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Research Paper

Change of White Matter Integrity in Children With Hematopoietic Stem Cell Transplantation

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ABSTRACT

Background: Advances in hematopoietic stem cell transplantation have improved the survival rate of malignant diseases and congenital immunodeficiencies. It has become important to assess long-term complications in survivors. To assess neurological abnormalities in children treated by transplantation, diffusion tensor imaging was performed.

Methods: Forty children who underwent head diffusion tensor imaging before and after their first transplantation were enrolled. Patients with brain lesions on conventional MRI were excluded. Fractional anisotropy and mean diffusivity were compared between patients and 28 control subjects using tract-based spatial statistics. The Strengths and Difficulties Questionnaire was administered as a behavioral evaluation after transplantation, and diffusion tensor images of patients with and without behavioral abnormalities were compared.

Results: The age of patients and controls was 0 to 19 years and 0 to 16 years, respectively. The date of diffusion tensor imaging was 10 to 57 days before and 40 to 153 days after transplantation. Tract-based spatial statistics showed fractional anisotropy reduction in widespread white matter in patients before and after transplantation. Mean diffusivity was high before transplantation and normalized after transplantation. Analysis comparing before and after hematopoietic stem cell transplantation shows no difference in fractional anisotropy and significantly high mean diffusivity before hematopoietic stem cell transplantation. In patients with behavioral abnormalities, low fractional anisotropy and high mean diffusivity remained after transplantation.

Conclusions: Longitudinal diffusion tensor imaging showed white matter abnormalities in children without conventional MRI abnormalities, which were related to behavioral problems after transplantation. Diffusion tensor imaging is useful for behavioral assessment in children undergoing transplantation.

Introduction

Advances in hematopoietic stem cell transplantation (HSCT) have improved survival rates in children with hematologic, malignant, and immunodeficiency disorders. Along with the improved survival rate, it has become important to assess long-term

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complications in survivors, such as endocrine, cardiovascular, pulmonary, renal, and central nervous system (CNS) complications.[1] Neurological complications related to transplantation have a wide variety of causes, such as CNS infections, vascular diseases, drug-induced neurotoxicity, irradiation, metabolic disturbances, and carcinogenesis.[2,3] Moreover, cognitive function and adaptive behavior in children declined one year after HSCT from baseline.[4] Given these observations, it is important to assess the neurological conditions of children treated with HSCT, even for individuals without major neurological complications on routine clinical evaluation.

Diffusion tensor imaging (DTI) is a quantitative magnetic resonance imaging (MRI) technique that can estimate the three-dimensional diffusion of water molecules within the tissues. DTI is useful to evaluate white matter integrity and detect microstructural abnormalities in the white matter of children with various disorders, such as developmental disorders, epilepsy, or preterm infants.[5,6]

In the present study, cranial DTI was completed in children before and after HSCT to assess HSCT-related white matter abnormalities. We hypothesized that subtle white matter abnormalities can be detected even in children with no obvious neurological complications, and that the subtle white matter changes are related to neuropsychologic functions after HSCT.

Patients and Methods

This study was approved by the Research Ethics Committee at Nagoya University Graduate School of Medicine. As the analysis was performed retrospectively, informed consent for the research was not obtained from the patients and caregivers at the time of MRI scans. When we interviewed the caregivers about the developmental status, written informed consent for the research was obtained from the patients and caregivers.

Patients

Between January 2012 and December 2016, 112 children aged less than 20 years received their first HSCT at Nagoya University Hospital. The diagnosis was solid tumor in 38 patients, bone marrow failure in 26, leukemia in 25, primary immunodeficiency syndrome in 14, myelodysplastic syndrome in seven, and other conditions in two. Of the 112 patients, 64 did not undergo DTI because of lack of availability of the MRI scanner for the present study or poor physical condition of the patients. Of the remaining 48 patients who underwent DTI both before and after HSCT, eight were excluded from the present study for the following reasons: abnormal findings on conventional MRI (hemorrhages [n = 2], infarction [n = 1], encephalopathy [n = 1], brain atrophy [n = 1], and postoperative brain injury [n = 1]) or image artifacts [n = 2]). The remaining 40 patients were finally enrolled in the present study.

