Neuro-Oncology

Neuro-Oncology 18(11), 1470–1471, 2016
doi:10.1093/neuonc/now202

Evidence of cerebral microbleeds and neurocognitive impairment following cranial radiation therapy for pediatric brain tumors: a new opportunity for improved care

F. Daniel Armstrong

Department of Pediatrics, Mailman Center for Child Development, University of Miami Miller School of Medicine and Holtz Children's Hospital, Miami, Florida

Corresponding Author: F. Daniel Armstrong, PhD, P.O. Box 016820 (D-820), Miami, FL 33101 (darmstrong@miami.edu).

See the article by Roddy et al. on pages 1548–1558.

For more than 3 decades, neurocognitive impairment has been reported as a long-term outcome in children treated for brain tumors or acute lymphoblastic leukemia (ALL) using cranial radiation therapy (CRT), with or without chemotherapy. Impairment has most often been reported in the areas of processing speed, working memory, visual-spatial-motor speed and accuracy, inattention, and complex activities involving executive function. The severity of outcomes has been linked to CRT dose, younger age at diagnosis, and, in ALL, female gender. Neuroimaging of survivors has most often identified changes in white matter, primarily in the frontal cortex and connecting structures, with other areas of abnormality noted depending on the location of the tumor and type of neurosurgery involved.[1] Calcifications have also been reported in children treated with both methotrexate and CRT for ALL.[2]

In their multicenter evaluation of 149 survivors of pediatric brain tumors (110 treated with CRT), Roddy and colleagues[3] identified cerebral microbleeds (CMBs) as another possible mechanism for neurocognitive impairment in children treated for brain tumors. The reported incidence of CMBs in children treated with CRT at 1 year posttreatment was 10.8% and increased to 48.8% at 5 years posttreatment. Surprisingly, dose of CRT was not associated with an increased rate of CMB development, but breadth of exposure (whole-brain vs focal) was. Younger age was not a predictor of CMBs, but the inclusion of an anti-angiogenic drug (bevacizumab) resulted in an increase of CMB development that was 6.2 times greater than in those not exposed to the drug.

Vascular abnormalities have not been considered as contributors to neurocognitive outcomes in adults or children treated for brain tumors. However, similar kinds of neurocognitive outcomes have been reported in children and adults with sickle cell anemia who have experienced overt stroke, silent cerebral infarcts, and localized abnormalities detected using segmental analysis on MRI.[4,5] In sickle cell anemia, vasculopathy, endothelial dysfunction, hypoxia, and poor oxygen perfusion are all mechanisms associated with neurocognitive impairment independent of evidence of specific white matter or other CNS structural injury.[6] It is, therefore, not surprising that similar patterns of neurocognitive function following CRT might be related to CMBs and that the neurocognitive outcomes observed are similar to those in diseases with primary CNS vasculopathy.

Previous models have suggested that the severity and specific areas of neurocognitive impairment in children treated for brain tumors emerge over time.[7] One explanation is that this is related to early interference with the normal white matter growth trajectory in the developing brain. The finding that the incidence of CMBs increased over time suggests that in some children treated with CRT, and perhaps even more treated with a specific anti-angiogenic drug, the neurocognitive developmental trajectory may be related to an increasing accumulation of CMBs over time. This does not invalidate a neurodevelopmental model that has focused on white matter development, but offers a second possible mechanism for exploration.

The presence of CMBs, and the increasing rate of CMBs over time, has some meaningful clinical implications and consequences. The presence of CMBs in more than 10% of the children at 1 year posttreatment may support MRI evidence of CMBs as a marker for children who are at increased risk for neurocognitive impairment as they age, particularly those who have no evidence of other structural or white matter abnormality. This offers an opportunity to identify these children and evaluate the effectiveness of early neurobehavioral intervention as a way to prevent or lessen the intensity of long-term impairment. Similarly, the nearly 6-fold increase in the incidence of CMBs in children treated with anti-angiogenic medications provides strong evidence to support an aggressive approach to clinical neurocognitive evaluation of patients and research focused on evaluation of best-practice early intervention with this high-risk group of children.[8]

Proton-beam CRT is believed to result in lower toxicity than traditional photon-beam CRT.[9,10] The finding that whole-brain CRT exposure results in a greater incidence of CMBs than focal CRT exposure offers a new measure of outcome in proton versus photon-beam CRT studies and may provide a robust and relatively short-term (1- to 2-y posttreatment) measure of treatment toxicity for the 2 approaches. Early identification of differences in CMBs can be used to improve decision making about type of CRT to use and influence health policy and access related to the most effective and least toxic treatment.

