Pediatric Cancer Survivors at Risk for Stroke

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Childhood survivors of brain tumors and leukemia are at particular risk for stroke later in life, according to research conducted through the University of Texas (UT) Southwestern Medical Center at Dallas. The medical center is one of 26 facilities involved in the Childhood Cancer Survivor Study (CCSS), a large, ongoing research investigation on the long-term effects of cancer and its treatment in the pediatric population.

The study reviewed self-reports of stroke occurrence 5 or more years after recovery from oncological disease in 4828 survivors of pediatric leukemia and 1871 survivors of pediatric brain tumors. Stroke occurrence also was examined in a random sample of 3846 siblings of pediatric cancer survivors. The team, led by Daniel C. Bowers, MD, associate professor of pediatrics at the University of Texas Southwestern Medical School, reported in their article recently published in the *Journal of Clinical Oncology* that stroke was 2 to 3 times more likely to occur down the road in survivors of pediatric leukemia and 8 to 10 times more likely to occur in survivors of pediatric brain tumors than in siblings of cancer survivors.

"Our research started off as an observation," Bowers explained. "We had a few kids from our institution who were survivors of brain tumors. We noted that 5, 10, 15 years later, they had strokes. This was quite shocking and frightening for the parents of these patients. A survey of the literature revealed that this was an unknown area, so we took it on."

Bowers and his team began to examine stroke incidence among young persons who had been treated for brain tumors at UT Southwestern Medical Center and confirmed an increased prevalence of stroke. "We used the findings of our single-institution experience to propose that the CCSS examine the correlation between childhood cancer and stroke risk," said Bowers.

Getting the go-ahead, Bowers and his team recapitulated their original study using the CCSS database, which contains detailed information on the medical history, diagnosis, therapy, and complications of therapy of thousands of cancer survivors who have been followed for 5 to 30 years. "In looking through the data, we realized that childhood survivors of Hodgkin disease, leukemia, and brain tumors were at high risk for stroke later in life," said Bowers. Data on Hodgkin disease, which affects adolescents more than young children, were separated from data on leukemia and brain tumors.

"Although people think that brain tumors and leukemia are different, they are similar, so we batched them together," Bowers explained. "Both leukemia and brain tumors affect a similar age group—mean age, 5 years. These are young children who are going through a lot of developmental changes. Also, these diseases both require CNS-directed therapy."

Whereas increased risk of stroke was not exceptionally high among survivors of childhood leukemia (1% at 25-year follow-up), the risk rate for survivors of childhood brain tumors at 25-year follow-up was 6%. "These are kids diagnosed at age 5 years—and 6% are at risk for stroke at age 30. That's significant, considering that stroke in 30-year-olds is a rare event," Bowers commented.

Treatment with cranial radiation therapy (mean dose, 30 Gy or higher) appeared to be a major determinant of risk and was dose-dependent; highest risk was associated with cranial radiation therapy at doses of 50 Gy or higher. Patients with recurrent oncological disease also were at particularly high risk for stroke, but this observation, Bowers noted, probably was related to increased radiation exposure.

Bowers and coinvestigators' data on survivors of Hodgkin disease, which were published earlier than the data on leukemia and brain tumors, also showed that survivors were at increased risk for stroke.
later in life (ie, after more than 5 years). In that study, it was shown that mantle radiation therapy was a major determinant of stroke risk.\textsuperscript{2}

**COGNITIVE COMPLICATIONS ALSO**

Another study conducted by Bowers' team showed that radiation therapy also compromises cognitive development.\textsuperscript{3} In this study, 16 persons who had received radiation therapy for medulloblastoma at a mean age of 7 years were evaluated at about 22 years. "That study was quite sobering. In that study, the majority of patients were very delayed or impaired," said Bowers. "Their processing speed was slow, their IQs were low, and from a functional standpoint, they were very impaired. Most hadn't graduated from high school, held a job, or dated or had a significant relationship, and most could not drive." Bowers added that cognitive effects were not evaluated in the more recent studies on stroke and Hodgkin disease and leukemia and brain tumors. "The CCSS data are based on self-reports and not designed to chart cognitive effects," he explained.

**MECHANISMS AND PREVENTIVE MEASURES**

The mechanism through which radiation therapy puts childhood cancer survivors at risk for stroke and other complications such as cognitive deficits needs further elucidation, but it may be related to large cerebral vessel injury incited by radiation therapy, Bowers explained. Preventive measures have begun with a push toward reducing the dose of cranial radiation used in pediatric patients.

Bowers noted that the Children's Oncology Group, a consortium that sets the pace for treating children with brain tumors in the United States, is working on this. Bowers said that his team's research "reminds us that kids are not supposed to be radiated. More efforts are needed to identify therapies that do not include radiation to the brains of these youngsters. We know new agents are coming out and current protocols use less radiation than they did 30 years ago. Maybe 30 years from now, no radiation will be used. Our study provides very persuasive data in that direction."

He and colleagues will next embark on a study to find a method to screen at-risk patients and then move on to developing preventive interventions. "We are going to screen a substantial number of children to look at the prevalence of silent cerebral vascular diseases. If it is high—which I anticipate it will be—we might embark on some kind of intervention study," confided Bowers. Whether screening initiatives are needed for survivors of childhood cancer and what kinds of interventions can be instituted in young persons are open questions that may take many years to define, Bowers added.

**REFERENCES**