medicine at Cairo University gave its approval to the study (Ethical clearance number: MS-585-2021). Before patients' enrollment, the patients' legal guardians provided their informed permission. All procedures were carried out in compliance with the Declaration of Helsinki, 1964, and any subsequent revisions or similar ethical norms.

Statistical methods

Data were statistically reported using the mean, standard deviation (SD), median, and interquartile range (IQR) or frequencies (number of occurrences) and percentages as applicable. Using the chi-square test for categorical data and the *t*-test or Wilcoxon rank sum test, as applicable, for continuous variables, characteristics of patients with or without an indication for HSCT were compared. A *p* value of 0.05 or less was regarded as significant. IBM SPSS (Statistical Package for the Social Science; IBM Corp., Armonk, NY, USA), release 25 for Microsoft Windows, was used to do all the statistical mathematical calculations.

Results

A cohort of 128 SCD children ≤ 18 years representing a sample of SCD children following at the New Cairo University Children's Hospital's Pediatric Hematology Outpatient Clinic were enrolled in the study; their mean age at enrollment was 9.63 (± 4.0) years and mean age at diagnosis was 2.17 (± 2.18) years. Consanguinity was found in 72.7%. Most of our patients (93%) gave a history of previous blood transfusion with a median of 6.0 yearly transfusions (IQR 3–10), 77.3% gave a history of previous hospitalization mostly due to vaso-occlusive crisis (VOC), and 2.3% were splenectomized. One hundred twenty-five (97.7%) of our patients were receiving hydroxyurea, and 41.6% were receiving iron chelation due to high serum ferritin levels with a median level of 561.50 ng/ml (IQR 300–1109).

Out of the 128 children enrolled in the study, the number of children who were eligible for HSCT was 69; 53.9% of the studied SCD cohort (Table 1). The most common HSCT indication among those children was recurrent severe pain episodes despite hydroxyurea therapy. Out of 69 eligible candidates, 37 had just one indication and 32 had 2 or more indications for transplantation (Table 2).

Among those indicated for HSCT ($n = 69$); 17 children (24.6% out of 69) did not have any healthy siblings without SCD. Fifty-two (75.3%) had 1 or more healthy siblings without SCD who could potentially serve as donors

Table 1 Indications for HSCT among the studied SCD children ($n=128$)

Indications for HSCT	Number (percentage) [total number of patients = 128]
Overt stroke	2 (1.6%)
Cerebrovascular disease	2 (1.6%)
Alloimmunization to red blood cells with a recognized indication for a chronic transfusion regimen	1 (0.8%)
Recurrent severe pain episodes despite hydroxyurea (≥ 3/year)	66 (51.6%)
Recurrent acute chest syndrome despite hydroxyurea	6 (4.7%)
Increased TCD velocity is neither responsive to hydroxyurea nor a chronic transfusion regimen	11 (8.6%)
Elevated pulmonary artery pressure or detection of a tricuspid valve regurgitant jet velocity ≥ 2.7 m/s by echocardiography	5 (3.9%)
Bone and joint affection	15 (11.7%)
Total number of patients with any HSCT indication[a]	69 (53.9%)

SCD sickle cell disease, *TCD* transcranial doppler, *HSCT* hematopoietic stem cell transplantation

[a] Patients may have multiple indications

Table 2 Number of SCD children according to indications for HSCT

Number of indications for HSCT	Number (percentage)
0 indication	59 (46.1%)
1 indication	37 (28.9%)
2 indications	27 (21.1%)
≥ 3 indications	5 (3.9%)

SCD sickle cell disease, *HSCT* hematopoietic stem cell transplantation

for transplantation, and only 31 (44.9%) had 2 or more healthy siblings.

Children having at least one HSCT indication and those without were compared based on their characteristics (Table 3). Hemoglobin level was lower in HSCT candidates, while reticulocyte count, serum ferritin, and aspartate aminotransferase levels were higher in HSCT candidates (p value < 0.001). HSCT candidates had a significantly higher prevalence of splenomegaly (p value = 0.013). Considering treatment, pediatric candidates for HSCT were on higher doses of hydroxyurea (p value = 0.005) and received a higher number of blood transfusions.