Control subjects

The age-matched control group for DTI analysis consisted of 28 children with a median age 4.5 years (range, 0 to 16 years). Control subjects underwent MRI because CNS abnormalities had been suspected on presentation but were later ruled out. Conventional MRI did not show any abnormalities on visual inspection.

Subgroup analysis of the patients

Subgroup analysis according to the conditioning regimen for transplantation was conducted. First, the patients were divided into subgroups based on the intensity of the conditioning regimen. A myeloablative conditioning (MAC) regimen was defined as follows: busulfan greater than 8 mg/kg and total body irradiation (TBI) $\geq$5 Gy single dose or $\geq$8 Gy fractionated.[7] A reduced intensity conditioning (RIC) regimen was one that did not meet the definition for MAC. The details of the conditioning regimen for each patient were decided by the attending physician based on the disease status and donor source. The patients were also divided into subgroups with or without TBI, because TBI is known to have adverse effects on the CNS.

Neuropsychologic assessment

All patients were followed up at our hospital after HSCT. The patients underwent neuropsychologic assessments one to five years after HSCT. The Strengths and Difficulties Questionnaire (SDQ) was used for a brief behavioral screening.[8] It consisted of five scales including emotional symptoms, conduct problems, hyperactivity-inattention, peer relationship problems, and prosocial behavior. The SDQ was scored with the manual on the web site, and patients were categorized into normal, borderline, and abnormal in five scales using the cutoff values of the original version[9] (https://www.sdqinfo.org/). The versions for two- to four-year-olds and four- to 17-year-olds were used according to the age of the patients. The normative data for children aged less than three years are shown on the SDQ web site (http://www.sdqinfo.org/norms/UK3yearNorm.html). When a patient had an abnormal or borderline level on at least one scale of the SDQ, the patient was classified into the abnormal neuropsychologic group. When all scales were within normal limits, the patient was classified into the normal neuropsychologic group.

Image acquisition of MRI

Scans were performed as part of the clinical routine to search for neurological abnormalities before and after HSCT. MRI before HSCT was scheduled within two months before HSCT, and MRI after HSCT was performed between one and six months after HSCT. When sedation was needed for young children, the patients were sedated with oral chloral hydrate (80 mg/kg) before the examination. When patients did not appear sufficiently sedated after chloral hydrate intake, intravenous midazolam or ketamine was administered. MRI was performed using a 3T scanner (Magnetom Trio A Tim System; Siemens, Erlangen, Germany) with a 32-channel phased array head coil. DTI data were acquired with the following parameters: 12 noncollinear diffusion directions (b value = 1000 s/mm^2) with a nondiffusion gradient (b value = 0 s/mm^2); repetition time, 7800 ms; echo time, 84 ms; field of view, 269 $\times$ 269 mm^2; matrix, 128 $\times$ 128; and 64 axial sections (voxel size = 2.1 $\times$ 2.1 $\times$ 2.1 mm^3). In addition to DTI data, the following conventional magnetic resonance images were acquired to examine structural abnormalities: axial T1WI, T2WI, fluid-attenuated inversion recovery, sagittal T1WI, and coronal T2WI.

Image processing

DTI analyses were performed using tract-based spatial statistics (TBSS) in the functional MRI of the Brain software package (FSL; http://www.fmrib.ox.ac.uk/fsl). For each subject, all images were coregistered using affine transformation to the b0 image to correct for eddy current-induced distortion and subject motion effects. The correction was performed by affine registration to a reference volume that is included in the FMRIB Diffusion Toolbox (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT).

