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Enhanced Long-Term Brain Magnetic Resonance Imaging Evaluation of Children with Sickle Cell Disease after Hematopoietic Cell Transplantation

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Progressive neurovasculopathy in children with sickle cell disease (SCD) results in decreased cognitive function and quality of life (QoL). Hematopoietic cell transplantation (HCT) is believed to halt progression of neurovasculopathy. Quantitative analysis of T2-weighted fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) for white matter hyperintensity (WMH) burden provides a meaningful estimate of small vessel cerebrovascular disease. We asked if quantitative analysis of WMH could complement standardized clinical assessment of MRI/magnetic resonance angiography (MRA) for assessing SCD central nervous system vasculopathy before and after HCT. Retrospective longitudinal clinical examination of scheduled annual MRI/MRA and quantitative analysis of WMH were performed before and 1 to 7 years after HCT at scheduled annual intervals, along with QoL measurements, in children who had engrafted after HCT. Of 18 patients alive and persistently engrafted (median age, 9.1 years), pretransplantation MRI demonstrated that 9 and 5 had sickle-related stroke and/or small infarcts, respectively. Patients were divided into WMH severity tertiles based on pretransplantation WMH volumes. MRI and WMH were assessed 1 to 7 years after HCT. MRI/MRA and WMH volume were stable or slightly better in 17 of 18 patients. By parent- and self-report, post-HCT QoL improved for children in the lowest WMH tertile significantly more than in the other groups. Based on this single-institution retrospective sample, we report that WMH appears to quantitatively support MRI-based findings that HCT stabilizes long-term small and large vessel cerebrovascular changes and is associated with the degree of improved QoL. While confirmation in larger prospective studies and evaluation by neurocognitive testing are needed, these findings suggest that WMH is a useful biomarker of neurovasculopathy after transplantation for SCD.

INTRODUCTION

Sickle cell disease (SCD) is the most common cause of stroke in children. Strokes and "clinically silent" infarcts are caused by progressive sickle vasculopathy in large and small vessels [1-4], leading to SCD brain vasculopathy. Both stroke types can affect neurological and cognitive function starting early in childhood [1,2,5-9]. Stroke or stroke risk is a frequent indication for pediatric SCD transplantation [10-12]. Based on several studies using brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), hematopoietic stem cell transplantation (HCT) is believed to halt progression of vasculopathy [10,12-16]. However, at least 1 case series reported progressive damage soon after HCT [17].

Standard MRI and MRA scans for neuroradiologic assessment of sickle vasculopathy visualize abnormalities in brain parenchyma and large and medium cerebral arteries, respectively. These scans typically provide clinical assessment of occurrence, evolution, or resolution of large or small infarcts over time using standardized approaches [18]. However, small vessel damage is not typically assessed quantitatively in the clinical review of these scans [18]. Moreover, clinical

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reads can be compared but typically do not provide standardized information to track change over time or to compare between individuals.

Quantitative analysis of T2-weighted fluid attenuated inversion recovery (FLAIR) MRI for white matter hyperintensity (WMH) burden can provide a meaningful estimate of small vessel cerebrovascular disease [19,20]. In adult non-SCD populations, increased WMH is a risk factor for stroke and also can track longitudinal changes in subclinical disease [20]. In children with SCD, larger volume of WMH is associated with decreased cognitive function [8]. Analysis of WMH burden may complement clinical MRI evaluation by providing quantitative information on amount of small vessel involvement, which may not have obvious clinical correlation but could provide insight into the degree of brain involvement and risk for future events.

Using a retrospective sample, we asked whether quantitative WMH analysis could add to the clinical MRI/MRA evaluation of central nervous system (CNS) vasculopathy over time, starting from before transplantation and at subsequent annual intervals. The purposes of this study were to: (1) examine CNS involvement in SCD transplantation patients by considering both standard and quantitative WMH analysis of MRI scans; (2) explore whether analysis of WMH supports the MRI-based perspective that HCT halts long-term progression of sickle vasculopathy [13,14,21]; and (3) assess a relationship between WMH and post-HCT changes in quality of life (QoL), the latter as a marker of patient-reported function [22].

METHODS

This study was approved by Columbia University's institutional review board.

A single-site retrospective analysis examined pretransplantation WMH and standard MRI/MRA clinical read to sequential analyses from 1 to 7 years after HCT, accompanied by a prospective functional assessment. Eligible patients included all of those younger than 22 years who underwent HCT for symptomatic sickle hemoglobinopathy, HbSS or HbS-B^0 thalassemia, at our site between 2003 and April 2014 and who were stably engrafted more than 1 year after HCT. Required observations included a standard clinical head MRI/MRA within 2 months before HCT, including a T2-weighted FLAIR sequence, and annually after HCT for as long as patients returned for follow-up assessment. For the current analysis, study inclusion required at least 1 annual post-HCT scan available for review at the study site. Patients with graft loss were not included. Only annual MRI/MRA scans were included in the analysis reported, including the most recent scheduled MRI, even if interim scans had been performed for acute clinical indications. MRIs included the most recent follow-up scan for each patient. The same 1.5-Tesla scanner was used for all scans analyzed in this sample. Transplantation outcomes of 10 of the 18 subjects have been published previously [23], but details of outcomes of neurologic imaging had previously not been described.