Discussion

For SCD patients, hematopoietic stem cell transplantation (HSCT) promises a cure; yet, the insufficient number of matched sibling donors (MSD) remains a roadblock. People of African ancestry have just a 16% chance of finding an HLA-MSD, according to the USA NMDP (United States of America National Marrow Donor Program) donor registry [8]. Additionally, due to the severe accompanying toxicity, not all SCD patients are candidates for transplantation. Transplantation is only for SCD patients with severe phenotype or complicated cases as agreed by many researchers [5]. Young individuals with severe SCD symptoms and an available HLA-MSD should always be given the option of transplantation. [4]. This highlights the importance of searching for eligibility criteria for HSCT in the pediatric age group to transplant them early before the development of debilitating or life-threatening SCD complications. We identified 128 SCD children ≤ 18 years, described their profile, and children having at least one HSCT indication and those without were compared based on their characteristics. Sixty-nine patients (53.9%) were indicated for HSCT (42 were Sβ; 60.9% and 27 were SS; 39.1%) and 59 patients (46.1%) had no HSCT indication. The indications for HSCT upon which we categorized our patients were those adopted by Kassim and Sharma, all of which denoted severe SCD phenotype [7]. The most common indication for HSCT among our studied cohort was recurrent severe vaso-occlusive episodes (VOEs) despite optimum hydroxyurea dosage. Many researchers reported similar indications; Krishnamurti et al. [5] reported that 68.1% (15 out of 22) of SCD patients eligible for HSCT had recurrent VOEs, and Alsultan et al. [9] reported that 25 (60.9%) out of 41 transplanted SCD patients had recurrent VOEs. On the contrary, stroke was the most frequent indication for HSCT in numerous previous studies [10, 11]. In the early clinical trials of HSCT for SCD, stroke was the most common indication in 57% of patients [12]. The increased awareness regarding recurrent VOEs being an appropriate HSCT indication might explain this shift in HSCT indications among SCD patients along with successful primary stroke prevention through TCD screening and proper management of the high-risk SCD population [13–15].

Three quarters (≈ 75%) of those indicated for HSCT had ≥ 1 healthy sibling who could potentially serve as

Table 3 Comparison between SCD patients without an HSCT indication and those with ≥ 1 HSCT indication regarding the different studied parameters

	0 HSCT indication (*n* = 59) Number (%)	**≥ 1 HSCT indication (*n* = 69) Number (%)**	***P***
Demographic/clinical and treatment data			
Gender male/female	28/31 (47.5%/52.5%)	43/26 (62.3%/37.7%)	0.092
Weight (kg) (mean ± SD)	30.97 ± 13.01	30.41 ± 19.52	0.851
Height (cm) (mean ± SD)	127.25 ± 15.62	125 ± 18.99	0.469
Splenomegaly yes/no	4/55 (6.8%/93.2%)	16/53 (23.2%/76.8%)	0.013*
Frequency of yearly transfusions (mean ± SD)	2.56 ± 1.76	8.57 ± 4.03	< 0.0001*
Hydroxyurea treatment yes/no	56/3 (94.9%/5.1%)	69/0 (100%/0%)	0.058
Hydroxyurea dose in mg/kg (mean ± SD)	18.38 ± 6.05	21.43 ± 5.74	0.005*
SCD phenotype			
Sβ	27 (45.8%)	42 (60.9%)	0.087
SS	32 (54.2%)	27 (39.1%)	
Laboratory data (mean ± SD)			
Hemoglobin (gm/dl)	9.17 ± 1.31	7.96 ± 1.20	< 0.001*
TLC ($\times 10^3/mm^3$)	8.48 ± 3.43	10.24 ± 4.74	0.039*
PLT ($\times 10^3/mm^3$)	334.80 ± 126.08	313.33 ± 165.56	0.176
Reticulocyte count (%)	4.63 ± 3.45	8.27 ± 4.76	< 0.001*
Serum ferritin (ng/ml)	434.27 ± 348.49	1020.74 ± 588.33	< 0.001*
AST (U/l)	35.88 ± 13.94	47.57 ± 21.98	< 0.001*
HbS (%)	69.13 ± 10.29	70.11 ± 11.57	0.615
HbF (%)	5.49 ± 8.26	7.08 ± 7.15	0.245

HSCT hematopoietic stem cell transplantation, *SCD* sickle cell disease, *Sβ* sickle-beta thalassemia, *SS* homozygous sickle cell anemia, *SD* standard deviation, *TLC* total leukocyte count, *PLT* platelet count, *AST* aspartate aminotransferase, *HbS* sickle hemoglobin, *HbF* fetal hemoglobin

