Biol Blood Marrow Transplant 25 (2019) e174–e178

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Functional and Radiologic Assessment of the Brain after Reduced-Intensity Unrelated Donor Transplantation for Severe Sickle Cell Disease: Blood and Marrow Transplant Clinical Trials Network Study 0601

Allison A. King[1,*], Robert C. McKinstry[2], Juan Wu[3], Mary Eapen[4], Regina Abel[5], Taniya Varughese[5], Naynesh Kamani[6], Shalini Shenoy[7]

[1] *Dept. of Pediatrics, Division of Hematology and Oncology, Program in Occupational Therapy, Washington University School of Medicine, St. Louis Children's Hospital, St Louis, Missouri*
[2] *Dept. of Radiology, Section of Neuroradiology, Washington University School of Medicine, St. Louis Children's Hospital, St Louis, Missouri*
[3] *The Emmes Corporation, Rockville, Maryland*
[4] *Dept. of Medicine, Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin*
[5] *Program in Occupational Therapy, Washington University School of Medicine, St. Louis Children's Hospital, St Louis, Missouri*
[6] *Division of Allergy Immunology, Children's National Medical Center, Washington, DC*
[7] *Dept. of Pediatrics, Division of Hematology and Oncology, Washington University School of Medicine, St. Louis Children's Hospital, St Louis, Missouri*

Article history:
Received 18 October 2018
Accepted 1 January 2019

Key words:
Sickle cell disease
Stem cell transplantation
Brain MRI
Neurocognition

A B S T R A C T

Stroke and cognitive decline are hallmarks of sickle cell disease (SCD). The natural history of SCD predicts progressive loss of 1 IQ point per year attributable to disease-related pathology. Hematopoietic cell transplantation (HCT) is curative by reverting to donor-derived erythropoiesis, but evidence that HCT can positively influence disease-induced cognitive decline is lacking. The Sickle Cell Unrelated Transplant Trial prospectively evaluated cognition and brain magnetic resonance imaging (MRI) findings at 2 years after reduced-intensity conditioning followed by unrelated donor HCT. Thirteen study participants completed pre-HCT and post-HCT assessments of intelligence. The mean age of participants was 12.5 ± 3.3 years (range, 6.7 to 17.4 years). Eleven of the 13 recipients completed imaging studies at baseline and post-HCT. Seven had overt stroke pre-HCT, and 1 had an elevated transcranial Doppler velocity with abnormal MRI. The mean Full-Scale IQ was stable: 90.9 ± 13 at baseline and 91.2 ± 13 post-HCT. The mean Performance IQ was 89.9 ± 13 at baseline versus 90.9 ± 13 post-HCT, and mean Verbal IQ was 93.4 ± 13 at baseline versus 93.2 ± 13 post-HCT, respectively. Six recipients had stable MRI; 2 showed resolution of all areas of infarction. Three had additional infarcts post-HCT noted at the 2-year time point. This is the first report describing stabilization of IQ and central nervous system outcomes after unrelated donor HCT despite previous central nervous system morbidity and post-HCT posterior reversible encephalopathy syndrome. These preliminary results post-HCT suggest that HCT may stabilize the cognitive decline of SCD and should continue to be followed over the long term.

INTRODUCTION

Sickle cell disease (SCD) results in hemolysis, endothelial damage, and vasculopathy. The brain is particularly susceptible to infarctions; overt and silent strokes are noted in >40% of patients before adulthood [1]. Declines in cognition and IQ are common even without any radiologic evidence of stroke [2,3]. Following successful hematopoietic cell transplantation (HCT), patients report improvements in pain and quality of life, and hospitalization rates and transfusion requirements decline. It is hoped that HCT will serve to ameliorate cognitive decline, but functional assessments of affected organs, such as the brain, are rarely reported post-HCT, and prospective systematic outcome analysis is lacking [4–8].

