Moyamoya phenomenon after radiation for optic glioma

JOHN R. W. KESTLE, M.D., M.Sc., F.R.C.S.(C), HAROLD J. HOFFMAN, M.D.,
F.R.C.S.(C), and ANTONIO R. MOCK, M.D.

Division of Neurosurgery, The Hospital for Sick Children and University of Toronto, Toronto, Ontario, Canada

The role of radiotherapy in the management of patients with optic pathway glioma is controversial. In a series of patients with optic pathway glioma treated at The Hospital for Sick Children in Toronto, five children were encountered who developed moyamoya phenomenon after radiotherapy. A retrospective review of the medical records was undertaken in order to assess the relationship between optic pathway glioma, neurofibromatosis type 1 (NF1), radiation therapy, and moyamoya disease.

Forty-seven patients with optic pathway glioma were operated on at The Hospital for Sick Children between 1971 and 1990. The moyamoya phenomenon did not occur in any of the 19 patients not receiving radiotherapy. Among the 28 patients who received radiotherapy, five developed moyamoya disease (two of 23 without NF1 and three of five with NF1). There was a statistically significant relationship between radiotherapy and moyamoya disease when the analysis was stratified according to the presence of NF1 (Mantel-Haenszel chi-squared test 15.23, p < 0.01). The high incidence of moyamoya disease (three of five cases, or 60%) in patients with NF1 who have undergone radiotherapy suggests a synergistic relationship that should be considered when formulating a treatment plan for NF1 patients with optic pathway glioma.

Key Words: moyamoya disease, neurofibromatosis, optic glioma, radiation therapy

Optic pathway gliomas in childhood are typically low-grade astrocytomas, which follow a highly unpredictable course. Some remain static and quiescent for many years, which led Hoyt and Bagdasarian to regard them as hamartomas. Others, however, take an aggressive course, increase rapidly in size, and frequently lead to the death of the patient. This unpredictability has led to a divergence of opinion about the management of these tumors. Some physicians advocate resection without any further therapy, others recommend radiation therapy or chemotherapy, and still others believe these tumors require no treatment.

In the past, radiation therapy was the common mode of treatment for optic pathway glioma. As reports about the harmful effects and unsatisfactory results of this therapy emerged in the literature, other modalities gained prominence. Chief among these was chemotherapy, which has proven effective despite the benign nature of these tumors. Furthermore, direct surgery on these tumors is now feasible with good results.

The potentially harmful effects of irradiation on the developing central nervous system have been well documented. One of the common sequelae, especially in children, is postradiation vasculopathy of the moyamoya type. This has been particularly noted in patients irradiated for optic pathway glioma. About one-third of patients with optic glioma are found to have neurofibromatosis type 1 (NF1), which is itself associated with the moyamoya phenomenon. It is possible that the effects of NF1 and radiotherapy are additive, resulting in a high risk of moyamoya disease. In order to investigate this relationship we studied patients with histologically proven optic pathway astrocytomas.

Clinical Material and Methods

A retrospective review of the office and hospital records of patients with histologically confirmed optic pathway astrocytoma operated on between 1971 and 1990 at The Hospital for Sick Children was performed. Patients without recent follow-up evaluation were contacted by telephone. Data were entered on a desktop personal computer and analyzed with commercially available statistical software. Proportions were compared with the chi-squared test, and means were compared with a t-test for independent means.

Results

A total of 47 patients with optic pathway astrocytoma were identified, 44 of whom received their initial surgery at The Hospital for Sick Children. Three patients underwent tumor surgery elsewhere and were subsequently referred to us. Twenty-six tumors involved the optic chiasm, 12 were centered primarily in the hypo-
Moyamoya phenomenon after radiation for optic glioma

