

Role of diffusion kurtosis imaging for detecting brain microstructural changes in complete remission childhood survivors undergoing chemotherapy for acute lymphoblastic leukemia

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Abstract

Objectives

Some children with acute lymphoblastic leukemia receiving chemotherapy may sustain brain microstructural damages that impair their neurocognitive function and affect their quality of life to varying degrees. This study aims to determine whether diffusion kurtosis imaging could detect brain microstructural changes in newly diagnosed acute lymphoblastic leukemia patients before and after normalization in complete remission after chemotherapy.

Methods

Twenty newly diagnosed patients with acute lymphoblastic leukemia and 20 healthy controls matched by sex and were enrolled in this study in the Shenzhen Children's Hospital from August 2019 to December 2020. Head MRI scans were performed mean kurtosis, axial kurtosis and radial kurtosis values were calculated before and after complete remission.

Results

There were significant decreases observed in mean kurtosis and axial kurtosis in both the genu and splenium of the corpus callosum after chemotherapy among patients under 5 years old who have also achieved complete remission. The diffusion kurtosis imaging parameters were measured in the bilateral frontal lobe and corpus callosum; there were no obvious changes observed among patients older than 5 years old.

Conclusion

Brain microstructure damage can occur in patients with acute lymphoblastic leukemia during the early stage of chemotherapy. The location of the damage is significantly correlated with the patient's age. Early recognition of changes in diffusion kurtosis imaging parameters of brain microstructure damage in acute lymphoblastic leukemia patients may help improve patient prognosis.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common primary malignant tumour in children, commonly occurring at ages 2 to 5 years old [1]. The incidence of ALL accounts for 29% of all cancers in children, and 74% of all leukemias[2].

The cornerstone in the treatment of ALL was high dose methotrexate (MTX), administered intravenously and intrathecally. The dose of the drug was adjusted according to the degree of risk. With the continuous

development of individualized therapy, the cure rate of ALL continues to increase and the 10-year overall survival rate now reaches 90%[1]. However, studies have found that about 65% of patients with ALL can have recurrence of extramedullary leukemia during remission, mainly in the CNS due to the protective effect of the blood-brain barrier[3]. In the past, craniocerebral radiotherapy has been used to prevent the recurrence in the CNS, but it may lead to a variety of sequelae include secondary cancer, neurocognitive dysfunction, and endocrine disorders. Consequently, intrathecal chemotherapy with MTX was introduced as an alternative instead of craniocerebral radiotherapy to avoid sequelae. This enabled the recurrence of ALL in the CNS to be reduced to 5%[4].

Children with ALL receiving chemotherapy alone had a lower prevalence of neurocognitive dysfunction compared to cranial radiotherapy (CRT); however, neurotoxicity was likely to occur during treatment and subsequently persist for a long time. Leukoencephalopathy, vascular damage, epilepsy, brain microstructure change and neurocognitive dysfunction are neurological side effects caused by chemotherapy[5]. Studies have shown that leukoencephalopathy caused by chemotherapy has nothing to do with the neurocognitive dysfunction[6, 7]. Chemotherapy can cause widespread brain gray matter (GM) and white matter (WM) volume loss in areas including the frontal lobe, temporal lobe, parietal lobe, thalamus, caudate nucleus, hippocampus, and corpus callosum, thus damaging neurocognitive functions such as memory, attention, and executive functions[1, 8, 9] thus affecting long-term quality of life. By studying the changes in brain structure and function, early clinical intervention for children with possible neurocognitive changes have become essential to improving long-term quality of life.

Currently, DTI is often used to assess microstructural changes in the brain of patients with ALL. DTI is an imaging technique based on the hypothetical model of the Gaussian distribution of water molecules. However, DTI is applied on actual, complex, and biological tissue environments containing different kinds of cells and biofilms, where the actual diffusion of water molecules deviate from the standard Gaussian distribution, showing different degrees of non-Gaussian properties. Diffusion kurtosis imaging (DKI) extends conventional DTI by estimating the diffusion and kurtosis tensors to quantify non-Gaussian diffusion that occurs in biological tissues[10, 11]. Studies have proved that DKI is more comprehensive and sensitive than DTI in characterizing normal or pathological brain tissues[12, 13]. Currently, most microstructural studies on the brains of children with ALL are mainly focused on long-term changes after chemotherapy; short-term studies are lacking. In this study, we aimed to assess whether DKI could evaluate changes in brain microstructure before treatment and after complete remission (CR) in patients with ALL.