Matched sibling donor (MSD) HCT has proven advantageous to this treatment modality in the majority of recipients (>90%) with a suitable donor and has led to subsequent clinical trials of HCT with alternative donors. A single French trial of MSD HCT reported stabilization of cognition after transplant [9]. However, MSD HCT is limited by <25% donor availability

Financial disclosure: See Acknowledgments on page e178.
* Correspondence and reprint requests: Allison A. King, 4444 Forest Park Blvd, CB 8505, St. Louis, MO 63108.
E-mail address: king_a@wustl.edu (A.A. King).
https://doi.org/10.1016/j.bbmt.2019.01.008
1083-8791/

in the United States [10]. The use of unrelated donors (URDs) and haploidentical donors expand the access to HCT. Graft-versus-host disease (GVHD) and graft rejection have generated new trials to offset complications while maintaining the use of alternative donors for eligible patients [11,12]. The first URD HCT trial in children with SCD (Blood and Marrow Transplant Clinical Trials Network [BMT CTN] 0601; ClinicalTrials.gov identifier NCT00745420) prospectively evaluated cognition and brain imaging by magnetic resonance imaging (MRI) following reduced-intensity HCT. Here we report the findings of that trial on behalf of the BMT CTN.

METHODS

BMT CTN 0601 was a phase 2 trial. Thirty children (age 4 to 19 years) were enrolled between 2008 and 2014, of whom 29 were evaluable for primary outcomes. Eligibility included SCD with overt stroke, persistently elevated transcranial Doppler velocity, recurrent pain, or acute chest syndrome. The primary objective was 1-year event-free survival following HLA allele-matched URD HCT. The conditioning regimen included alemtuzumab, fludarabine, and melphalan. GVHD prophylaxis included calcineurin inhibitor, methotrexate, and methylprednisolone. Outcomes have been published previously [13].

Secondary Outcome Measures

Cognitive assessments were performed at ≤60 days before the initiation of alemtuzumab and were repeated 2 years post-HCT. Age-appropriate testing included the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition [14] or the Wechsler Abbreviated Scale of Intelligence [15] for IQ. The latter, a 30-minute measure of Full-Scale IQ (FSIQ), includes Block Design, Matrix Reasoning, Vocabulary, and Similarities. Performance IQ (PIQ) is a composite of fluid abilities evaluating pattern recognition, abstract reasoning, and problem solving. Verbal IQ (VIQ) is a composite of crystallized abilities and acquired knowledge, such as vocabulary.

Central nervous system (CNS) complications (eg, seizures, hemorrhage, new-onset stroke) and posterior reversible encephalopathy syndrome (PRES) were tracked for 2 years post-HCT.

Brain MRI was obtained ≤30 days before initiation of alemtuzumab and 2 years post-HCT. Images were compared and categorized as (a) no infarct or (b) infarct if fluid-attenuated inversion recovery T2-weighted MRI signal hyperintensity ≥3 mm in linear dimension was visible in 2 orthogonal planes using established imaging criteria [16,17]. Neuroimaging was centrally adjudicated by a single expert radiologist who was blinded to the clinical details. Overt stroke was defined as an MRI lesion associated with neurologic deficit persisting for >24 hours; silent infarct, as an MRI lesion without focal neurologic deficit. MRI progression was defined as a new or enlarging MRI lesion detected post-HCT. PRES was defined as increased diffusion coefficient in areas of T2 hyperintensities on diffusion-weighted MRI in the context of headache, seizures, visual disturbances, or altered level of consciousness [18,19]. Cognitive assessments were performed locally and reviewed centrally. Scaled scores were normalized for age. Patients who completed both pre-HCT and post-HCT assessments are included in this report.

Statistical Methods

Descriptive statistics were completed with SPSS version 25 (IBM, Armonk, NY). Continuous data were analyzed using the t test, and a P value ≤.05 was considered statistically significant.

RESULTS

Thirteen of 29 participants completed both sets of measurements of intelligence. Sixteen were incomplete due to graft rejection (3), death (5), and financial barriers to travel to complete testing (8). The mean age of recipients was 12.5 ± 3.3 years (range, 6.7 to 17.4 years). Eleven of 13 recipients completed imaging studies pre-HCT and post-HCT. Seven had overt stroke pre-HCT, and 1 had an elevated transcranial Doppler with abnormal MRI. Table 1 presents cognition and CNS imaging outcomes by recipient with HCT indication and toxicities. Of the 13 evaluable patients, 7 were off immunosuppressive therapy (IST) before 2 years, and 2 were off after 2 years. One patient continued IST beyond 2 years. Three others were on IST at 1 year but were missing 2-year follow-up data.