A brain mask was created from the first b0 image. A diffusion tensor model at each voxel was fitted, and fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) maps were computed. FA and MD represent the degree of anisotropy and the magnitude of the diffusion process, respectively. AD and RD correspond to the amount of water movement parallel and perpendicular to the fiber bundles, respectively. Next, an FA image was identified as the template, and all FA data for a subject were nonlinearly aligned to it. The mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. Aligned FA data for each subject were then projected onto this skeleton, and the resulting data were fed into voxelwise cross-subject statistics. Statistical analysis was performed voxel by voxel to detect regions of significant differences in FA between two groups of subjects, by using FSLRandomise (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Randomise) with 5000 permutations. The Threshold-Free Cluster Enhancement option in Randomise was used to avoid an arbitrary initial cluster-forming threshold. Age was used as a nuisance covariate of no interest. Results are reported at a corrected threshold of $P < 0.05$. On TBSS, FA, MD, AD, and RD were analyzed before transplantation versus control, after transplantation versus control, and before transplantation versus after transplantation. Analyses were also performed between subgroups of patients before or after transplantation. Patients were divided into those with and without neuropsychologic abnormalities after HSCT, and the two groups were compared by TBSS.

Statistics

Data were analyzed using SPSS version 24 (IBM Japan Ltd, Tokyo, Japan). The two-sample *t* test or Mann-Whitney test was used when testing for a significant difference in age between patients and control subjects or within subgroups. The differences in clinical characteristics between subgroups of patients were tested by the χ^2 test. $P < 0.05$ was defined as statistically significant.

Data availability statement

Anonymized data will be available on request from any qualified investigator.

Results

The characteristics of the patients are summarized in Table 1. The median age of patients and control subjects was 4.5 years (range, 0 to 19 years) and 4.5 years (range, 0 to 16 years), respectively. The age at MRI was not significantly different between patients and control subjects. The diagnoses of the 40 enrolled patients were solid tumor in 13 patients (neuroblastoma in 11 and others in two), bone marrow failure in 12 (aplastic anemia in six, Diamond-Blackfan anemia in three, and others in three), leukemia in six, primary immunodeficiency syndrome in five, myelodysplastic syndrome in three, and chronic active Epstein-Barr virus infection in one. Conditioning regimens were as follows: MAC regimens were a TBI-based regimen with the combination of TBI, melphalan, and antithymocyte globulin in seven, a busulfan-based regimen with the combination of busulfan, melphalan, antithymocyte globulin, and fludarabine in 15, and other chemotherapy-based regimens in combination with melphalan, etoposide, and carboplatin in two. RIC regimens were combinations with low-dose TBI, antithymocyte globulin, melphalan, and fludarabine in 12 patients, with low-dose TBI, melphalan, and fludarabine in two, with low-dose TBI, antithymocyte globulin, and cyclophosphamide in one, and with antithymocyte globulin and cyclophosphamide in one.

TABLE 1
Patient Characteristics

	Patient (n = 40)
Gender	
Male, female	28, 12
Diagnosis	
Solid tumor (neuroblastoma 11, others 2)	13
Bone marrow failure (aplastic anemia 6, Diamond-Blackfan anemia 3, and others 3)	12
Leukemia	6
Primary immunodeficiency	5
Myelodysplastic syndrome	3
Chronic active Epstein-Barr virus infection	1
Type of HSCT	
BMT	19
PBSCT	10
CBT	9
BMT + PBSCT	2
Outcome	
Survival	36
Dead	3
Lost to follow-up	1
Neuroimaging evaluation	
Age at MRI, median (range)	4.5 (0-19) years
MRI imaging date from HSCT, Median (range)	
Pre-HSCT	21.5 (10-57) days
Post-HSCT	85.5 (40-153) days
Neuropsychologic assessment	
Age, median (range)	6 (2-16) years
Date from HSCT, median (range)	31 (11-56) months
Total difficulties score, median (range)	5.5 (0-31)

Abbreviations:
BMT = bone marrow transplantation
CBT = cord blood transplantation
HSCT = hematopoietic stem cell transplantation
MRI = magnetic resonance imaging
PBSCT = peripheral blood stem cell transplantation

