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Original Article

Late Cerebrovascular Complications After Radiotherapy for Childhood Primary Central Nervous System Tumors

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ABSTRACT

BACKGROUND: Brain radiotherapy plays a central role in the treatment of certain types of childhood primary central nervous system tumors. However, damage to surrounding normal brain tissue causes different acute and chronic medical and neurological complications. Despite the expected increase in number of childhood primary central nervous system tumor survivors, studies assessing the occurrence of late cerebrovascular complications, such as cavernoma, moyamoya, microbleeds, superficial siderosis, and stroke are sparse. **METHODS:** We undertook a retrospective consecutive case series review describing the occurrence and characteristics of late cerebrovascular complications in 100 survivors of childhood primary central nervous system tumors treated with radiotherapy. Demographic, clinical, and radiological findings including gradient echo brain magnetic resonance data were retrieved. **RESULTS:** Late cerebrovascular complications were found in 36 (36%) of the patients included in the study. Mean age at radiotherapy was 8.6 years (3-17) and at diagnosis was 23.9 years (3-38). The majority were males (21; 58%). The most common complications were microbleeds (29/36; 80.6%) and cavernomas 19 (52.8%). In seven (19.4%), late cerebrovascular complications were symptomatic: epilepsy (two), motor and language deficit (two), and sensorineural hearing loss and progressive ataxia (three) associated with cavernomas, stroke, and superficial siderosis, respectively. Follow-up length was associated with an increased diagnosis of late cerebrovascular complications ($P < 0.0001$). Late cerebrovascular complications occurred more commonly in children treated with whole-brain radiation therapy ($P = 0.046$). Factors such as sex, chemotherapy, and histological type of tumor were not correlated with the occurrence of late cerebrovascular complications. **CONCLUSION:** Although not usually symptomatic, late cerebrovascular complications occur frequently in survivors of childhood primary central nervous system tumors treated with radiotherapy. Prolonged follow-up increases the probability of diagnosis. The impact and prognostic value of these late cerebrovascular complications is yet to be clarified.

Keywords: radiotherapy, late complications, microbleeds, cavernoma, superficial siderosis, stroke

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Introduction

The management and prognosis of childhood primary central nervous system tumors (PCNST) improved significantly in the past few decades. In certain types of childhood PCNST, brain radiation therapy is a valuable treatment option.[1-3] Regardless of radiation therapy (RT) optimization, damage to surrounding normal brain tissue still occurs.[3] Indeed, RT is an established cause of endothelial dysfunction[4] and a risk factor for late cerebrovascular complications

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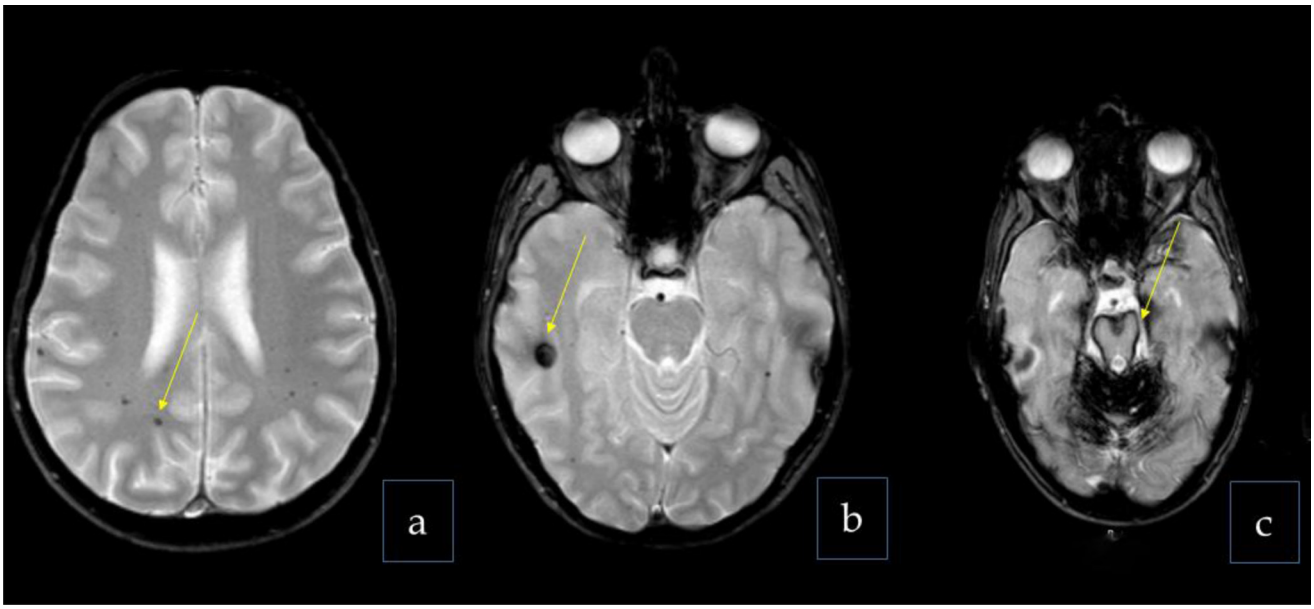