IQ Was Stabilized or Improved in Most Participants at 2 Years Post-HCT

On average, FSIQ was stable over 2 years (Figure 1). The average FSIQ score was 90.9 ± 13 at baseline and 91.2 ± 13 post-HCT. The average PIQ was 89.9 ± 13 at baseline versus 90.9 ± 13 post-HCT, and average VIQ was 93.4 ± 13 at baseline versus 93.2 ± 13 post-HCT. The differences do not reach statistical significance and thus indicate stability rather than improvement at this early time point.

Effects of HCT on CNS Imaging

Six recipients had stable MRI findings; 2 had resolution of all areas of infarction. Two of these 8 had PRES post-HCT. Three had more infarcts on the 2-year MRI; however, the timing of new infarcts post-HCT was unknown, and they were detected at the 2-year time point. IQ was decreased in 1 patient by 10 points and was stable in the other 2 patients.

DISCUSSION

This report is the first describing stabilization of IQ and CNS outcomes after URD HCT despite previous CNS morbidity and post-HCT neurologic complications (Table 1). Significant cognitive decline did not occur post-HCT even though 7 children had previously experienced stroke, and 4 developed transient PRES symptoms in the early post-HCT period. These preliminary results suggest that alternative donor HCT may stabilize the cognitive decline associated with SCD, with children with SCD expected to lose approximately 1 FSIQ point per year [2]. Eight of the 13 children had higher FSIQ and PIQ at follow-up (Figure 1A and B), and 7 of the 13 had higher or stable VIQ at follow-up (Figure 1C). Although there is a possibility of a practice effect with improved scores on repeated assessments [20], this effect is more of an issue with shorter retest intervals, such as weeks, as opposed to the 2-year interval in the present study. Fluid cognition is impacted by anemia. A stable hemoglobin concentration with fewer sickled cells likely contributed to this stabilization. The greatest decrease in performance was seen in participant 5. This child had a high burden of CNS injury with 6 silent infarcts and an overt stroke before HCT. We speculate that this burden of CNS injury may take a longer time to stabilize even if a transplantation procedure is able to stabilize the same. Limitations of a small sample size and a single follow-up time point precludes us from completing a more detailed analysis of these outcomes. None of those participants with a decrease in IQ had a longer duration of IST compared with those who improved, and we found no evidence of an association between GVHD and IQ.

Early progression of CNS pathology on imaging studies followed by longer-term stability following MSD HCT has been reported previously [21,22]. The timing of the new lesions in 3 patients is unknown, except that it was noted at the 2-year time point. Of 11 engrafted participants with imaging, 3 had progressive infarcts. Two children with additional infarcts did not have clinical neurologic events post-HCT; 1 child had PRES. No association between GVHD and IST was found. Chronic blood transfusion therapy has been found to be palliative in children with SCD and overt strokes, with additional or progressive infarcts reported in 45% [23]. Although the 27% progression in this cohort appears to be superior to transfusion, and infarcts may appear or improve with time depending on the vascular milieu in the brain, our follow-up was only 2 years. Inclusion of brain imaging in HCT protocols is important to identify the long-term impact of HCT on the brain.

In the only report of cognitive assessment in 15 French children (median age, 8.8 years; range, 4.7 to 13.2 years) following

Table 1
Demographic Data and Wechsler Abbreviated Scale of Intelligence Scores of Participants in the Sickle Cell Unrelated Transplant Trial

ID	Age, yr	Sex	Indication	Post-HCT Complications	Hemorrhage		Infarct		FSIQ Pre	FSIQ Post	PIQ Pre	PIQ Post	VIQ Pre	VIQ Post	IST
					Pre	Post	Pre	Post							
1	6.7	Male	VOE	Limited cGVHD	0	0	0	0	98	99	84	91	112	106	Off
2	8.3	Male	Stroke ×1, ICH ×1, SCI ×5	PRES, AIHA, extensive cGVHD	1	S	5	NC	87	93	76	91	97	96	Off
3	9	Male	Stroke ×1, moyamoya disease, EDAS	PRES, limited cGVHD	0	0	5	0	77	75	79	88	80	69	On at 1 yr
4	9.9	Male	Stroke ×1	Limited cGVHD	0	0	8	0	92	92	89	86	97	100	On
5	10.7	Female	Stroke ×1	None	0	0	6	7	95	85	103	86	88	89	Off
6	13	Male	VOE	Pulmonary embolism, sepsis, extensive cGVHD	0	0	0	0	96	105	96	107	96	103	Off at 3 yr
7	13	Male	Stroke ×2	None	0	0	1	S	83	79	93	76	76	86	Off
8	13.5	Male	ACS ×2	Extensive cGVHD	0	0	0	0	100	92	86	85	114	102	On at 1 yr
9	14.4	Female	Stroke ×1	None	0	0	5	6	97	100	91	89	102	109	Off
10	15.3	Female	Stroke ×1, AVN	PRES, extensive cGVHD	0	1	3	5	83	83	92	92	77	77	Off at 3 yr
11	15.8	Female	↑ TCD ×2 (311 cm/s), abnormal MRI	PRES, extensive cGVHD	ND	ND	ND	ND	101	100	95	96	107	102	On at 1 yr
12	15.9	Male	VOE	None	ND	ND	ND	ND	86	86	89	94	87	82	Off
13	17.4	Female	VOE	Limited cGVHD	0	0	0	0	87	96	96	101	81	91	Off