MRI/MRA Interpretation

Each scan underwent 2 independent reviews by board-certified neuroradiologists: 1 for the initial clinical interpretation and 1 performed for this study (A.L.). Discrepancies in interpretation, if any, were addressed by the study neuroradiologist. By T-2–weighted FLAIR, infarct sizes were graded per the SWiTCH trial classification for parenchymal thrombosis [18]: small (<5 mm), medium (5-15 mm), or large (>15 mm). By MRA, stenosis was noted if ≥2 mm. Extracranial internal carotid arteries were not examined.

WMH volume was estimated following a 3-step operator-driven approach described previously [24]. First, a scan-specific intensity threshold was applied to the FLAIR images to define the range of hyperintense values. Second, gross regions-of-interest were manually drawn that included hyperintense voxels but excluded nonparenchymal artifacts (eg, dermal fat). Third, the thresholded image was concatenated with the manual regions-of-interest and the intersecting regions defined the hyperintensities. A single volumetric value for each patient was obtained by multiplying the number of labeled voxels by voxel dimensions [24,25]. For descriptive purposes, participants were divided into 3 (tertiles) based on the range of their WMH severity before HCT. By definition, tertile 1 had little or no WMH. The z-scores were calculated to assess the standardized change (ie, mean, 0; SD, 1) in WMH volume from one year to the next. For example, a patient with a z = .16 increase in WMH volume from year 1 to year 2 was .16 SD greater than the mean of the total sample.

Age-Specific QoL

Data were collected using the PedsQL 4.0 Generic Core Scale [22,26]. The scale exists in 2 versions, a self-report format for children ages 5 to 18 years and a proxy report for parents of children ages 2 to 18 years. The scale contains 23 items that assess overall QoL, which consists of physical (8 items), social (5 items), psychological (5 items), and school functioning (5 items). Scores range from 0 to 100, with higher scores indicating higher QoL. Data were collected from patients and their caregiver before transplantation and were requested annually. Completion at annual intervals varied; the most recently completed follow-up QoL was used here to maximize subject data. Participants and their caregivers independently completed either the English or Spanish version of the PedsQL 4.0 at each time point. Participants' QoL data were previously published [27]; in all cases, from earlier in the post-HCT period.

Statistical Analysis

Demographic comparisons between study subgroups were calculated using unpaired students *t*-test and paired signed rank test.

Mixed-effect linear modeling with restricted maximum likelihood estimation was used to examine WMH volume over time. For this analysis, time (in years) was considered a fixed factor and intercept and subject were considered random factors. For descriptive purposes, participants were divided into 3 tertiles based on the range of their WMH severity before HCT. By definition, tertile 1 had little or no WMH. We calculated z-scores for annualized rates of WMH volume change from baseline values. For these calculations, the difference of WMH volume at the second and third MRI scan and WMH at baseline and transformed these difference scores into a z-score distribution (ie, with mean = 0 and SD = 1).

Descriptive statistics for overall QoL variables were calculated by parent- and self-report at baseline (ie, before transplantation) and the most recent annual follow-up QoL form for 2 groups, tertile 1 (little or no WMH) and tertiles 2 and 3 (abnormal) combined based upon their baseline MRI FLAIR results. The *change in QoL over time* was defined as the difference in QoL measure between the most recent follow-up and baseline. The comparison was analyzed with the Wilcoxon 2-sample test for 2 groups and with the Kruskal-Wallis test for the 3 groups.

RESULTS

All 18 eligible patients with a ≥ 1-year follow-up MRI were included in this analysis (Table 1). The median age of our sample at HCT was 9.2 years (range, 2.2 to 20.2); the ratio of male to female was 13:5. Of the 18, 13 had HbSS and 5 had HbS-B^0thalassemia. The primary clinical indication for HCT in 6 patients was CNS pathology: stroke (n = 5) and multiple silent cerebral infarcts (SCI) (n = 1). Transplantation indications for the remaining patients are listed as SCD complications not affecting the CNS (Table 1), even if MRI abnormalities were revealed upon pretransplantation MRI evaluation by the study neuroradiologist (A.L.). Several patients had more than 1 indication for HCT. Before HCT, 4 patients had been on chronic transfusion for CNS or other severe SCD complications.

Differing conditioning regimens, stem cell sources, and graft-versus-host disease (GVHD) prophylaxis regimens were used, according to institutional review board–approved transplantation protocols [23]. Stem cell sources were related bone marrow [8] or cord blood [3] or unrelated marrow [4] or cord blood [3]. Conditioning regimens were either myeloablative (n = 14) with busulfan (12.8 mg/kg to 16 mg/kg), fludarabine (180 mg/m^2), and alemtuzumab (54 mg/m^2) or reduced intensity (n = 4) with fludarabine (150 mg/m^2), melphalan (140 mg/m^2), and alemtuzumab (48 mg). GVHD prophylaxis included tacrolimus and mycophenolate mofetil (n = 14); tacrolimus, mycophenolate mofetil, and prednisone (n = 1); or tacrolimus, methotrexate, and methylprednisone (n = 3).

After transplantation, neurologic complications included hemorrhagic stroke at 0 months after transplantation (n = 1) or posterior reversible encephalopathic syndrome (n = 1).