Brain Perfusion and Diffusion Abnormalities in Children Treated for Posterior Fossa Brain Tumors

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Objective To compare cerebral perfusion and diffusion in survivors of childhood posterior fossa brain tumor with neurologically normal controls and correlate differences with cognitive dysfunction.

Study design We analyzed retrospectively arterial spin-labeled cerebral blood flow (CBF) and apparent diffusion coefficient (ADC) in 21 patients with medulloblastoma (MB), 18 patients with pilocytic astrocytoma (PA), and 64 neurologically normal children. We generated ANCOVA models to evaluate treatment effects on the cerebral cortex, thalamus, caudate, putamen, globus pallidus, hippocampus, amygdala, nucleus accumbens, and cerebral white matter at time points an average of 5.7 years after original diagnosis. A retrospective review of patient charts identified 12 patients with neurocognitive data and in whom the relationship between IQ and magnetic resonance imaging variables was assessed for each brain structure.

Results Patients with MB (all treated with surgery, chemotherapy, and radiation) had significantly lower global CBF relative to controls (10%-23% lower, varying by anatomic region, all adjusted $P < .05$), whereas patients with PA (all treated with surgery alone) had normal CBF. ADC was decreased specifically in the hippocampus and amygdala of patients with MB and within the amygdala of patients with PA but otherwise remained normal after therapy. In the patients with tumor previously evaluated for IQ, regional ADC, but not CBF, correlated with IQ ($R^2 = 0.33$-0.75).

Conclusions The treatment for MB, but not PA, was associated with globally reduced CBF. Treatment in both tumor types was associated with diffusion abnormalities of the mesial temporal lobe structures. Despite significant perfusion abnormalities in patients with MB, diffusion, but not perfusion, correlated with cognitive outcomes. *(J Pediatr 2017;185:173-80).*

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The management of pediatric brain tumors has improved markedly over the years and has resulted in increased survival at unprecedented rates, particularly for medulloblastoma (MB). Many survivors, however, suffer from long-term cognitive impairments and behavioral problems that can diminish their quality of life.[1-4] Deficits in processing speed, working memory, attention, and general intellectual ability can result from the composite effect of injury from disease burden and treatment toxicity.[5]

Radiation therapy has been associated with chronic microglia-mediated neuroinflammation,[6,7] white matter atrophy, and decreased neurogenesis.[6,8,9] Studies on the dose-response relationship between irradiation of specific brain regions and cognitive impairment[2,3] as well as preserved cognitive function in hippocampal-sparing radiation therapy[10,11] suggest that cognitive dysfunction can result from radiation. The omission of prophylactic whole-brain radiation from the management of pediatric acute lymphoblastic leukemia has led to improvements in quality of life. In the absence of radiation therapy, however, surgery[12,13] and/or chemotherapy[14,15] also can contribute to long-term cognitive deficits.

ADC	Apparent diffusion coefficient
ASL	Arterial spin labeling
CBF	Cerebral blood flow
DWI	Diffusion-weighted imaging
FOV	Field of view
MB	Medulloblastoma
MRI	Magnetic resonance imaging
PA	Pilocytic astrocytoma
TR	Repetition time
WISC-IV	Wechsler Intelligence Scale for Children – Fourth Edition

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Various neuroimaging methods have shown structural brain changes after therapy that may relate to clinically observed cognitive impairment.[16] For example, white matter volume loss after tumor irradiation[17-19] and altered white matter integrity assessed by diffusion metrics regardless of adjuvant therapy[20-28] have been shown to correlate with cognitive deficits. Few studies have assessed gray matter structures, and these have yielded conflicting results.[20,29-31] Cerebral blood flow (CBF) may be altered in the setting of cerebral vasculopathy after radiation therapy. Also, CBF is coupled tightly to brain metabolism and may have a role as a potential biomarker of regional brain function.[32,33] Studies on cerebral perfusion after therapy, however, are sparse, limited to adults after brain irradiation[34-36] and children with a history of cerebellar mutism and adjuvant therapy.[12] Furthermore, at present, no study has examined CBF and associated diffusion changes of specific regions of the cerebrum reflecting microstructural changes in children after therapy.

Here, we conducted a retrospective, cross-sectional analysis of cerebral arterial spin-labeling (ASL) perfusion and diffusion metrics in patients with MB treated with radiation, posterior fossa surgery, and adjuvant chemotherapy; patients with pilocytic astrocytoma (PA) treated with posterior fossa surgery alone; and a cohort of neurologically normal pediatric patients. We hypothesized that CBF and apparent diffusion coefficient (ADC) are altered in these patients, correlating with a compromise in IQ.

