Clinical Variations of Trilateral Retinoblastoma: A Report of 13 Cases

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ABSTRACT

Of 440 consecutive children with retinoblastoma whom we treated between April 1972 and April 1992, 13 (3%) developed a midline intracranial neoplasm. Four of these 13 patients had bilateral familial retinoblastoma, 7 had bilateral sporadic retinoblastoma, and 1 patient had unilateral familial retinoblastoma. The twin brother of the latter patient developed pinealoblastoma without retinoblastoma. In this series, the incidence of trilateral retinoblastoma was 8% of all bilateral familial retinoblastoma and 5% of all bilateral sporadic retinoblastoma. The retinoblastoma was diagnosed at a mean age of 4.5 months and the midline intracranial tumor was diagnosed at a mean age of 23 months. The mean time interval between the diagnosis of retinoblastoma and the intracranial tumor was 22 months (range, 0 to 48 months). Seven patients (55%) were asymptomatic and their intracranial neoplasm was found on routine brain-imaging studies. The primary intracranial neoplasm had a pineal location in 10 cases and parasellar location in three cases. Despite aggressive combined treatment, 12 patients (92%) have died at a mean interval of 11 months after the diagnosis of intracranial malignancy. The mean survival of patients with midline intracranial neoplasm who were asymptomatic was significantly longer than that of symptomatic patients (P=.05). Because an early diagnosis of the intracranial neoplasm is statistically associated with longer survival and despite the high cost of brain-imaging studies, we usually recommend that children with bilateral and/or familial retinoblastoma until age 4 years undergo regular contrast-enhanced magnetic resonance imaging of the brain to detect asymptomatic early pineal and parasellar tumors.

INTRODUCTION

Trilateral retinoblastoma is a term that has been used to describe the association of bilateral retinoblastoma and neuroblastic tumor in the pineal gland or other midline structures.1-19 The term trilateral retinoblastoma was chosen because the brain tumor, which is histopathologically identical to retinoblastoma, occurs in patients with bilateral retinoblastoma. Subsequently, midline intracranial malignancies also have been found in unilateral familial or sporadic retinoblastoma.1-2,5,9,18-20 Two major reviews of reported cases from various institutions have been compiled by Zimmerman9 and Lueder et al10 In this report, we describe 13 cases of retinoblastoma with midline intracranial neoplasm that were referred to our service for primary treatment of retinoblastoma from April 1972 to April 1992. Seven of the 13 cases have been cited in previous reports.1,13,14 To our knowledge, our 13 cases is the highest number of cases reported from one institution.

PATIENTS AND METHODS

In this retrospective study, we reviewed the records of 440 patients with retinoblastoma who were evaluated and managed in the Ocular Oncology Service at Wills Eye Hospital between April 1972 and April 1992.

RESULTS

Of 440 children with retinoblastoma managed by us over a 20-year period, 238 patients were diagnosed with unilateral retinoblastoma and 202 with bilateral retinoblastoma (52 were familial and 150 sporadic). Thirteen (3%) of these 440 children have developed midline intracranial malignancy. There were five boys (40%) and eight girls (60%).

Among those 13 patients with midline intracranial tumor, 12 patients had retinoblastoma (Table 1). Using life-table analysis, this represents 6% of all bilateral retinoblastoma, 8% of bilateral familial retinoblastoma, 5% of bilateral sporadic retinoblastoma, and 0.05% of all unilateral retinoblastoma. The identical twin brother (patient 13) of a patient with unilateral familial retinoblastoma and pinealoblastoma (patient 11) was found to have a pinealoblastoma without retinoblastoma and was included in this study. The clinical presentation and treatment of the retinoblastoma are summarized in Table 1. Among the 12 patients with retinoblastoma, bilateral familial retinoblastoma was diagnosed in 4 cases (33%),
bilateral sporadic retinoblastoma in 7 cases (58%), and unilateral familial retinoblastoma in 1 case (9%).

Retinoblastoma was diagnosed at a mean age of 4.5 months (range, 0.5 to 9 months). Six eyes (6 patients) were enucleated for advanced disease. Ten eyes (7 patients) received external beam radiotherapy (EBRT), 4 eyes cryotherapy, 3 eyes (3 patients) plaque radiotherapy, and 1 eye laser photocoagulation. After reviewing with radiation oncologists the isodose curves of radiation treatment, we found that the pineal region of patients treated with shielded plaque radiotherapy or with lateral field EBRT receives no radiation. The pineal region of patients treated with anterior field EBRT (4000 cGy to the intraocular tumor) received ≈3000 cGy. In this series, among the seven patients treated with EBRT, one child received lateral field EBRT, one child received anterior field EBRT, and data were not available in five cases. Therefore, in seven patients (patient 13 was not irradiated, patients 6 and 9 were treated with other methods than radiation, patients 1, 5, and 11 with plaque radiotherapy, and patient 8 with lateral field EBRT), the pineal region was not irradiated. In one case, the pineal gland received a potentially dangerous radiation level. However, the small number of cases did not allow statistical conclusions.

