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Original article

Susceptibility-weighted magnetic resonance imaging of cerebrovascular sequelae after radiotherapy for pediatric brain tumors

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ABSTRACT

Background and purpose: Due to sensitive neuroimaging techniques, cerebrovascular complications such as cerebral microbleeds (CMB) and cerebral cavernous malformations (CCM) are increasingly recognized as considerable late effects after treatment for pediatric brain tumor. The aim of this study was to analyze CMB in a cohort of patients after cranial irradiation therapy for medulloblastoma or other pediatric brain tumors using susceptibility-weighted magnetic resonance imaging (SWI).

Materials and methods: Forty former pediatric brain tumor patients were enrolled in this prospective cross-sectional study and examined by cranial MRI including SWI sequences. Cerebral microbleeds, clinical symptoms and disability were evaluated.

Results: Thirty-six (90%) of the examined individuals (mean follow-up age 22.2 y; mean follow-up time 13.5 y) were affected by CMB. Longer follow-up time and higher craniospinal irradiation doses correlated with higher total lesion count ($p < 0.01$). Thirteen patients (32.5%) presented with clinical symptoms. Individuals with CMB were more severely disabled than patients without CMB ($p < 0.05$).

Conclusions: Cerebrovascular sequelae occur frequently after treatment for pediatric brain tumor. In this study, a remarkable part of pediatric brain tumor patients presents with CMB. As a sign of vascular damage, they can cause clinical symptoms and may correspond to neurocognitive decline. Further studies are needed to standardize MRI protocols and to improve quality of long-term follow-up.

Brain tumors are the most common solid childhood tumors with an incidence rate of 3.4 per 100 000 children under the age of 15 years per year across Europe [1]. Radiotherapy plays a crucial role in treatment of pediatric brain tumors and contributed to the recent increase in survival rates. Nevertheless, despite advanced technologies and modern treatment planning, cranial irradiation can induce side and late effects including cognitive impairment which is thought to result from cerebrovascular injury [2]. The latter comprises both cerebral microbleeds (CMB) and vascular lesions such as cerebral cavernous malformations (CCM) also known as radiation-induced cavernoma (RIC). CCM are diagnosed a median of 10–12 years after radiotherapy whereas higher radiation dose seems to be associated with more rapid onset of CCM development [3–6]. Radiation-induced CCM or CMB are reported to occur with a prevalence of 20% in children after cranial irradiation [7,8]. Formation of RIC presumably involves a multitude of interplaying factors such as vascular injury, proliferation and dilation of vascular endothelium, and hyalinization and fibrinoid necrosis of blood vessel walls [4,9,10].

Due to the paramagnetic hemosiderin deposits within CMB and CCM, magnetic resonance imaging (MRI) provides a highly accurate non-invasive method of diagnosing and characterizing CCM [11,12]. Zabramski et al. classified CCM into four types according

Abbreviations: 3D, three-dimensional; BT, brain tumor patient (other than medulloblastoma); CCM, cerebral cavernous malformation(s); CMB, cerebral microbleed(s); CNS, central nervous system; CSI, craniospinal irradiation; DVH, dose–volume histogram; $D50_{CMB}$, median dose to the CMB volume; $D50_{Enceph}$, median dose to the encephalic volume; MRI, magnetic resonance imaging; MB, medulloblastoma patient; MRI, magnet resonance imaging; RIC, radiation-induced cavernoma; SWI, susceptibility-weighted imaging; T2*GRE, T2*-weighted gradient-echo; T2WI, T2-weighted image; WBRT, whole brain radiotherapy.

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to MRI appearance [13]. Using increasingly sensitive methods such as T2∗-weighted gradient echo (T2∗GRE) sequences or susceptibility-weighted imaging (SWI), CMB present as small punctate, hypointense lesions [14–19].

CCM seen on conventional MRI are speculated to be just the "tip of the iceberg" and might serve along with smaller dot like CMB as an early imaging marker for small vessel disease [20,21].

Prevalence and risk factors of late effects after childhood cancer are major research fields to guide risk adapted care in childhood cancer survivors and optimize current treatment strategies toward a lower risk of late effects. The purpose of this prospective cross-sectional study was to evaluate cerebrovascular sequelae after radiotherapy for pediatric brain tumor using susceptibility-weighted MRI. In order to do this, we aimed to determine the prevalence of clinical and subclinical CMB in a cohort of patients who had received cranial radiation therapy for medulloblastoma or other pediatric brain tumors.

Materials and methods

Patient population

An overall cohort of 99 individuals diagnosed with medulloblastoma at the University Medical Center Mainz in the years 1969–2015 was identified. Out of this cohort, 59 former medulloblastoma patients (MB) were invited to participate in the study; reasons for loss to follow-up were death or lack of actual physical address despite inquiry at respective registration offices.