TBSS analysis between patients and control subjects

TBSS showed significant FA reduction widely in the white matter, including the genu of the corpus callosum, internal capsule, bilateral frontotemporal white matter, left parietal white matter, and cerebral peduncle of the patients before and after HSCT compared with the control subjects (Fig 1A, B, Supplemental Fig 1). There was no significant difference in FA between before and after HSCT (Fig 1C). The mean FA values of the skeletons with significant differences on TBSS in each patient are shown in Fig 2. Both before and after HSCT, there was no specific distribution of low FA by age. Before HSCT, MD, AD, and RD were higher widely in the white matter of patients than of control subjects (Fig 1A). There was no area with significant differences in MD and AD between patients after HSCT and control subjects, and increased RD remained in the genu of the corpus callosum (Fig 1B). Analysis between before and after HSCT showed significantly high MD, AD, and RD values before HSCT (Fig 1C).

Subgroup TBSS analysis

The features of the subgroup were as follows: the numbers of patients in each group were 24 in MAC, 16 in RIC, 22 in TBI, and 18 in non-TBI. The median ages at HSCT were three years (range, 0 to 19 years), 7.5 years (range, 1 to 15 years), seven years (range, 1 to 19 years), and two years (range, 0 to 15 years), respectively. Patients with MAC were younger than patients with RIC ($P = 0.03$). Patients

with TBI were older than patients without TBI ($P < 0.001$). In the TBI group, the median irradiation dose was 5 Gy (range, 3 to 12 Gy).

On TBSS, there were no areas with a significant difference in FA between pre-HSCT and post-HSCT in all subgroups, MAC, RIC, TBI, and non-TBI. On TBSS of MD, there was no area with a significant difference in MD before and after HSCT in the RIC group, whereas MD was higher before HSCT than after HSCT in the left tempoparietal white matter in the TBI group and in the widespread bilateral white matter in the MAC and non-TBI groups. On TBSS of AD, there was no area with a significant difference in AD before and after HSCT in the RIC, TBI, and non-TBI groups, whereas AD was higher before HSCT than after HSCT in the widespread bilateral white matter in the MAC group. On TBSS of RD, there was no area with a significant difference in RD before and after HSCT in the RIC group, whereas RD was higher before HSCT than after HSCT in the left temporal white matter in the TBI group and in the widespread bilateral white matter in the MAC and non-TBI groups.

Neuropsychologic assessment

Of the 40 patients, 36 survived, three died, and one was lost to follow-up at the time of neuropsychologic assessment. Neuropsychologic assessment was performed in 26 survivors. The median age at the time of evaluation was six years (range, 2 to 16 years), and the median duration after HSCT was 31 months (range, 11 to 56 months). Five of 26 patients underwent additional HSCT before the assessment. Fourteen patients were classified into the normal neuropsychologic group, and 12 were classified into the abnormal neuropsychologic group. The clinical characteristics of each group are shown in Table 2. There were no significant differences between the two groups except for sex ($P = 0.01$). The number of patients who were borderline or abnormal in the five scales was as follows: conduct problems (n = 6), emotional symptoms (n = 1), hyperactivity (n = 5), peer problems (n = 4), and prosocial behavior (n = 6).

On TBSS, the normal SDQ group had no areas with a significantly different FA from that of control subjects both before and after HSCT. MD was high in the genu of the corpus callosum before HSCT and not significantly different after HSCT compared with control subjects (Fig 3A). The abnormal group had significantly lower FA and higher MD in the deep white matter of the right hemisphere, bilateral frontal lobes, and corpus callosum than control subjects before and after HSCT (Fig 3B). Both the normal and abnormal groups had no significant differences in FA between DTIs before and

