Do severe headaches portend greater stroke risk following CRT for childhood brain tumor?

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Children with brain tumors are more likely to survive, with survival rates improving consistently over several decades and well over 70% of patients now surviving 5 years from diagnosis.[1] The vast majority of these children will become long-term survivors. As cure rates improve, a greater focus has been placed on enduring patient health after cancer treatment.

Cranial radiotherapy (CRT) is an effective treatment option for many pediatric brain tumors. Although CRT has had a role in advancing brain tumor cure rates, it is not without risks, particularly to the developing brain. Potential long-term complications of CRT include neurocognitive deficits, endocrine abnormalities, growth retardation, secondary neoplasms, cerebral vasculopathy, and arterial ischemic stroke.[2–8] CRT can cause a spectrum of cerebral vascular lesions, many of which can develop several years after the radiation exposure. Radiation-induced damage to the capillary endothelial cells results in a microangiopathy with consequent vessel rupture and thromboses.[9] Medium- and large-sized blood vessels can develop neointimal proliferation, fibrinoid necrosis, atheromatosis, thrombosis, and (in rare cases) arterial rupture.[9] Stenoses and occlusions of the principal cerebral arteries lead to a moyamoya-type syndrome in some children and adults after CRT.[3] Several factors, including higher cranial radiation doses, focal dosing to the circle of Willis, and the presence of neurofibromatosis type I, seem to increase the risk of developing neurovascular complications.[2,3,6] Screening guidelines directed at prestroke detection of cerebral vasculopathy are not currently available.

The identification of signs or symptoms that portend neurovascular events among brain tumor survivors would have substantial clinical implications for patient monitoring and primary stroke prevention. In this issue of *Neurology*®, Kranick et al.[10] describe a retrospective cohort study of 265 childhood brain tumor survivors treated with CRT over a 10-year period. Subjects were designated as having severe, recurrent headaches if they complained of headaches at 2 or more follow-up visits and the head pain was not readily attributable to tumor growth, shunt malfunction, CNS infection, or headaches occurring at the end of life. Patients with intraoperative or perioperative strokes were excluded, as were patients with additional stroke risk factors or risk factors for cerebral vasculopathy, including neurofibromatosis type I. The investigators showed that patients with severe headaches had a greater rate of arterial ischemic stroke and TIAs than those without severe headaches. Seven (19%) of the 37 headache patients had a total of 11 neurovascular events; by contrast, 6 (3%) of the 228 nonheadache patients had 8 total events. Median follow-up time for the entire cohort was 6 years. Median time to the first neurovascular event was 4.9 years. The total radiation dose received by headache patients was lower than that received by nonheadache patients, but radiation to the circle of Willis was similar between groups. Associated treatment with chemotherapy did not alter risk.

Could severe headaches be the primary cause of neurovascular events in this population? In otherwise healthy individuals, migraine with aura can be associated with an approximately 2-fold higher stroke risk.[11] However, the headaches and the neurovascular events observed in this study more likely represent long-term complications involving cerebral vascular changes after CRT. Even if every headache patient in this study had migraine with aura, it would not fully explain the observed 5-fold increase in risk of the neurovascular events.

What are we to do with this new information? The Children's Oncology Group Guidelines for long-term follow-up are available online (www.survivorshipguidelines.org). These guidelines are 222 pages long and are not trivial to navigate, even for neuro-oncologists. The listed recommendations vary based on the type of cancer treated, the radiation dose, and the head and neck regions involved. Annual neurologic assessment is standard. Follow-up after radiotherapy to the neck should include annual examination of the carotid arteries for bruits and diminished pulses with consideration of carotid Doppler ultrasonography. MRI with magnetic resonance angiography is recommended "as clinically indicated."[8] The guidelines raise questions for our neurology practices: Does the presence of severe and recurrent headaches in cancer survivors now warrant neuroimaging? Should antiplatelet therapy be considered?

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The findings of Kranick et al. should fuel further research that addresses the long-term risks of CRT and the potential benefits of screening for vasculopathy in this population. As more children with brain tumors survive into adulthood, efforts at keeping them healthy and maintaining a high quality of life cannot be overemphasized. A better understanding of stroke risk after CRT may provide future opportunities for primary stroke prevention.

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