Among four of the six enucleated eyes in which the pathology report was available, choroidal invasion of retinoblastoma was found in 2 eyes, prelaminar optic nerve invasion in 1, and laminar optic nerve invasion in 1. Brain-imaging studies were performed on each patient (nos. 1 to 11) at the time of retinoblastoma diagnosis. Metastatic work-up, including bone scan, bone marrow examination, and spinal fluid cytologic analysis, disclosed no other evidence of metastatic tumor. Chromosome studies were normal in the seven children on whom karyotyping was performed. DNA analysis is presently under study in several cases.

The midline intracranial malignancy was diagnosed at a mean age of 23 months (range, 4 to 49 months) (Table 2). The mean interval between the diagnosis of retinoblastoma and the diagnosis of the intracranial disease was 22 months (range, 0 to 48 months). In one patient (no. 12) the retinoblastoma was diagnosed 5 months after the diagnosis of symptomatic pinealoblastoma. One patient (no. 13) developed symptomatic pinealoblastoma without retinoblastoma. He was the identical twin brother of patient 11. Among the 13 patients with midline intracranial malignancy, 6 patients (45%) were symptomatic, with headache in 1 case, ataxia in 2 cases, and somnolence in 3 cases (Figs 1). Seven patients (55%) were asymptomatic and the tumor was found on routine contrast-enhanced computed tomography (CT) in three patients (patients 7, 8, 11) and on gadolinium-DTPA-enhanced magnetic resonance imaging (Gd-DTPA enhanced MRI) in four patients (nos. 1, 2, 9, 10) (Figs 2-3). Initial Gd-DTPA-enhanced MRI at the time of retinoblastoma diagnosis found the asymptomatic parasellar neoplasm in patient 2. Brain-imaging studies performed on the 13 patients showed hydrocephalus in seven cases (55%) and the midline intracranial tumor was partially calcified in six cases (45%). Although seven patients had hydrocephalus, papilledema was found in only one patient. The midline intracranial tumor was located in the pineal region in 10 cases (77%) and in the parasellar region in three cases (23%). Metastatic examination including bone scan, bone marrow analysis, spinal fluid cytologic analysis, and myelography did not show any other evidence of tumor.

The treatment modalities of the midline intracranial malignancy are shown in Table 2. Five children received EBRT, chemotherapy, and partial excision of the brain tumor. Four children received EBRT and chemotherapy.
One child had partial excision of the brain tumor and supplemental chemotherapy. Two children received chemotherapy only, and one child was not treated due to the advanced stage of his intracranial tumor. Biopsy or excision of the midline brain tumor showed pineoblastoma with malignant features in all cases.

Among the 13 cases of trilateral retinoblastoma, 12 (92%) died of their midline intracranial malignancy (Table 3). The mean age at death was 34 months (range, 15 to 73 months). The mean interval between the diagnosis of retinoblastoma and death was 34 months (range, 16 to 69 months). The mean interval between the diagnosis of midline intracranial malignancy and death was 11 months (range, 1 to 28 months). The log-rank for censored survival time analysis was used to evaluate the survival time of the 12 patients who succumbed to their disease. We found that the mean survival (42.6 months, range 22 to 73 months) of patients who were asymptomatic and diagnosed with intracranial malignancy on routine brain-imaging studies was significantly longer than the mean survival (25.6 months, range 15 to 42 months) of patients who were symptomatic from their intracranial tumor ($P = .05$). The mean interval time between the diagnosis of midline intracranial malignancy and death among the asymptomatic patients (12.8 months, range 6 to 28 months) was also statistically longer than that in the six symptomatic patients (8.3 months, range 1 to 20 months) ($P = .03$).

Multivariate logistic regression analysis was not performed because there were almost as many variables as patients, so any appropriate conclusion would not have been possible. One patient (no. 1) is still alive 30 months after her diagnosis of midline brain neoplasm found on MRI. She is currently receiving intravenous and intrathecal chemotherapy (Fig 4). There was no craniospinal irradiation or neurosurgical procedure in her case.

**DISCUSSION**

The designation of trilateral retinoblastoma was initially used to describe the association of bilateral retinoblastoma with pineoblastoma. However, cases of unilateral multifocal or unifocal retinoblastoma associated with pineoblastoma have since been reported.1,2,5,9,18-20

The results of our study support the known fact that patients with retinoblastoma and midline brain tumors are more likely to have a positive family history and bilateral ocular involvement than in children with retinoblastoma alone.1,3,10 This suggests that children with bilateral retinoblastoma and midline brain tumor may have a "stronger" allele of the retinoblastoma gene.3 In our series, the incidence of midline intracranial malignancy...
was 8% among all bilateral familial retinoblastoma, 5% of all bilateral sporadic retinoblastoma, and 0.05% of all unilateral retinoblastoma.

Primary midline intracranial neoplasms associated with retinoblastoma are most often located in the pineal region but they can occur in parasellar or suprasellar location. Studies have shown a difference in time of diagnosis between the midline intracranial tumors of pineal origin and those of parasellar or suprasellar origin, with the latter being recognized at an earlier age.1,4,5 Midline brain
neoplasms identified in children before the diagnosis of retinoblastoma have been reported to have a suprasellar location.\textsuperscript{1,4} Our data are consistent with these previous reports.