VOE indicates vaso-occlusive episode; cGVHD, chronic GVHD; ICH, intracranial hemorrhage; SCI, silent cerebral infarct; AIHA, autoimmune hemolytic anemia; EDAS, encephaloduroarteriosynangiosis; ACS, acute chest syndrome; AVN, avascular necrosis; NC, no change; ND, no data; MRI, magnetic resonance imaging; TCD, transcranial Doppler.

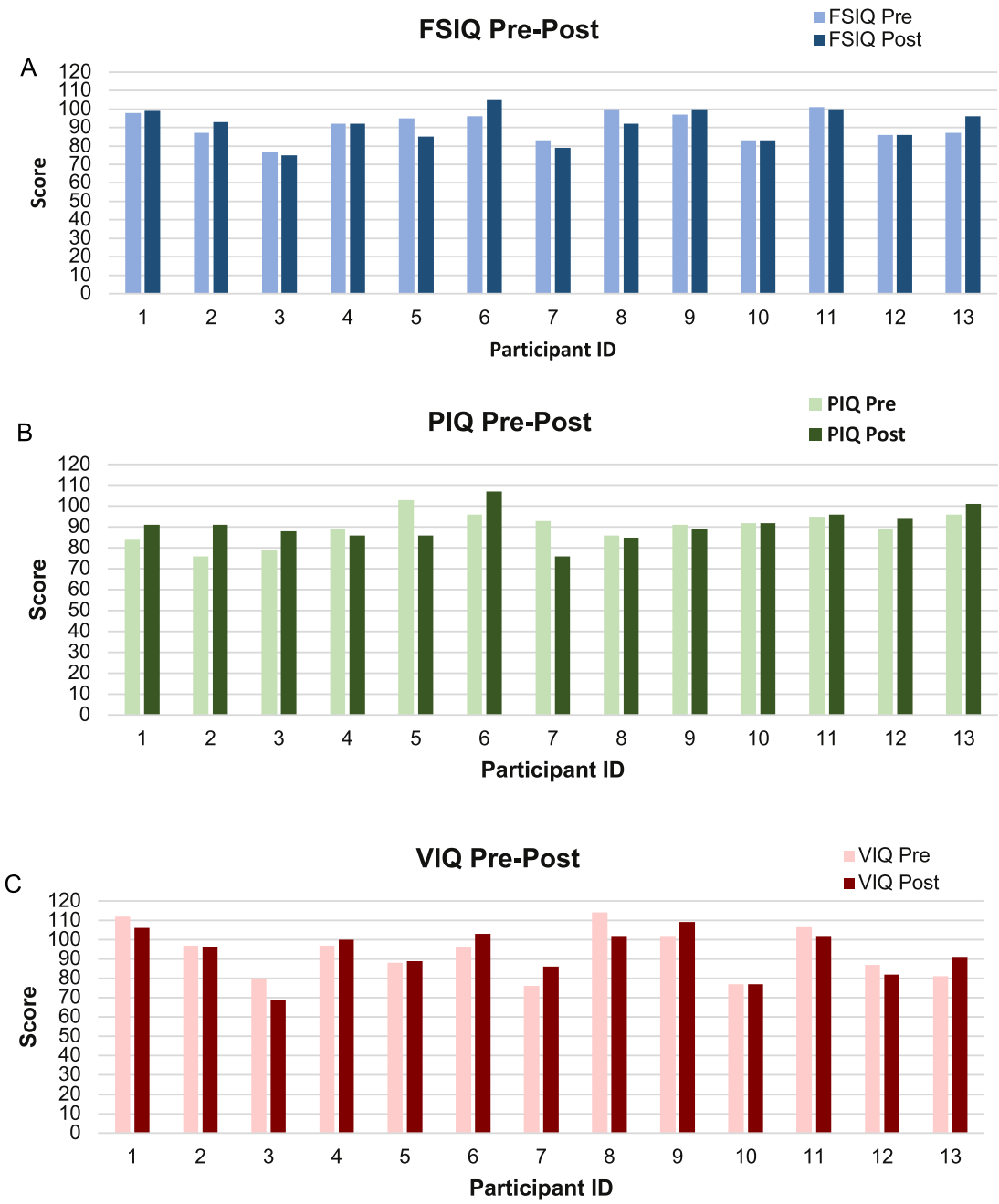

Figure 1. IQ assessment before and after unrelated donor HCT for severe sickle cell disease. (A) FSIQ. (B) PIQ. (C) VIQ.

MSD HCT for cerebral vasculopathy, median FSIQ increased from 87 to 94 at 3 years post-HCT and remained stable at 5 years post-HCT, with no imaging correlation. With a shorter follow-up of 2 years, we documented stable IQ in most children despite a more complicated transplantation process and despite the expected decline of 1 FSIQ point per year in in children with sickle cell anemia based on previous studies [2]. As techniques for alternative donor HCT improve and clinical trials target improved outcomes, similar measurements of secondary CNS outcomes in more HCT recipients are crucial to make informed decisions regarding indications, timing, benefits, and methods of HCT. A lengthier set of measures of cognition was included in this protocol, but adherence to obtaining these was challenging for logistical reasons despite a budget inclusion. Financial support to study participants and widespread ability to perform the testing in uniform fashion could facilitate this process. IQ measurements were completed in more participants than the scans.

HCT trials can now incorporate more accessible and efficient cognitive assessment sets, such as the National Institutes of Health Toolbox Cognitive Battery, an iPad-based application that allows evaluation of several cognitive constructs and yields scores in individual domains, a crystalized cognition composite, a fluid cognition composite, and an overall composite score [24]. The