Methods

All patients with posterior fossa tumor at our children's hospital from May 2010 to October 2013 were reviewed retrospectively after approval by the institutional review board (protocol 28674). Because this was a retrospective review, our institutional review board waived the requirement of informed consent. The study cohort was identified with the following inclusion criteria: previous surgical resection with a pathologic diagnosis of either MB or PA and ASL perfusion imaging and diffusion-weighted imaging (DWI) at 3 T (as a standard protocol) during a patient follow-up visit. All patients with PA were operated on only once and were considered "tumor free." The patients had varying times since diagnosis; many patients had not undergone ASL perfusion imaging earlier in their follow-up over the years, because the ASL sequence had not yet been implemented at our children's hospital. Thus, for patients with serial imaging, we selected their most recent scan for analysis to be consistent.

Exclusion criteria included inadequate data or image registration, evidence for neurofibromatosis type 1, underlying cardiac disease, epilepsy, migraines, hemorrhage, vascular lesions (aneurysm, arteriovenous malformation, fistula, or stenoocclusive disease), or previous strokes, given their potential impact on CBF and diffusion. Only patients older than 4 years of age were included because CBF and ADC have been shown to increase in a predictable linear fashion after that age.[37]

The control group consisted of subjects with no known neurologic, neurocognitive, developmental, or behavioral deficits who had normal-appearing brains on magnetic resonance imaging (MRI). Control patients had been imaged as a standard of care for syncope, nausea, family history of aneurysm or cancers, scalp nevus, isolated facial lesions, orbital strabismus, cholesteatoma of the ear, isolated headaches without migraine characteristics or other neurologic symptoms, sinus disease or inflammatory nasal obstruction, and familial short stature. This control group study population has been described previously.[37]

Imaging Methods

All subjects underwent MRI of the brain at 3 T (Discovery 750; GE Healthcare, Milwaukee, Wisconsin) with an 8-channel head coil on a single MRI scanner. The technique used to perform perfusion ASL MRI has been described by Dai et al[38] and has established reproducibility.[39,40] In summary, our vendor-supplied ASL technique used a pseudocontinuous labeling period of 1500 milliseconds and a 1500-millisecond postlabel delay. We acquired whole-brain images with a 3-dimensional background-suppressed fast spin-echo stack-of-spirals method, with a repetition time (TR) of approximately 5 seconds. We used multiarm spiral imaging with 8 arms and 512 points acquired on each arm (bandwidth, 62.5 kHz), yielding in-plane and through-plane spatial resolutions of 3 and 4 mm, respectively. Four separate inversion pulses spaced around the pseudocontinuous labeling pulse achieved a high level of background suppression. The sequence required 5 minutes for acquisition and also included proton-attenuation images for CBF quantitation. The sagittal image following the 3-plane localizer was used for alignment in graphic prescription of the ASL. We generated quantitative CBF datasets with microsphere methodology described by Buxton et al.[41] Other ASL MRI variables were TR/echo time = 4632/10.5 milliseconds; field of view (FOV) = 24 cm; matrix = 512 × 8; and 3 excitations.

We also obtained echo planar whole-brain DWI with TR = 1500 milliseconds, echo time = 37 milliseconds, flip angle 90°, FOV = 24 cm, acceleration factor = 2, in-plane resolution 0.94 mm^2, acquisition matrix = 128 × 128 interpolated to a 256 × 256 matrix, 44 sections with 4-mm slice thickness, no skip, FOV = 24 cm, and 2 diffusion weightings of b = 0 s/mm^2 and b = 1000 s/mm^2, with diffusion gradients acquired in 3 directions averaged for the latter. ADC, derived from DWI, has demonstrated reproducibility.[42]

Image Processing

We used a custom image processing pipeline to extract quantitative values of regional brain CBF and ADC values, previously described by Forkert et al.[37] To summarize, the ASL CBF and b = 1000 s/mm^2 DWI dataset were registered rigidly to the corresponding T2-weighted DWI dataset (b = 0 s/mm^2). Aligned DWI datasets were then used to calculate each ADC map. The 152-MNI brain atlas[43] was registered nonlinearly to each subject's anatomy together with the gray matter structures defined in the Harvard-Oxford subcortical atlas brain regions. Two experienced observers visually checked all registration results to ensure suitable data and registration quality. After registration of all datasets, we determined median ADC and CBF