After all, 29 former MB were willing to participate and were examined in the context of this prospective cross-sectional single center study at the University Medical Center Mainz. All MB included ($n = 29$) had been diagnosed between 1970 and 2014 and had undergone treatment in terms of neurosurgical tumor resection as well as craniospinal irradiation (CSI) and chemotherapy.

Furthermore, we prospectively enrolled 11 patients with a history of pediatric brain tumor other than MB (brain tumor patients (BT)) treated with chemoradiotherapy and receiving follow up MRI in our outpatient clinic.

Prior to recruitment, data concerning patients' disease and therapy had been retrospectively assessed by medical record research. Patients were eligible if they had completed irradiation at least 12 months prior to study participation/follow-up MRI. All patients aged 6 years and above signed an informed consent form approved by the local ethics review committee. In case of minors, written informed consent was obtained from the legal guardian. All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments. All individuals studied underwent an interview and physical examination. Anthropometric data such as bodyweight and height were measured. Clinical CMB symptoms (dizziness, headache, seizure, history of stroke or transient ischemic attack) were assessed by a structured interview using a standardized anamnestic questionnaire. According to physicians' judgement, patients' disability was ranked on a five-point scale [22]: none (age-appropriate, i.e. no symptoms, no handicaps), mild (mildly handicapped, i.e. symptomatic but without relevant handicap for daily life), moderate (disability affects daily routine, i.e. symptomatic with moderate handicap comparable to slight hemiparesis, still allowing free-walking and use of both hands), severe (constant assistance required, i.e. severe handicap comparable to complete blindness) and extreme (restricted to bed/wheelchair, virtually no verbal communication, i.e. most severe handicap comparable to a patient with tetraparesis and mutism). Global physicians' disability assessment was based on clinical examination as well as on the interview with patients and parents.

Brain imaging

Cerebral MRI was performed using a 1.5 T or 3 T whole-body scanner (Magnetom® Espree/Magnetom® Skyra Siemens, Erlangen, Germany) with a 20-channel combined head/neck coil. Routine scan protocol consisted of non-contrast and post-contrast T1- and T2-weighted sagittal, axial and coronal images (contrast agent: gadoterate meglumine, Dotarem, Guerbet, Villepinte, France). Furthermore, axial SWI was acquired with a 3T MR imaging system and analyzed for CMB and CCM. The SWI sequence consisted of one 3D block (transverse images) with 80 slices (slice thickness 1,5 mm, 20% distance factor, 10% slice-oversampling, FOV 220 × 200, TR/TE = 27 ms/20 ms). If SWI was not evaluable ($n = 5$), an axial T2∗GRE sequence was used instead. SWI and T2∗ are both gradient-recalled echo sequences exploiting the signal loss of paramagnetic hemosiderin. SWI maximizes this so called "susceptibility effect" by combining a high-resolution 3D gradient echo sequence with a long echo time, and using both the magnitude and phase information [23].

MRI image evaluation

CMB were identified as small round or ovoid hypointense foci with a minimum diameter of 1 mm on SWI or T2∗GRE sequences that did not correspond to vessels on consecutive slices (corresponding to type IV lesions as classified by Zambramski et al. [13]). Cerebral microbleeds ≥5 mm also visible on T2-weighted images (T2WI) were considered as suspicious for CCM (Fig. 1). All lesions within a 0.5 cm margin around the surgical resection site were excluded from the evaluation. All MRI images were analyzed and prepared using Sectra PACS radiologist workstation IDS7™, Version 18.18 (Sectra AB, Linköping, Sweden).

A mixed quantitative and qualitative evaluation was independently performed by 2 experienced neuroradiologists (S.K.; Y.T.) both blinded to clinical information. For each dataset, lesions were manually labeled, measured and counted by the two neuroradiologists. The localizations of the lesions were distinguished as supra- and infratentorial. The CMB were classified by size into three groups: (1) CMB <2 mm; (2) CMB ≥2 mm and <5 mm; (3) CMB ≥5 mm.

For all initial discordant readings, consensus agreement was achieved between the neuroradiological examiners.

Details of radiation therapy

We retrospectively assessed details of radiation therapy by medical record research. Cumulative irradiation doses of first line treatment and relapse treatment were added to total irradiation doses.

Furthermore, a detailed analysis of dose distribution and CMB distribution was performed if original treatment planning data were available electronically and if initial treatment planning was based on three-dimensional (3D) imaging. Radiation dose distribution was computed de novo and matched with the current MRI studies using Eclipse™ treatment planning system Version 13 (Varian Medical Systems Inc., Palo Alto, CA, USA). Both CMB and irradiated encephalon were identified and contoured manually by two examiners and reviewed by a third examiner. Dose–volume histograms (DVH) were generated for each individual to calculate dose metrics such as median dose to the CMB volume ($D50_{CMB}$) and to the whole encephalon ($D50_{Enceph}$). To relate $D50_{CMB}$ with $D50_{Enceph}$, dose ratios were computed ($D50_{CMB}$/ $D50_{Enceph}$).

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