### TABLE 1

**Summary of patients with moyamoya phenomenon***

<table>
<thead>
<tr>
<th>Factor</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>gender</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>neurofibromatosis-1</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>age (yrs)</td>
<td>3.8</td>
<td>1.6</td>
<td>1.3</td>
<td>3.0</td>
<td>4.4</td>
</tr>
<tr>
<td>at optic glioma diagnosis</td>
<td>3.8</td>
<td>2.3</td>
<td>1.3</td>
<td>3.0</td>
<td>4.5</td>
</tr>
<tr>
<td>at radiotherapy</td>
<td>5,150</td>
<td>2,500</td>
<td>5,000</td>
<td>5,000</td>
<td>5,500</td>
</tr>
<tr>
<td>moyamoya disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>time to development (yrs)</td>
<td>1.8</td>
<td>7.2</td>
<td>3.3</td>
<td>3.1</td>
<td>3.0</td>
</tr>
<tr>
<td>presentation</td>
<td>none (anticonvulsants for seizures)</td>
<td>rt EDAS</td>
<td>TIA's, then stroke</td>
<td>stroke</td>
<td>TIA's</td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>follow-up period</td>
<td>10 mos</td>
<td>rt hemisphere</td>
<td>TIA's 6 wks postop, resolved on ASA</td>
<td>1.8 yrs</td>
<td>5.3 yrs</td>
</tr>
<tr>
<td>follow-up findings</td>
<td>progressive neurological deterioration to death aged 8.9 yrs</td>
<td>rt hemisphere</td>
<td>TIA's 6 wks postop, resolved on ASA</td>
<td>no further ischemic events</td>
<td>no further ischemic events</td>
</tr>
</tbody>
</table>

* TIA = transient ischemic attack; EDAS = encephaloduroarteriosynangiosis; ASA = acetylsalicylic acid (aspirin) treatment.

---

**FIG. 1.** Case 1. Lateral carotid arteriogram showing occlusion of the terminal internal carotid artery and extensive moyamoya vessels; this patient eventually died of moyamoya disease.

**FIG. 2.** Case 1. Cross section of the internal carotid artery at postmortem examination. Sclerotic changes in the vessels are evident.

---

...thalamus, eight involved a single optic nerve, and one involved both optic nerves. Twenty-eight of the 47 patients underwent radiotherapy at some point in their treatment. Of the 47 patients reviewed, five were found to have exhibited the moyamoya phenomenon at some time after tumor treatment (Table 1). These five patients ranged in age from 1.3 to 4.4 years at the time of treatment of their optic tumor (average age 2.8 years). They were all Caucasian; four were boys and one was a girl.

All five patients who developed moyamoya disease had received radiotherapy less than 6 months postoperatively. Four patients received 5000 rad or more and one patient received 2500 rad. At the time of radiotherapy, patients ranged in age from 1.3 to 4.5 years (mean 3.1 years). There was a mean interval of 3.7 years between radiotherapy and the development of moyamoya disease.

The presentation of moyamoya disease was ischemic in four of the five cases. Two patients presented with transient ischemic attacks (TIA's), one presented with TIA's followed by a stroke, and the fourth initially suffered a stroke. The fifth patient had a large chiasmatic glioma and was treated with biopsy and radiotherapy at 3 years of age. By 5 years of age he had suffered progressive neurological deterioration, with mental retardation and seizures that were difficult to control. His workup for the seizures included an angiogram, which demonstrated marked moyamoya disease changes (Fig. 1). He did not undergo a revascularization procedure and died at 8.9 years of age. Autopsy revealed advanced sclerotic changes in the vessels at the base of the brain (Fig. 2), and numerous scattered small vessels in the basal ganglia showing concentric hyaline thickening.

In all five cases there was bilateral involvement of the intracranial vessels; usually the anterior and middle cerebral arteries were involved. Three of the five patients with moyamoya disease in this series also had...
J. R. W. Kestle, H. J. Hoffman, and A. R. Mock

NF1: however, none disclosed other risk factors for moyamoya disease, such as family history, sickle-cell disease, Down’s syndrome, hypertension, or connective-tissue disorder. The treatment given to this group of patients was primarily surgical. Four patients underwent encephaloduroarteriosynangiosis, which was performed bilaterally in three patients and unilaterally in one (Figs. 3 and 4). In three of these four patients, aspirin was also given. One patient had been taking aspirin prior to revascularization surgery, but despite this he suffered a stroke and was then referred for the revascularization procedure. Two patients had TIA’s within a few months after the revascularization procedure, which responded to aspirin therapy. The four surviving patients have now been followed for an average of 2.1 years. None of these four who underwent revascularization procedures for moyamoya disease has subsequently developed a stroke.