There have been few long-term survivors of patients with trilateral retinoblastoma. Conventional treatment of the intracranial neoplasm consists of neurosurgical intervention, craniospinal irradiation, and intravenous and/or intrathecal chemotherapy.\textsuperscript{1,5,21-23} Although the efficacy of vincristine and cyclophosphamide in regression of midline suprasellar neoplasms has been reported, the rationale for using these drugs was based on two anecdotal cases and the tumor ultimately progressed in both patients.\textsuperscript{24} Recently, Nelson and associates reported their relatively limited experience of three patients with trilateral retinoblastoma successively treated with systemic and intrathecal chemotherapy and craniospinal irradiation.\textsuperscript{25} These three patients are alive with no sign of active disease 96, 33, and 12 months, respectively, after diagnosis of the lesions.\textsuperscript{26} According to several studies,\textsuperscript{4,9,11,12,14-19} mean survival for patients with trilateral retinoblastoma is 18 months after the diagnosis of intracranial neoplasm. In our experience, death from the intracranial neoplasm occurred at a mean of 11 months after the diagnosis of that tumor.

This poor prognosis is related to the failure to control the primary midline intracranial neoplasm and its metastasis within the central nervous system.\textsuperscript{5} The major cause of death in our patients was spinal metastases from the midline intracranial neoplasm. In light of the aggressiveness of this disease, it is important to realize the clinical behavior of pineal tumors. Pineal tumors are classified into parenchymal tumors (pinealoblastomas, pineocytomas), germ cell tumors (embryonal cell carcinomas, teratomas, germinomas), glial tumors (astrocytoma, ganglioglioma), and ganglioneuroblastomas.\textsuperscript{21-23} Pineal parenchymal tumors (pinealoblastomas, pineocytomas) constitute 11% to 30% of the total.\textsuperscript{21-23} Pinealoblastoma, which is the type of tumor associated with retinoblastoma, has a high propensity to seed via cerebrospinal fluid pathways, and recent reports emphasized the necessity and efficacy of neuraxis radiotherapy.\textsuperscript{5,21-23,26} We agree that surgical excision of the midline intracranial neoplasm followed by whole neuraxis irradiation associated with intravenous and/or intrathecal chemotherapy are advisable to control metastasis. Kingston and associates concluded from their experience that doses of radiation less than 30 Gy are insufficient to eradicate the primary tumor.\textsuperscript{5}

Our data do not suggest that prior radiotherapy for the retinoblastoma predisposed the patient for the development of midline intracranial neoplasms.\textsuperscript{1} However, depending on the radiation fields used, significant scatter of the beam may occur, particularly following an anterior portal field. This aspect must be realized when considering further neuraxis radiotherapy for midline brain neoplasm or eventual CNS metastasis.

Another factor probably related to the poor survival of patients with trilateral retinoblastoma is the advanced stage of the disease at diagnosis. Symptoms and clinical signs of increased intracranial pressure such as lethargy, ataxia, irritation, vomiting, headache, hydrocephalus, and optic disc edema are clues to the diagnosis of midline intracranial tumor.\textsuperscript{1,9,21-25} When a child with retinoblastoma presents with these manifestations, it is likely that the intracranial tumor is already too large to respond to...
conventional therapy. Among the 12 patients who succumbed to their disease, the mean interval time between the diagnosis of midline intracranial malignancy and death among the asymptomatic patients (12.8 months) was statistically longer than that in the six asymptomatic patients (8.3 months). We are unsure if this may represent a lead time bias, that is the earlier discovery may not necessarily mean mean longer survival, but just longer awareness of tumor presence. The only patient still alive after 30 months was also diagnosed with the midline brain neoplasm on routine MRI.

Most authorities currently recommend routine brain imaging in management of patients with bilateral retinoblastoma. This may explain the relatively high number of patients in our series who were asymptomatic at the time of diagnosis of the midline brain tumor. Moreover, in our study this early detection of midline brain tumor in asymptomatic patients was significantly associated with a longer survival. Because of the high soft tissue contrast deficiency of MRI, its non-ionizing aspect, and the safety of gadolinium-DTPA as a contrast agent, we believe that routine contrast-enhanced MRI of the brain in bilateral and/or familial retinoblastoma every 6 months until age 2 years and yearly until age 4 years is more appropriate than contrast-enhanced CT for earlier detection of midline intracranial malignancy and to provide longer survival. We understand the financial implications of this recommendation, but in our series the only patient alive was diagnosed with routine contrast-enhanced MRI of the brain. These routine brain-imaging studies (in particular, contrast-enhanced MRI), to rule out pinealoblastoma in asymptomatic patients, could represent one way to decrease the mortality of this disease. However, the prevalence of trilateral retinoblastoma may be too low to justify expensive serial MRI scanning of all patients with bilateral and/or familial retinoblastoma.

REFERENCES