* Statistically significant at $p \leq 0.05$

donors for transplantation. HLA compatibility should be tested among healthy siblings of SCD children with an HSCT indication to determine the actual number of suitable donors. Unfortunately, there was no available information on the HLA matching of siblings. A range of probabilities for identifying an HLA-MSD has been reported across studies. According to Mentzer et al. [16], SCD patients had an 18% chance of having fully HLA-MSD identified. The likelihood was 24.1% in Brazilian research [17]. Estimating that our HSCT-eligible patients have a likelihood of 18–24% HLA-compatible siblings, we may predict that 9–12 of the 69 identified candidates will likely have a suitable donor and be eligible for transplantation.

On comparing SCD children with no HSCT indication to those with one or more HSCT indications, hemoglobin level was found to be lower in HSCT candidates, while reticulocyte count and serum ferritin were higher (p value < 0.001), this might be attributed to the fact that the majority of our patients (69; 53.9%) were double heterozygous for sickle-beta-thalassemia (HbSβ). HSCT candidates had a significantly higher prevalence of splenomegaly (p value = 0.013), were on higher doses of hydroxyurea (p value = 0.005), and received a higher number of transfusions. The anemia, reticulocytosis, hyperferritinemia, reaching the maximum tolerated dose of hydroxyurea, and the transfusion burden, all these are seen as indicators of the severity of SCD, making it more probable that the patient required a transplant. Similar findings were reported by Flor-Park et al. who stated that SCD children who were candidates for HSCT, were more likely to be on higher doses of hydroxyurea in an attempt to control disease manifestations and also were more likely to receive more frequent transfusions [11]. Flor-Park et al. found no significant differences regarding different laboratory parameters (p value > 0.05) with the exception of fetal hemoglobin that was higher in the group with no indication for transplantation (p value < 0.001) highlighting the role of HbF in ameliorating the SCD phenotype; however, this finding was contradictory to the results of our study, as fetal hemoglobin was lower in the group with no indication for transplantation and thus was not shown to ameliorate the SCD phenotype [11].

Conclusion

In conclusion, our results suggest that more than half of our studied SCD cases were eligible for performing HSCT; therefore, we should think about HSCT as a potential treatment for the disease, especially for individuals who have appropriate donors. About two-thirds of the transplant-eligible patients had at least one healthy sibling who may potentially serve as a donor. Those meeting the requirements for HSCT eligibility should be advised to perform HLA testing of their unaffected siblings.

Limitations of the study

The absence of HLA compatibility testing for healthy siblings of SCD patients who were eligible for HSCT, which would have confirmed the precise number of donors available and the precise number of transplants to be carried out, was a weakness in our study. Additionally, we calculated the number of patients qualified for HSCT based on a clear indication without taking into account the patient's suitability for the procedure.

Abbreviations

SCD	Sickle cell disease
HSCT	Hematopoietic stem cell transplantation
HPLC	High-performance liquid chromatography
HbSS	Homozygous sickle cell anemia
HbSβ	Sickle-beta thalassemia
ACS	Acute chest syndrome
TCD	Transcranial doppler
SD	Standard deviation
IBM	International Business Machines Corporation
SPSS	Statistical Package for the Social Science
NY	New York
USA	United States of America
VOC	Vaso-occlusive crisis
HLA	Human leukocyte antigen
MSD	Matched sibling donor
NMDP	National Marrow Donor Program
VOE	Vaso-occlusive episode

Acknowledgements
Not applicable.

Authors' contributions
All authors listed have contributed sufficiently to the research. KS formulated the design of the work, while AA and YMMS were responsible for data collection, analysis, and interpretation. All authors read and approved the final manuscript.

Funding
The authors' submitted work was not funded by any organization.

Availability of data and materials
The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The Research Ethics Committee of the Department of Pediatrics at the Faculty of Medicine at Cairo University (Ethical permission number: MS-585-2021) gave its approval to the study. Before patients' enrollment, the patients' legal guardians provided their informed permission. All procedures were carried out in compliance with the 1964 Declaration of Helsinki and any subsequent revisions or similar ethical norms.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 8 December 2023 Accepted: 3 January 2024
Published online: 01 February 2024

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