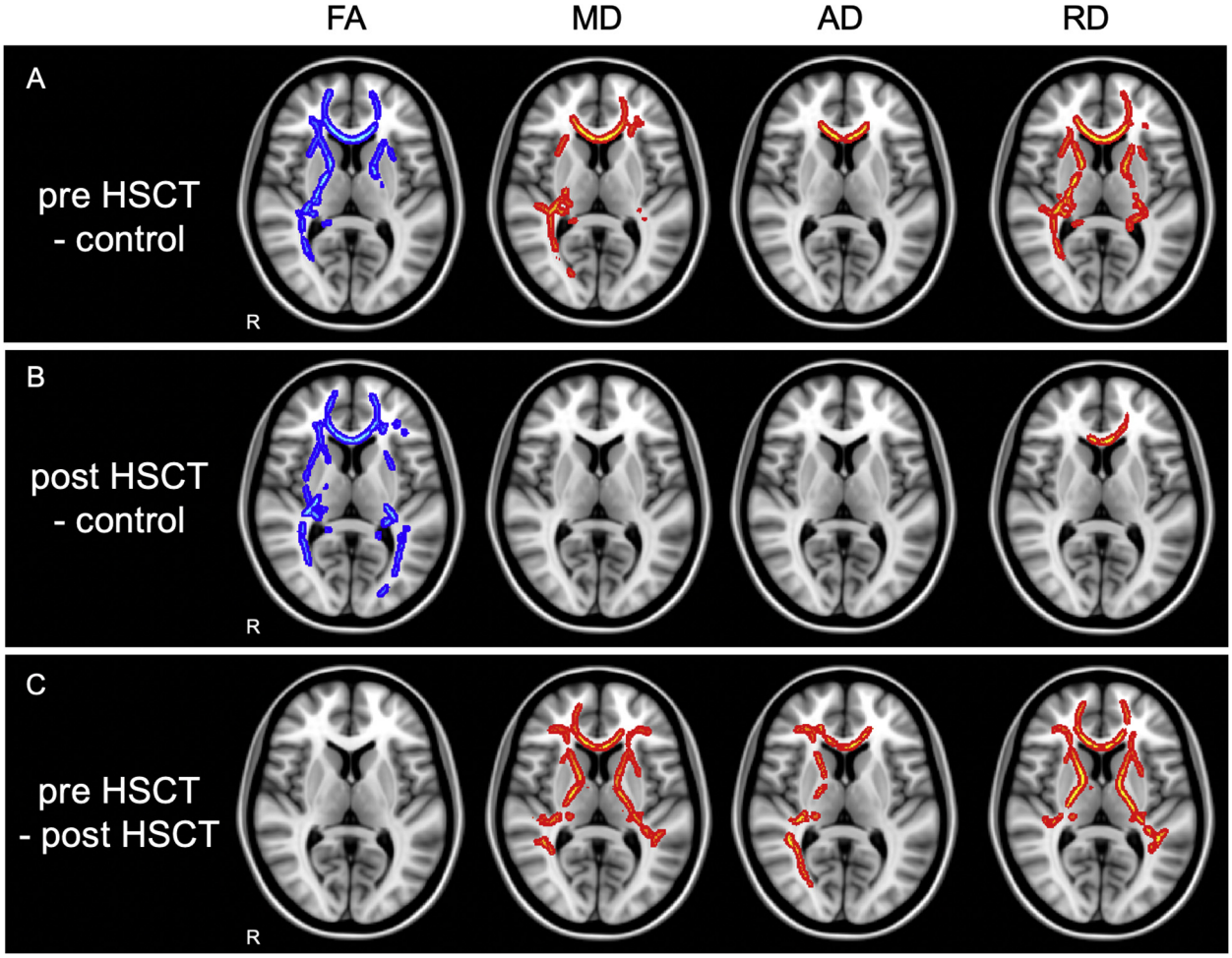

FIGURE 1. Tract-based spatial statistics (TBSS) analysis before and after hematopoietic stem cell transplantation (HSCT). (A) TBSS analysis between patients before HSCT and control subjects shows low fractional anisotropy (FA) (blue areas) in the genu of the corpus callosum, internal capsule, and frontotemporal white matter of patients. Mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) are increased within the area of decreased FA (red-yellow areas). (B) Analysis comparing patients after HSCT and control subjects shows low FA (blue areas) widely in the white matter as before HSCT. Although MD and AD are not significantly different from those of control subjects, increased RD (red-yellow areas) remains in the genu of the corpus callosum. (C) Analysis comparing before and after HSCT shows no difference in FA, and significantly high MD, AD, and RD (red-yellow areas) before HSCT. The color version of this figure is available in the online edition.