Methods

Patients

Twenty patients (11 boys and 9 girls, aged 3 to 12 years; mean age, 6.27 ± 3.21 years; median age, 7 years) admitted to our hospital between May 2019 and October 2020 were included in the study. They were clinically diagnosed with ALL with bone marrow histopathology confirmation. All patients had two

brain MRI examinations, with DKI measurement: one before treatment and another one after CR. The interval between MRI examinations was 46–56 days. Patients who did not reach CR after 46–56 days of chemotherapy were not included.

CR criteria are as follows: (1) absence of anaemia, haemorrhage, infection, and leukemic cell infiltration, (2) blood parameters must show haemoglobin ≥ 90 g/L, normal or reduced white blood cells, no naive cells, platelet count $\geq 100 \times 10^9 / L$, and bone marrow primitive cells $\leq 5\%$.

Risk ratings are based on age at onset, white blood cell count, presence of CNS or testicular leukemia, immunotyping, cytogenetics, DNA index, and treatment response. There were 10 patients each in low-risk and middle-risk categories, and high-risk patients were not included in our study. Patients received chemotherapy regimens based on the institution in our college (CCCG - ALL - 2015, V2019). Patients in the low risk and middle risk groups received 3 and 4 intrathecal injections, respectively, during the induction remission treatment, the drugs included MTX, cytarabine (Ara-C) and dexamethasone (Dex). Intravenous drugs included prednisone (Pred) and vincristine (VCR), daunorubicin (DNR), and L-asparaginase (L-Asp). Patients with neurocognition-related disorders such as epilepsy, consciousness disorders, and congenital brain dysplasia and patients with prior CRT treatment or brain tissue affecting drugs such as methotrexate, carbamazepine.

Control subjects

A total of 20 age-matched control subjects (11 boys and 9 girls, aged 3 to 13 years; mean 6.60 ± 3.60 years; median 7.2 years) who underwent the same MRI protocols were selected for comparison. Indications for MRI in these children were headache, convulsion, and dizziness. The exclusion criteria for control subjects were history of low birth weight or preterm delivery, congenital brain dysplasia, epilepsy, metabolic disorders, consciousness disorders, and systemic diseases. Children with a history of treatment that might affect brain microstructure were also excluded. They were subsequently deemed to be healthy on follow-up visits.

Imaging and analysis

All subjects underwent MRI examination with a 3-T scanner (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany). DKI source images were obtained using a single-shot spin-echo echo-planar-imaging (EPI) sequence with a motion-probing gradient in 30 orientations using the following parameters: repetition time, 5200ms; echo time, 102ms; b-values = 0, 1000 and 2500s/mm²; the field of view, 220mm \times 220mm; slice thickness, 4.0mm without inter-slice gaps. The acquisition time for DKI data was 6 minutes and 20 seconds. Each patient was provided with ear protection throughout the MR examinations. The uncooperative children were given 10% chloral hydrate 0.5 \times 1.0ml/kg enema sedation 30min before the examination, with the total dose not exceeding 10ml. Patients were examined after induction into sleep. Conventional MRI included axial T1-weighted images and T2-weighted images, sagittal T1-weighted images were also obtained.

DKI analysis included characterization of mean kurtosis (MK), axial kurtosis (AK) and radial kurtosis (RK). DKI-derived tractography was performed using diffusional kurtosis estimator software (<http://www.nitrc.org/projects/dke/>). Quantitative values for MK, AK and RK of all determinate regions of interest (ROIs) were measured. Usually, a total of four ROIs, which strictly corresponded to the location of WM on T1-weighted images and T2-weighted images, were placed on right and left frontal lobe WM, the genu and splenium of the corpus callosum (CC) in the midline (Fig. 1). Two neuroradiologists (ten and nine years of experience in pediatric MRI, respectively) reviewed MRI findings and the ROIs carefully chosen on DKI maps. They were blinded to age, sex, and other pertinent clinical histories. Any discrepancies in image interpretation and ROI placement were resolved by consensus. The values on DKI maps were independently measured by two readers.

Statistical analysis

Descriptive statistics of continuous variables are presented as mean, standard deviation and median. Statistical analyses were performed using SPSS 25.0. A series of statistical analyses were performed to examine the relations of right and left frontal lobe WM, the genu and splenium of the CC. First, a two-sample paired t-test was used to compare DKI parameters between the control group and ALL patients before chemotherapy. A paired-sample t-test was used to compare the DKI parameters between patients before and after induction. After that, the case group was accordingly divided by age into a ≤ 5 -year-old group (10 patients) and > 5 -year-old group (10 patients) [14, 15], the low-risk and middle-risk groups were compared to see whether there were any differences between the two groups before chemotherapy and after CR in terms of DKI parameters.

