Stroke After Pituitary Irradiation

James Bowen, MD, and C. Alvin Paulsen, MD

**Background and Purpose:** Cranial irradiation may lead to accelerated atherosclerosis over several years. Stroke has been described after cranial irradiation administered for a number of conditions. However, pituitary irradiation has only rarely been associated with stroke.

**Case Descriptions:** Two patients, 39 and 46 years of age, suffered strokes 13 and 20 years, respectively, after irradiation for pituitary tumors. Strokes were in the territories of small perforating arteries, but large vessels such as the carotid siphon and anterior cerebral arteries were also abnormal. Other risk factors for stroke were absent.

**Conclusions:** It is suggested that pituitary irradiation increases the risk of subsequent stroke due to the known effects of ionizing radiation on vascular walls.

**Key Words:** arteriosclerosis • cerebrovascular disorders • pituitary gland • radiation effects

Endocrine or vascular complications occasionally follow irradiation of pituitary tumors. Hypopituitarism is the most common medical complication after irradiation of the pituitary or hypothalamus. Vascular complications include delayed radiation necrosis of the brain or optic pathways. Occlusion of small and medium-sized blood vessels is felt to be responsible for this disease. Larger vessels may also develop disease after irradiation. Atherosclerosis is accelerated in these vessels, but strokes have only rarely been reported. We report two cases of cerebral infarction occurring 13 and 20 years after pituitary irradiation.

**Case Reports**

**Case 1**
A right-handed woman developed a pituitary mass at age 26. Angiography showed minimal deviation of vessels, with supracellular elevation of the internal carotid arteries. At surgery, a chromophobe adenoma was partially resected. She suffered several seizures in the immediate postoperative period, but these have not recurred, and she has not required long-term anticonvulsants. Diabetes insipidus was also transiently present postoperatively. Over a 2-month period, 5,000 cGy whole-brain irradiation was administered. Since surgery, she has received replacement therapy for panhypopituitarism. Mild diabetes insipidus is present but does not require medication.

At age 39, she was hospitalized after the abrupt onset of unusual behavior. She failed to go to work and was found outside her apartment, unable to open the door with her key. She was unable to recognize a close friend and appeared confused and dazed. Neurological evaluation found her to be somnolent, confused, and oriented only to person. Cranial nerves were normal, aside from decreased saccades noted when a hand-held optokinetic nystagmus strip was moved toward her left. Her extremities showed normal strength, but she exhibited a slight right arm pronator drift and slightly slowed fast finger movements and rapid alternating movements with the right hand. Sensation, gait, and reflexes were normal, and toes were downgoing to plantar stimulation bilaterally.

A cranial computed tomographic (CT) scan with and without contrast was normal. Cranial magnetic resonance imaging (MRI) demonstrated a 1.8-cm infarction of the left anterior thalamus that was not enhanced when gadolinium was used (Figure 1). During electroencephalography, slowing was noted over the left frontal and frontopolar areas. Carotid angiography and vertebral digital subtraction angiography showed possible obliterative changes in anteromedial and posteromedial striate arteries bilaterally. Lumbar puncture revealed normal cerebrospinal fluid, and echocardiography was unremarkable. Results of tests for sedimentation rate, antinuclear antibodies, rapid plasma reagin for syphilis, anticardiolipin antibodies, and lupus anticoagulant were all normal.

Over 3 days' hospitalization, she returned to normal consciousness, with a normal neurological examination aside from cognitive changes. An extensive rehabilitation program was administered, but she has remained cognitively impaired and unable to return to work 30 months after the stroke.

A standard Halstead-Reitan neuropsychological test battery was administered 8½ months after the stroke. This demonstrated significant impairment in 1) higher cortical function, as evidenced by profound problems with verbal abstract reasoning, complex thinking, and flexibility in thinking; 2) memory for both immediate and delayed material, especially on visuospatial tasks; and clinically on verbal tasks when not cued; and 3) tasks requiring speed. Average to above-average performance was evident on tasks of basic arithmetic and visual problem solving.

**Case 2**
A right-handed male patient was noted to have growth arrest at age 12. A left temporal visual field abnormality was found at age 15. At age 26, a noncalcified suprasellar
mass (presumably a pituitary adenoma or craniopharyngioma) was diagnosed. Over 35 days, 3,560 cGy of irradiation was administered. Since age 32, he has required replacement for panhypopituitarism.

At age 46, he complained of right body sensory changes, and right arm pronator drift was found. A cranial CT scan showed calcification in the pituitary region that was felt to be caused by prior irradiation. A radionuclide brain scan revealed increased uptake in the left parietal area, and a repeat study 1 week later showed decreased perfusion of the left hemisphere. The patient was treated with aspirin and dipyridamole but experienced worsening symptoms, with right arm and leg weakness occurring 1 month later. Angiography revealed approximately 85% occlusion of the left internal carotid artery siphon, with delay of flow to the distal vessels in the inferior division of the middle cerebral artery. The right internal carotid and vertebral arteries were normal.