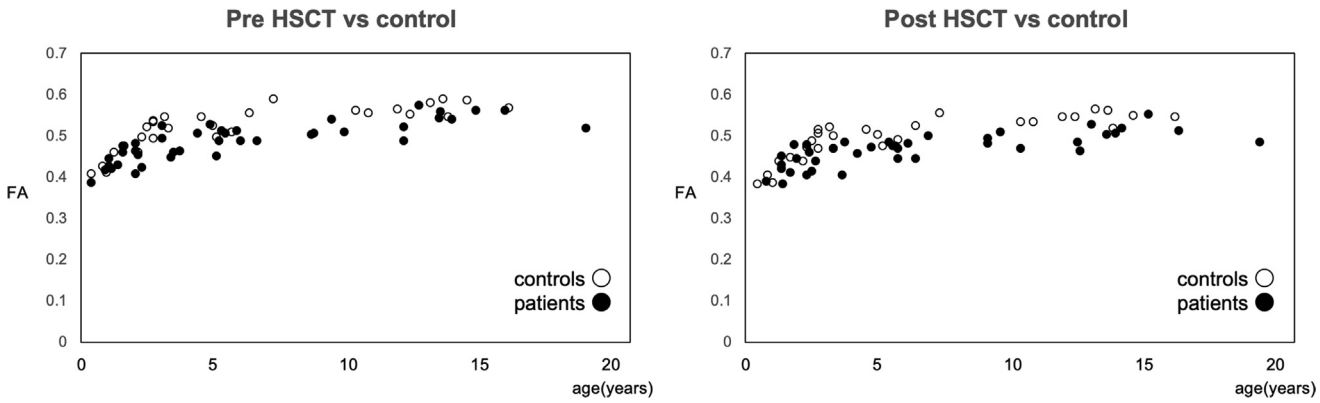

FIGURE 2. Mean fractional anisotropy (FA) in the skeleton with significant difference on tract-based spatial statistics. White dots represent control subjects, and black dots are patients. There is no specific distribution of low FA by age. HSCT, hematopoietic stem cell transplantation.

after HSCT. AD was not different in any areas in the normal or abnormal SDQ groups compared with control subjects both before and after HSCT. RD in the normal SDQ group was not different in any areas compared with control subjects both before and after HSCT. The abnormal SDQ group had significantly higher RD in the deep white matter of the right hemisphere, bilateral frontoparietal lobes, and corpus callosum than control subjects before and after HSCT.

Discussion

DTI analysis was performed in children with hematologic diseases, malignant diseases, or primary immunodeficiency syndromes before and after HSCT. Decreased FA was observed in the corpus callosum and widely in the white matter before and after HSCT. MD was high before HSCT and normalized after HSCT. In patients with abnormalities on neuropsychologic assessment, decreased FA and increased MD remained even after HSCT.

There was a longitudinal DTI study of adult patients with HSCT. In a report of 22 adult patients with HSCT for hematologic disorders and 10 control subjects, there were no significant differences between patients and control subjects at baseline before HSCT and one year after HSCT. However, longitudinal analysis from baseline to one year after HSCT showed a decrease in MD one year from baseline.[10] The present study showing high MD before HSCT and no difference from control subjects after HSCT showed a similar longitudinal change in MD as the adult patient study. Repair of the white matter damaged during chemotherapy or radiation possibly contributes to the normalized MD after HSCT. Although there were no areas of high MD and AD after HSCT, high RD remained in the corpus callosum after HSCT. It has been reported that experimental demyelination increased RD in the corpus callosum of mouse brains.[11] In infants, the myelination process affects the change in RD more than that in AD, and high RD can be caused by delayed myelination.[12] The change in RD in the present study may suggest abnormalities of myelin, such as demyelination or delayed myelination. Although the biologic nature of the DTI abnormalities is still not fully understood, longitudinal DTI is a promising tool to evaluate the CNS conditions of children who undergo HSCT with chemotherapy or radiotherapy. The present findings of low FA and high MD and RD before HSCT, with no worsening after HSCT, suggest that white matter abnormalities are caused by chemotherapy, radiotherapy, or original disorders rather than HSCT and its conditioning therapy.