cognitive domains assessed in this battery include attention, episodic memory, working memory, language, executive function, and processing speed. After a brief training session, team members can complete assessments without the need to rely on the availability of a neuropsychologist. This enhances serial long-term follow-up of neurocognition as providers and patients seek

to assess SCD-related complications to plan interventions and develop eligibility criteria for curative measures. Additional effort during clinical trial development, uniformity in comparative testing between protocols [25], and investment in registries to track patients receiving longer-term supportive care and curative therapies terms are immensely important to assess the value of therapeutic interventions for SCD.

ACKNOWLEDGMENTS

The authors are grateful to all participating institutions that enrolled patients in the trial and contributed to ancillary studies.

Financial disclosure: Support for this study was provided by Grant U10 HL069294 to the Blood and Marrow Transplant Clinical Trials Network from the National Heart, Lung, and Blood Institute and the National Cancer Institute, as well as by funding from the National Marrow Donor Program, Sickle Cell Disease Clinical Research Network, and National Center on Minority Health and Health Disparities. The content is solely the responsibility of the authors and does not necessarily represent the official views of these agencies.

Conflict of interest statement: There are no conflicts of interest to report.

Authorship statement: A.A.K., R.C.M., R.A., and T.V. directed ancillary studies and compiled and interpreted data. J.W. collected and prepared the dataset. A.K. drafted the manuscript. All authors participated in editing and critically reviewing the manuscript and approved the final manuscript. N.K. and S.S. contributed equally to this work and should be considered co-senior authors.