Recurrent episodes of slurred speech occurred, and he was reevaluated at age 54 with worsening dysarthria and a propensity to fall. On examination, pseudobulbar palsy was noted, with dysarthria and emotional incontinence. A cranial MRI scan showed evidence of multiple small strokes in the left frontal white matter, right head of the caudate nucleus, and right external capsule (Figure 2). An electroencephalogram was diffusely slow.

At age 56, seizures developed in the patient, and a cranial CT scan showed a 4×4×5-cm enhancing mass abutting the left sphenoid wing. Angiography again demonstrated narrowing of the internal carotid artery distal to the siphon (Figure 3). Embolization of the tumor was performed during angiography followed by surgical removal of a meningioma. Presently, 3 years after resection of the tumor, he remains in a nursing home with dysarthria and episodes of syncope.

Discussion

Accelerated atherosclerosis is a well-recognized complication of irradiation. Initial reports of extracranial disease were soon followed by reports of intracranial vascular disease. Small-vessel pathology includes fibrinoid necrosis, endothelial damage, adventitial fibrosis, and peri-vascular infiltrates of lymphocytes. Medium- and large-vessel pathology includes atherosclerotic changes such as plaques, calcifications, fragmentation of the internal elastic lamina, fibrosis of the vessel wall, and fat-laden macrophages. Small arteries of the vasa vasorum are fibrotic and may contribute to the atherosclerotic changes of large vessels. The atherosclerotic process may progress to total occlusion and, if the carotids are involved, a picture of moyamoya disease. Although most reported cases received irradiation doses of at least 4,000 cGy, carotid damage has been reported with doses as low as 1,000 cGy. Affected patients are younger and have less coronary and peripheral vascular disease compared with nonirradiated subjects with vascular disease. Irradiation was administered for a number of conditions, including optic glioma, other primary brain tumors, craniopharyngioma, and hemangioma. However, few cases have been reported after pituitary irradiation.

Darmody et al described a patient suffering a delayed stroke after irradiation for pituitary tumor. Initially, 7,000 cGy was administered; 4 years later, 3,500 cGy was given for a presumed recurrence. A stroke
occurred 3 years after the second course of irradiation. Angiography demonstrated narrowing of the proximal intracranial vessels, with eventual occlusion of the middle cerebral artery.

Hashimoto et al\textsuperscript{10} reviewed 257 cases of pituitary adenoma; 139 of the patients received 4,000–6,000 cGy of irradiation. Ten suffered cerebral ischemic events, three of which were felt to be caused by radiation angiopathy. Strokes occurred 5, 7, and 8 years after irradiation in these three patients, and angiography demonstrated severe stenosis of the terminal internal carotid arteries, anterior cerebral artery occlusions, and diffuse narrowing of the intracranial portions of the internal carotid arteries.

In reviewing 156 patients irradiated for pituitary adenomas, Flickinger et al\textsuperscript{11} found that seven suffered strokes. The occurrence of these strokes was delayed 3.2–14.6 years after irradiation. Multivariate analysis found the risk of stroke to be related to age but not to dose of irradiation. There was no significant difference in stroke incidence between the irradiated group and a nonirradiated control population. The seven patients with strokes differ from those in our case reports because they were older (61–70 years of age) and had vascular disease outside the irradiated field (three patients). Details regarding their strokes were not included in the analysis, although one was reported to have a lacunar thalamic infarct.

Our subjects were relatively young (39 and 46 years of age) and had few risk factors for stroke other than irradiation. Hypertension, diabetes, other vascular disease, cardiac valvular disease, and drug abuse were absent. The patient in case 2 smoked cigarettes and drank excessive alcohol in the past, but had abstained from these risk factors since his mid-thirties. Strokes occurred 13 and 20 years after irradiation and were recurrent in the second case. Lacunar infarctions were seen that affected small penetrating arteries arising from proximal intracranial vessels near the base of the brain. In case 2, the patient also showed large-vessel disease with 85% occlusion of the internal carotid artery. The field of irradiation administered to these patients includes the carotid siphon, proximal portions of the anterior and middle cerebral arteries, and small perforating vessels arising from the anterior and middle cerebral arteries. Intracranial vessels outside this field were spared in these patients. Extracranial carotid vessels were free of disease in both patients. The meningioma reported in case 2 may also have been related to prior irradiation.

These cases emphasize that strokes may occasionally be late complications of pituitary irradiation. Both large and small vessels may be affected. With improved therapies for pituitary tumors and hypopituitarism, patients are living longer and we are now seeing such delayed complications. Thus, the incidence of stroke after pituitary irradiation may increase as this population ages. It is hoped that recent advances limiting the field of irradiation may decrease vascular complications of pituitary irradiation.

References

Stroke after pituitary irradiation.
J Bowen and C A Paulsen

Stroke. 1992;23:908-911
doi: 10.1161/01.STR.23.6.908

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/23/6/908

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/