In the subgroup analysis of conditioning therapies for transplantation, there was no change in FA between pre-HSCT and post-

TABLE 2
Characteristics of Patients in the Normal and Abnormal Neurological Groups

	Normal (n = 14)	Abnormal (n = 12)
Age at HSCT, median (range)	4.5 (1-13) years	5 (0-12) years
Gender		
Male, female	5, 9	10, 2
Diagnosis		
Leukemia	2	3
Immune deficiency	1	2
Solid tumor	4	5
Myelodysplastic syndrome	1	0
Bone marrow failure	6	1
Chronic active Epstein-Barr virus infection	0	1
Number of patients performed additional HSCT	3	2
Conditioning regimen		
MAC	7	9
RIC	7	3
TBI (+)	9	6
TBI (−)	5	6

Abbreviations:
HSCT = hematopoietic stem cell transplantation
MAC = myeloablative conditioning
RIC = reduced intensity conditioning
TBI =total body irradiation

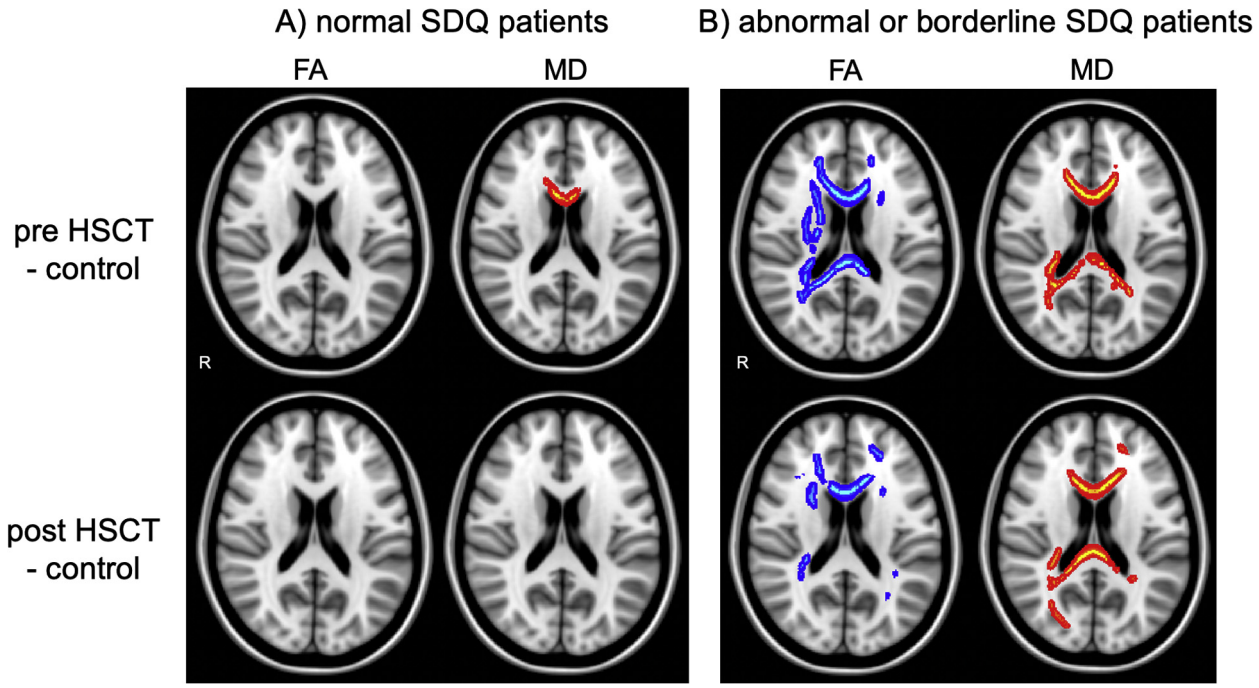

FIGURE 3. Tract-based spatial statistics analysis of patients in the normal and abnormal neurological groups. (A) Fractional anisotropy (FA) of patients with normal Strengths and Difficulties Questionnaire (SDQ) results is not significantly different from that of control subjects before and after hematopoietic stem cell transplantation (HSCT). Mean diffusivity (MD) is high in the genu of the corpus callosum before HSCT, with no difference from that of control subjects after HSCT. (B) FA of patients with abnormal or borderline SDQ results is significantly lower in the corpus callosum and a wide area of deep white matter than of control subjects before and after HSCT. MD is higher than that of control subjects before and after HSCT. The color version of this figure is available in the online edition.

HSCT in all subgroups. It has been reported that cranial radiotherapy in children with leukemia, lymphoma, or brain tumors caused white matter abnormalities on DTI.[13-15] In these reports, the dose of cranial radiation was 18 to 24, 15 to 25, and 45 to 59 Gy, higher than that of TBI in the present patients (3 to 12 Gy). It has also been reported that white matter damage evaluated by DTI correlated with radiation dose in adult patients with brain tumors.[16] The conditioning regimens with TBI in the present study may not affect the white matter compared with the previous DTI studies of radiation therapies, although the original disorders, numbers of patients, and study designs were not the same.

The developing brain in childhood is more vulnerable to chemotherapy or radiotherapy than the adult brain.[17] It is well known that methotrexate and radiation therapy cause white matter injury in children.[18,19] DTI studies of survivors of childhood acute lymphoblastic leukemia or lymphoma treated with chemotherapy and cranial radiotherapy showed a widespread decrease in FA more than 10 years after the treatments.[13,14] Although it has not been clarified whether FA reduction in the present patients will last until adulthood, the white matter damage during childhood can affect brain function for a long time.