Results

There were no statistically significant differences in DKI parameters between all patients before chemotherapy and the control group, between the low-risk group and the middle-risk group ($P > 0.05$). Compared to patients with ALL before chemotherapy, the patients who underwent complete remission CR had significantly lower ($P < 0.05$) MK and RK although the AK showed no significant changes ($P > 0.05$) in the genu and splenium of the CC (Table 1). Patients of ≤ 5 years old after CR had significantly lower MK and RK in the genu and splenium of the CC ($P < 0.05$) (Table 2).

Table 1 DKI in frontal lobe and corpus callosum in 20 ALL patients before therapy compared to after CR

	Before therapy Median(range)	After CR Median(range)	P Value
FLWM right MK	0.69(0.58-0.95)	0.68(0.56-0.77)	NS
FLWM right AK	0.61(0.55-0.80)	0.63(0.56-0.77)	NS
FLWM right RK	0.69(0.75-1.36)	0.79(0.57-1.24)	NS
FLWM left MK	0.69(0.56-0.98)	0.67(0.49-0.96)	NS
FLWM left AK	0.64(0.53-0.85)	0.66(0.55-0.83)	NS
FLWM left RK	0.82(0.54-1.34)	0.73(0.51-1.15)	NS
GCC MK	0.82(0.57-1.10)	0.75(0.50-0.94)	0.04
GCC AK	0.62(0.54-0.76)	0.65(0.52-0.73)	NS
GCC RK	1.07(0.61-1.55)	0.93(0.54-1.34)	0.01
SCC MK	0.86(0.59-1.00)	0.84(0.56-0.98)	0.01
SCC AK	0.65(0.56-0.76)	0.65(0.53-0.74)	NS
SCC RK	1.22(0.64-2.27)	1.11(0.60-1.38)	0.01

FLWM frontal lobe white matter, *GCC* genu of the corpus callosum, *SCC* splenium of the corpus callosum, *MK* mean kurtosis, *AK* axial kurtosis, *RK* radial kurtosis, *NS* non-significant, *DKI* diffusion kurtosis imaging, *ALL* acute lymphoblastic leukemia

Table 2 DKI in frontal lobe and corpus callosum in 20 ALL patient before therapy and after CR of different age groups

	≤5years(n=8)			>5years(n=12)		
	Before therapy	After CR	P Value	Before therapy	After CR	P Value
	Median(range)	Median(range)		Median(range)	Median(range)	
FLWM right MK	0.69(0.64-0.92)	0.64(0.59-0.74)	NS	0.64(0.58-0.95)	0.79(0.55-0.90)	NS
FLWM right AK	0.63(0.55-0.71)	0.61(0.56-0.69)	NS	0.65(0.54-0.81)	0.69(0.60-0.78)	NS
FLWM right RK	0.88(0.66-1.36)	0.70(0.62-0.96)	NS	0.75(0.61-1.09)	0.83(0.57-1.24)	NS
FLWM left MK	0.71(0.60-0.93)	0.63(0.49-0.79)	NS	0.65(0.56-0.98)	0.73(0.52-0.96)	NS
FLWM left AK	0.59(0.52-0.73)	0.60(0.55-0.69)	NS	0.79(0.54-0.85)	0.67(0.58-0.83)	NS
FLWM left RK	0.86(0.60-1.34)	0.67(0.51-0.97)	NS	0.76(0.54-1.25)	0.83(0.55-1.15)	NS
GCC MK	0.80(0.61-0.97)	0.69(0.55-0.82)	0.02	0.82(0.57-1.10)	0.84(0.50-0.94)	NS
GCC AK	0.62(0.54-0.69)	0.61(0.52-0.67)	NS	0.65(0.51-0.77)	0.68(0.61-0.73)	NS
GCC RK	1.07(0.91-1.44)	0.81(0.58-1.15)	0.01	1.03(0.61-1.55)	1.01(0.54-1.34)	NS
SCC MK	0.89(0.74-1.09)	0.73(0.55-0.90)	0.01	0.83(0.59-1.21)	0.89(0.60-0.98)	NS
SCC AK	0.63(0.55-0.66)	0.60(0.53-0.68)	NS	0.65(0.56-0.77)	0.68(0.62-0.74)	NS
SCC RK	1.30(1.10-1.57)	0.97(0.60-1.34)	0.01	1.21(0.64-2.27)	1.25(0.80-1.38)	NS

FLWM frontal lobe white matter, GCC genu of the corpus callosum, SCC splenium of the corpus callosum, MK mean kurtosis, AK axial kurtosis, RK radial kurtosis, NS non-significant, DKI diffusion kurtosis imaging, ALL acute lymphoblastic leukemia

Discussion

MK could reflect the microstructure complexity of tissues; on the other hand, MK and RK could detect the integrity of myelin. Our study found that the patients had significantly lower MK and RK in the corpus callosum after CR, indicating that short-term chemotherapy could cause demyelinating changes in the corpus callosum. However, there were no significant changes in DKI parameters in bilateral frontal lobe WM indicating that chemotherapeutics had varying effects on different brain regions.