FIGURE 1.
Brain MRI (T2* gradient echo brain magnetic resonance imaging) showing cases of microbleeds (A), cavernoma (B), and superficial siderosis (C). (The color version of this figure is available in the online edition.)

(LCCs) such as cavernoma, moyamoya syndrome, microbleeds, and stroke.[2,5-13] In addition to their high potential for morbidity, LCCs are also entwined with other late complications of RT such as neurocognitive and endocrine dysfunction.[13-16] The expected increase in the number of childhood PCNST survivors contrasts with the paucity of studies addressing the occurrence of LCCs after RT. Therefore, exposing different experiences contributes to the awareness and knowledge on the topic. We sought to describe the occurrence and characteristics of LCCs in patients who underwent RT for pediatric PCNST during childhood in a tertiary oncological hospital.

Patients and Methods

We retrospectively reviewed a consecutive series of patients with LCCs after RT for childhood PCNST. All patients were being followed at the pediatric neuro-oncology unit from the Instituto Português de Oncologia Francisco Gentil of Lisbon (a comprehensive cancer center in Portugal) following 212 childhood PCNST survivors. Regular follow-up with at least one consultation per year included general and neurological examinations and brain imaging. Brain magnetic resonance imaging (MRI) was performed on a 1.5-T scanner (PHILIPS, Intera). The protocol included gradient echo conventional T2-weighted imaging (T2* GRE MRI) since 2006.

All manual and electronic clinical files of childhood PCNST survivors treated with RT were reviewed. Data on demographic information (age at RT and at the diagnosis of the LCC, sex, and race), tumor characteristics (location, pathology), treatment (resection, RT dose, and chemotherapy), presence, and location of any clinical or late radiological cerebrovascular complication were retrieved. Late or delayed cerebrovascular complication of RT was defined as any lesion secondary to small, medium, or large vessel abnormality occurring 6 months after treatment within the irradiated volume.[12] These LCCs include microbleeds, cavernomas, and superficial siderosis. Diagnosis of these lesions was based on the current international concepts. Microbleeds were defined by the presence of small rounded or ovoid well-defined hypointense lesions on T2* GRE MRI surrounded by brain parenchyma in at least half of the lesion, not being well seen on T1- or T2-weighted MRI, and absence of clinical history of traumatic diffuse axonal injury[17] (Fig 1A). Cavernoma was defined by the presence of the typical nidus with no surrounding cerebral edema and a heterogeneous signal intensity with a dark rim of hemosiderin on the lesion's core on MRI[18] (Fig 1B). Superficial siderosis was defined by the presence of a rim of hyperintensity on T2 in the surface of the brain and spinal cord[19] (Fig 1C).

All variables were analyzed using descriptive statistics measures and proportions comparison using chi-square tests and Student *t* tests. Confidence intervals were calculated by exact methods and significance level of 0.05 was considered. The analysis was performed using SPSS software for Windows (version 15.0).

Ethical permission was granted by the Instituto Português de Oncologia Francisco Gentil institutional ethics committee.

Results

We analyzed the clinical files of 100 (82.6%) of the 121 children treated with RT for PCNST included in our institutional database during the study period. Patients without T2* GRE MRI (21/17.4%) were excluded from the study. Loss to follow-up (n = 18) and death (n = 3) were the reasons for exclusion.

LCCs were found in 36 (36%) of the patients included in the study. Patient demographics and clinical characteristics are summarized in Table 1.

Standardized irradiation dose varied according to the histological diagnosis (Table 1), albeit with a progressive tendency toward lower doses over time.

Table 1 shows that cerebral microbleeds were the most common LCC diagnosed (29/36; 80.6%). During follow-up, the number of microbleeds increased in 7 (19.4%) patients (Fig 2).

Cavernomas were identified in 19 (52.8%) patients. In the majority of patients with cavernoma (15/36; 78.9 %), microbleeds were also found (Fig 3). In seven (19.4%), LCCs were symptomatic: epilepsy,[2] motor and language deficit,[2] sensorineural hearing loss, and progressive ataxia[3] associated with cavernomas, stroke, and superficial siderosis, respectively. Moyamoya was diagnosed in one patient with