It has been reported that children treated with HSCT had lower intelligence quotients one year after HSCT than at baseline.[4,20] In the previous DTI studies, it was reported that adults who had had chemotherapy and CNS radiotherapy for lymphoid malignancies during childhood had decreased FA that was correlated with neuropsychologic dysfunction 25 years after treatment.[14] It has also been reported that low performance on executive functioning was correlated with increased MD in children with brain tumors treated with chemotherapy and autologous hematopoietic progenitor cell rescue.[21] In the present study, children with abnormal or borderline SDQ results after HSCT showed low FA and high MD before and after HSCT. In contrast, children with normal SDQ results had no areas of low FA before and after HSCT, as well as high MD in the genu of the corpus callosum that normalized after HSCT. These findings suggest that longitudinal DTI before and after HSCT can be used as a marker to predict neuropsychologic outcomes in children with HSCT for various disorders. Early neuropsychologic intervention or neurorehabilitation for children with white matter abnormalities on DTI may improve their long-term neuropsychologic outcomes.

The present study has several limitations. First, the present study included patients with various disorders and different treatment protocols. Multiple factors may affect the results of the DTI analysis, such as type of original disorder, stage of the malignancies, protocol of chemotherapy, radiotherapy, and age of the patients. A subgroup analysis according to the intensity of conditioning regimen for HSCT was performed, but not all factors affecting the results can be distinguished. Second, the timings of DTI after HSCT and behavioral assessment were not the same: DTI was done from one to six months after transplantation, and behavioral assessment was performed 11 to 56 months after transplantation. Although DTI and behavioral assessment were not compared at the same time, later behavioral assessment may enable the evaluation of long-term performance and behavior in school or daily life. The behavioral assessment was performed only after HSCT. Because of the lack of assessment before HSCT, it is difficult to know if the behavioral abnormality existed before HSCT.

Conclusions

DTI showed an abnormality of white matter integrity in children with no obvious neurological complications and no abnormalities on conventional MRI before and after HSCT. The white matter changes on DTI were related to behavioral problems after

HSCT. Longitudinal DTI analysis is useful for the assessment of behavioral conditions in children treated with HSCT for various disorders.

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Supplementary data

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