Our patients were mainly given intravenous VCR and DNR, Pred, L-Asp, supplemented by intrathecal injection of MTX during the induction therapy. It is common knowledge that VCR can cause peripheral neuropathy [2], but it can also lead to generalized brain volume reduction, especially in terms of WM volume. The acute toxic reaction affects the organization of normal growth processes causing brain volume loss. DNR can also cause brain volume loss; however, DNR mainly affects GM volume[16]. Neither Pred nor L-Asp cause extensive injuries to WM[17, 18].

The volume of myelin in the corpus callosum increases sharply in early childhood, reaching 86% of the final volume at the age of 5[14, 19]. We observed that the patients ≤ 5 years old had significantly lower MK and RK after induction, while the patients ≥ 5 years old had not undergone similarly significant change DKI parameters, in the genu and splenium of CC. It is speculated that the WM damage was caused by VCR, which mainly affects the normal growth of tissues. However, whether this change could persist upon later treatment remains to be further studied. However, according to existing studies, younger patients with ALL treated with chemotherapy may experience more severe brain damage[20].

Previous studies have shown that the volume of the corpus callosum and bilateral frontal WM in patients who have completed chemotherapy were significantly lower in patients with ALL [8, 21]. As the brain finally matures, the frontal lobe WM is the most vulnerable to damage[22]. Our research found that bilateral frontal WM volume change was not obvious. Our findings suggested that the frontal WM could not be easily affected by VCR. Alternatively, there may be a threshold effect, where the damage to the frontal lobe caused by the current chemotherapy regimen was not sufficiently detectable by DKI.

AK increases reflect axonal injury. One of the main functions of the myelin sheath is to protect axons from injury. Once demyelination occurs and repair mechanisms are exhausted, axonal degeneration occurs in a predictable manner[23]. Therefore, axons remain intact in the early stage of demyelination, and the results of this study support the idea. Consequently, if demyelination can be detected quickly, it will help prevent axonal damage when remyelination is promoted. There is increasing evidence that inflammation is necessary for myelin repair; recent studies have found that celecoxib has anti-demyelinating effects and promotes myelin regeneration by improving the immune and inflammatory microenvironment[24].

ALL patients undergoing chemotherapy have long-term cognitive dysfunction such as diminishing executive power, working memory, processing speed and attention, and they are related to changes in brain microstructure in different regions[1, 5, 25]. However, different intervention measures can increase the volume of white matter used to complete different task areas; on the contrary, reduced external stimulation will lead to myelin sheath decline and impaired cognitive function[14]. Therefore, timely

implementation of interventions, such as skill learning and memory exercises, is very important for patients with ALL undergoing chemotherapy.

The corpus callosum is the largest WM junction in the human brain, serving as a connection between the left and right cerebral hemispheres. It is important for motor and sensory integration, attention, memory, and general cognitive functions[26]. It is necessary to further evaluate whether early WM damage in patients will cause related cognitive dysfunction, to detect potential problems early and provide timely intervention. However, this study did not perform a cognitive function test.

Current results suggest that WM damage can occur early in chemotherapy. There are several limitations in this study that could be addressed in future research. First, the study focused on brain structural changes after CR; the study cannot determine whether DKI changes were temporary. Second, this study did not have a neurocognitive function test component, so it could not assess the relationship between brain structural changes and cognitive function. Lastly, patients with immunosuppression and incomplete remission following induced remission were also excluded, so the number of patients in our study was relatively small.

Conclusion

We found, through DKI, that the corpus callosum injury may occur in children with ALL after induction of CR, which may be related to the use of VCR. It is necessary to further evaluate whether the injury persisted for the long term, to prevent possible neurocognitive dysfunction in the early stages and improve long-term quality of life in children with ALL.

Declarations

Acknowledgements

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Ethics approval

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Shenzhen Children's Hospital.

Consent to participate

Written informed consent was obtained from individual or guardian participants.

Consent for publication

Written informed consent for publication was obtained from all participants.