As neurocognitive impairment has become recognized as a significant late effect of CNS cancer treatment, a number of pharmacologic interventions have been proposed, but only a few tested. In a randomized clinical trial, methylphenidate has been shown to be effective in a number of children treated for CNS tumors,[11] but increases in side effects have been noted for subgroups of patients.[12] Other medications used in the treatment of adult cognitive dysfunction (e.g, memory disorders, dementia) have been suggested, but these often have contraindications for use in children. These may be elevated in children with potential, but undocumented, CNS vascular fragility. The Roddy et al[3] study provides the first clear evidence that children treated with CRT, and those treated with at least one antiangiogenic medication, are at substantial risk for microvascular injury. Therefore, the use of medications with a known CNS vascular mechanism should be approached with great care when used with children treated for brain tumors. Robust animal models and phase I/II human trials should be conducted before moving into phase III clinical trials or community use. At the same time, awareness of vascular injury in this group of children opens the door to consideration and evaluation of treatments that reduce inflammation or otherwise reduce vasculopathy.

The documentation of CMBs represents a significant contribution to both the science behind pediatric brain tumors and outcomes of treatment, but also provides incentive to rethink treatment protocols. We can and certainly should take steps to identify effective treatment for neurocognitive and CNS effects of primary therapy but at the same time remember that some of the most significant advances in improved survival and reduced toxicity have occurred when primary therapy has been altered in the face of toxicity. Roddy and colleagues have provided critical evidence needed to once again open this conversation.

Funding

Partial support for preparation of this commentary was provided by a grant from the Administration on Intellectual and Developmental Disabilities, 90DD0678-05.

References

1. Nathan PC, Patel SK, Dilley K, et al. Guidelines for identification of, advocacy for, and intervention in neurocognitive problems in survivors of childhood cancer: a report from the children's oncology group. *Arch Pediatr Adolesc Med*. 2007;161(8):798–806.
2. Duffner PK, Armstrong FD, Chen L, et al. Neurocognitive and neuroradiologic central nervous system late effects in children treated on Pediatric Oncology Group (POG) P9605 (standard risk) and P9201 (lesser risk) acute lymphoblastic leukemia protocols (ACCL0131): a methotrexate consequence? A report from the Children's Oncology Group. *J Pediatr Hematol Oncol*. 2014;36(1):8–15.
3. Roddy E, Sear K, Felton E, et al. Presence of cerebral microbleeds is associated with worse executive function in pediatric brain tumor survivors. *Neuro Oncol* 2016;18(11):1548–1558.
4. Mackin RS, Insel P, Truran D, et al. Neuroimaging abnormalities in adults with sickle cell anemia: associations with cognition. *Neurology*. 2014;82(10):835–841.
5. Vichinsky EP, Neumayr LD, Gold JI, et al. Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. *JAMA*. 2010;303(18):1823–1831.
6. DeBaun MR, Armstrong FD, McKinstry RC, et al. Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. *Blood*. 2012;119(20):4587–4596.
7. Armstrong FD. Neurodevelopment and chronic illness: mechanisms of disease and treatment. *Ment Retard Dev Disabil Res Rev*. 2006;12(3):168–173.
8. Olson K, Sands SA. Cognitive training programs for childhood cancer patients and survivors: a critical review and future directions. *Child Neuropsychol*. 2016;22(5):509–536.
9. Harrabi SB, Bougatf N, Mohr A, et al. Dosimetric advantages of proton therapy over conventional radiotherapy with photons in young patients and adults with low-grade glioma [published online ahead of print June 30, 2016]. *Strahlenther Onkol*. 2016. doi:1007/s00066-016-1005-9.
10. Kahalley LS, Ris MD, Grosshans DR, et al. Comparing intelligence quotient change after treatment with proton versus photon radiation therapy for pediatric brain tumors. *J Clin Oncol*. 2016;34(10):1043–1049.
11. Conklin HM, Reddick WE, Ashford J, et al. Long-term efficacy of methylphenidate in enhancing attention regulation, social skills, and academic abilities of childhood cancer survivors. *J Clin Oncol*. 2010;28(29):4465–4472.
12. Conklin HM, Lawford J, Jasper BW, et al. Side effects of methylphenidate in childhood cancer survivors: a randomized placebo-controlled trial. *Pediatrics*. 2009;124(1):226–233.