Fig. 3. Case 2, an infant with a large chiasmatic tumor. Left: Contrast-enhanced computed tomography scan showing the tumor obstructing the third ventricle and producing hydrocephalus. Right: Right internal carotid arteriogram showing normal vasculature. The child was treated by tumor resection and radiotherapy (2500 rad).

Fig. 4. Studies in Case 2 on presentation for moyamoya disease 7 years after tumor resection. Upper Left: Magnetic resonance image showing normal optic apparatus. Upper Right: Right common carotid arteriogram obtained at the same time showing occlusion of the intracranial portion of the right internal carotid artery. Lower: Right external carotid angiograms, anteroposterior (left) and lateral (right) views, obtained following an encephaloduroarteriosynangiosis procedure showing good collateral flow to the middle cerebral artery.
Moyamoya phenomenon after radiation for optic glioma

In order to assess the role of radiation therapy in the development of moyamoya disease in our group of 47 patients with optic pathway astrocytoma, we performed a stratified analysis according to the presence or absence of NF1 (Table 2). Five patients who had undergone radiation therapy also had NF1. Three (60%) of these patients developed moyamoya disease. There were 23 patients who underwent radiotherapy but did not have neurofibromatosis. Two (9%) of these developed moyamoya disease. Moyamoya disease did not occur in any of the 19 patients who were not irradiated (regardless of the presence or absence of neurofibromatosis). These proportions are significantly different (Mantel-Haenszel chi-squared test 15.23, p < 0.01).

Of the patients who developed moyamoya disease, the average age at the time of radiotherapy was 3 years, compared to 6 years in the patients who did not develop moyamoya disease. These mean ages are significantly different based on a t-test for independent means (t = 2.26, p = 0.03).

**Discussion**

We have reviewed a group of 47 patients with optic pathway glioma and identified five who developed the moyamoya phenomenon. All five had undergone radiation therapy prior to the age of 5 years. Moyamoya disease developed after an average interval of a little less than 4 years. These data suggest that there may be an association between radiotherapy and the development of the moyamoya phenomenon even when the presence or absence of neurofibromatosis is accounted for. These findings are in agreement with those of Beyer, et al., who found that patients with optic glioma and neurofibromatosis developed moyamoya disease after an average radiotherapy dose of 3927 rad, whereas patients with optic pathway glioma but without neurofibromatosis developed moyamoya disease after an average radiotherapy dose of 5164 rad. Patients with neurofibromatosis appear to be more susceptible to radiation-induced vascular injury. Younger patients particularly appear to be more susceptible to postradiation vascular injury. The majority of patients reported as having postradiation moyamoya disease received radiotherapy in the first few years of life. Patients who developed moyamoya disease in this series had a younger mean age (3 years) at the time of irradiation than those who did not develop moyamoya disease (6 years).

**Conclusions**

The high incidence of moyamoya disease in patients with NF1 who have undergone radiotherapy suggests a synergistic relationship that should be considered when a treatment plan is being formulated for patients with optic pathway glioma. This is particularly important when patients are younger than 5 years of age.

**References**


---

**TABLE 2**

Incidence of moyamoya phenomenon among 47 patients with optic pathway astrocytoma

<table>
<thead>
<tr>
<th>Feature</th>
<th>Total Cases</th>
<th>Cases with Moyamoya No.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT &amp; NF1</td>
<td>5</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>RT, no NF1</td>
<td>23</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>no RT, NF1 present</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>no RT, no NF1</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*RT = radiotherapy; NF1 = neurofibromatosis type I. Significance of difference: chi-squared test 15.23, p < 0.01.*

---

*Manuscript received October 5, 1992. Accepted in final form January 12, 1993.*

*Address reprint requests to: Harold J. Hoffman, M.D., Division of Neurosurgery, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.*

---

*J. Neurosurg. / Volume 79 / July, 1993*