Authors' contributions

Weiguo Cao was identified research topics and designed them. Yiwen Liang was interpreted data and wrote the first draft of the manuscript. Yiwen Liang, Weiguo Cao and Ke Wei cared for the patients. Longping Liu contributed the patient scan. Yiwen Liang and Ke Wei was in charge of data collection, analysis and observed the images.

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Conflicts of interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Availability of data and material

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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Figures

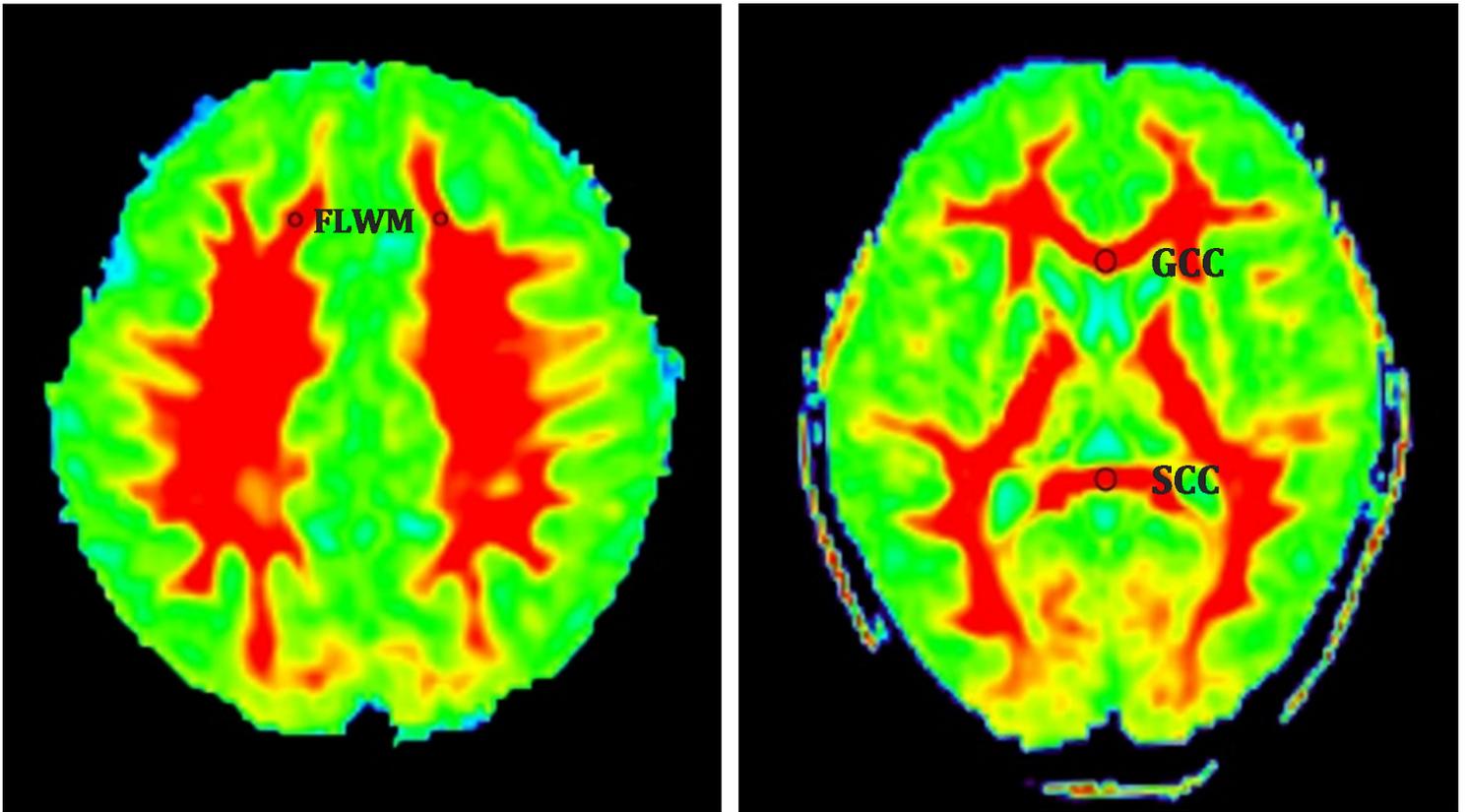


Figure 1

ROIs selection of MK images Red indicates white matter fibres. FLWM, frontal lobe white matter; GCC, genu of the corpus callosum; SCC, splenium of the corpus callosum; ROI, region of interest; MK, medial kurtosis

Supplementary Files

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