REFERENCES

1. DeBaun MR, Armstrong FD, McKinstry RC, Ware RE, Vichinsky E, Kirkham FJ. Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. *Blood*. 2012;119:4587–4596.
2. King AA, Strouse JJ, Rodeghier MJ, et al. Parent education and biologic factors influence on cognition in sickle cell anemia. *Am J Hematol*. 2014;89:162–167.
3. Wang W, Enos L, Gallagher D, et al. Neuropsychologic performance in school-aged children with sickle cell disease: a report from the Cooperative Study of Sickle Cell Disease. *J Pediatr*. 2001;139:391–397.
4. Nickel RS, Seashore E, Lane PA, et al. Improved splenic function after hematopoietic stem cell transplant for sickle cell disease. *Pediatr Blood Cancer*. 2016;63:908–913.
5. Walters MC, Hardy K, Edwards S, et al. Pulmonary, gonadal, and central nervous system status after bone marrow transplantation for sickle cell disease. *Biol Blood Marrow Transplant*. 2010;16:263–272.
6. Dallas MH, Triplett B, Shook DR, et al. Long-term outcome and evaluation of organ function in pediatric patients undergoing haploidentical and matched related hematopoietic cell transplantation for sickle cell disease. *Biol Blood Marrow Transplant*. 2013;19:820–830.
7. Saraf SL, Oh AL, Patel PR, et al. Nonmyeloablative stem cell transplantation with alemtuzumab/low-dose irradiation to cure and improve the quality of life of adults with sickle cell disease. *Biol Blood Marrow Transplant*. 2016;22:441–448.
8. Bernaudin F, Verlhac S, Arnaud C, et al. Long-term treatment follow-up of children with sickle cell disease monitored with abnormal transcranial Doppler velocities. *Blood*. 2016;127:1814–1822.
9. Bockenmeyer J, Chamboredon E, Missud F, et al. [Development of psychological and intellectual performance in transplanted sickle cell disease patients: a prospective study from pretransplant period to 5 years after HSCT]. *Arch Pediatr*. 2013;20:723–730. [in French].
10. Gragert L, Eapen M, Williams E, et al. HLA match likelihoods for hematopoietic stem-cell grafts in the US registry. *N Engl J Med*. 2014;371:339–348.
11. Shenoy S, Eapen M, Panepinto JA, et al. A trial of unrelated donor marrow transplantation for children with severe sickle cell disease. *Blood*. 2016;128:2561–2567.
12. Bolaños-Meade J, Fuchs EJ, Luznik L, et al. HLA-haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. *Blood*. 2012;120:4285–4291.
13. Kamani NR, Walters MC, Carter S, et al. Unrelated donor cord blood transplantation for children with severe sickle cell disease: results of one cohort from the phase II study from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). *Biol Blood Marrow Transplant*. 2012;18:1265–1272.
14. Wechsler D. *Wechsler Preschool and Primary Scale of Intelligence™ —third edition (WPPSI™-III)*. San Antonio, TX: The Psychological Corporation; 2002.
15. Wechsler D. *Wechsler Intelligence Scale for Children™ – fourth edition*. San Antonio, TX: The Psychological Corporation; 2003.
16. Liem RI, Liu J, Gordon MO, et al. Reproducibility of detecting silent cerebral infarcts in pediatric sickle cell anemia. *J Child Neurol*. 2014;29:1685–1691.
17. Kassim AA, Pruthi S, Day M, et al. Silent cerebral infarcts and cerebral aneurysms are prevalent in adults with sickle cell anemia. *Blood*. 2016;127:2038–2040.
18. Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med*. 1996;334:494–500.
19. Mukherjee P, McKinstry RC. Reversible posterior leukoencephalopathy syndrome: evaluation with diffusion-tensor MR imaging. *Radiology*. 2001;219:756–765.
20. Calamia M, Markon K, Tranel D. The robust reliability of neuropsychological measures: meta-analyses of test-retest correlations. *Clin Neuropsychol*. 2013;27:1077–1105.
21. Woodard P, Helton KJ, Khan RB, et al. Brain parenchymal damage after haematopoietic stem cell transplantation for severe sickle cell disease. *Br J Haematol*. 2005;129:550–552.
22. Walters MC, Sullivan KM, Bernaudin F, et al. Neurologic complications after allogeneic marrow transplantation for sickle cell anemia. *Blood*. 1995;85:879–884.
23. Hulbert ML, McKinstry RC, Lacey JL, et al. Silent cerebral infarcts occur despite regular blood transfusion therapy after first strokes in children with sickle cell disease. *Blood*. 2011;117:772–779.
24. Gershon RC, Wagster MV, Hendrie HC, Fox NA, Cook KF, Nowinski CJ. NIH toolbox for assessment of neurological and behavioral function. *Neurology*. 2013;80(11 suppl 3):S2–S6.
25. Shenoy S, Gaziev J, Angelucci E, et al. Late effects screening guidelines after hematopoietic cell transplantation (HCT) for hemoglobinopathy: consensus statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric HCT. *Biol Blood Marrow Transplant*. 2018;24:1313–1321.