Neuroophthalmological management of optic pathway gliomas

ANDREW G. LEE, M.D.

Departments of Ophthalmology, Neurology, and Neurosurgery at the University of Iowa Hospitals and Clinics, the H. Stanley Thompson Neuro-ophthalmology Clinic, Iowa City, Iowa

✓The growth rate of optic pathway gliomas (OPGs) is unpredictable and quite variable, especially in children with neurofibromatosis Type 1 (NF1). Close neuroophthalmological clinical follow-up with serial imaging (magnetic resonance imaging of the brain with and without contrast enhancement) is the recommended initial step in management to establish the growth rate of the lesion in an individual patient. Typically, only symptomatic and/or radiographically growing tumors require treatment, and observation is the accepted first-line option. Although both chemotherapy and radiotherapy can stabilize growth or even decrease the size of tumors, chemotherapy, especially in younger patients, has fewer side effects than radiation therapy (such as secondary tumors, radiation necrosis, and Moyomoya disease) and is generally considered the first-line treatment for progressive lesions in younger patients. The tumor location defines prognosis in OPGs; optic nerve gliomas (ONG) have the lowest rate of complications and death, and optic chiasm and retrochiasmal gliomas the highest. Although the major complication of an OPG is visual loss, hypothalamic involvement can lead to death. Resection is an option for ONGs but is generally reserved for tumors confined to the optic nerve with poor or no vision, or for patients with severe, cosmetically unappealing proptosis, producing severe pain or exposure keratopathy in a blind eye. Resection is generally not an option for intrinsic chiasmal or retrochiasmal OPGs. Extrinsic (exophytic) components can be debulked surgically, and surgery can be performed for hydrocephalus (ventriculoperitoneal shunt placement). The approach to a patient with OPG must be individualized based on tumor location, radiographic or clinical progression, the presence of NF1, and a risk–benefit comparison for treatment. (DOI: 10.3171/FOC-07/11/E1)

KEY WORDS • glioma • neurofibromatosis • optic pathway

OPTIC pathway gliomas are slow-growing neoplasms that may cause visual or neurological complications and death. They are typically described by location as involving the optic nerve or optic chiasm, and may affect the hypothalamus or third ventricle, producing hydrocephalus. Posterior visual pathway involvement may also occur in patients with OPGs. Dutton³⁰ reviewed the literature concerning OPGs through 1994 and summarized the clinical characteristics (Table 1). Lee and Dutton⁵¹ updated this literature review in 1999. The present study includes selected English language references from the two reviews, and an update from 1999 emphasizing reports on treatment.^{1–80} Optic pathway gliomas are typically seen in children (mean 8.8 years, median 7.0 years),^{30,51} but late-onset de novo OPGs and late progression of preexisting OPGs in children with NF1 have also been reported.^{52–54} There is no sex predilection for OPG. In children the lesion

tends to be low grade and benign, but in adults OPGs tend to be atypical and follow a more aggressive and malignant course. The present study will be confined to the discussion of the typical childhood-onset OPG.

Neurofibromatosis Type 1 and OPG

About 30% of patients with OPGs have NF1. There are conflicting reports in the literature over whether NF1 predicts a better prognosis for OPG. Shuper and colleagues⁷² found that NF1 was a favorable prognostic indicator in their series of 21 patients, but others have not confirmed improved survival rates with NF1. Jenkin and associates⁴⁹ demonstrated a “borderline favorable prognosis” ($p = 0.06$) for OPG in patients with NF1. Opocher et al.⁶⁴ performed a systematic literature review of 23 articles and reported three studies with multivariate analysis that supported better progression-free survival for patients with OPG and NF1 compared to those without NF1. Likewise, Listernick et al.^{52–54,80} believe that NF1 provides a better prognosis and that the presence of NF1 might influence decisions on treatment and follow-up.

Abbreviations used in this paper: MR = magnetic resonance; NF1 = neurofibromatosis Type 1; OCG = optic chiasm glioma; ONG = optic nerve glioma; OPG = optic pathway glioma; RT = radiation therapy.

TABLE 1
*Clinical characteristics of patients with optic pathway gliomas in the study by Dutton, 1994**

Characteristic	% of Patients
association with NF1	29
tumor location	
chiasm	75
optic nerve alone	24
optic disc	1.6
visual loss at presentation	87.5
optic disc edema	35
optic disc atrophy	59
proptosis	
orbital involvement	94
chiasmal glioma	18
ophthalmoplegia	
orbital involvement	27
chiasmal glioma	21
nystagmus	23
hypothalamic signs	26
headache	28

* Patients had an equal sex distribution and a mean age of 8.8 years (median 7.0 years).

Location of OPGs

Optic pathway gliomas can affect the optic nerve, optic chiasm, or the retrochiasmal visual pathway. By definition, optic nerve gliomas are confined to the optic nerve and represent 24% of OPGs, whereas the remaining 76% of cases involve the optic chiasm. In patients with OCGs, the chiasm alone is affected in 6.6%, the chiasm and optic nerve are both involved in 47.2%, and the chiasm and brain (usually the hypothalamus) in 46.2%.³⁰ In some patients there might also be retrochiasmal (especially of the optic tract) or posterior visual pathway involvement.⁵⁶

Clinical Symptoms and Signs in OPGs

Visual loss is the main deficit caused by OPGs. The neuroophthalmic presentation varies depending on the involvement of one or both optic nerves (unilateral or bilateral visual loss due to an optic neuropathy), the optic chiasm (bitemporal hemianopsia), or retrochiasmal pathway (hom-

onymous hemianopsia). Visual loss is common in patients with OPGs and is present in 87.5% at diagnosis.³⁰ The extent of visual loss is variable and a patient's vision may range from 20/20 to no light perception. The majority of patients (55%) have poor visual acuity of worse than 20/300 in one (ONG) or both eyes (OCG or bilateral ONG). Optic pathway gliomas tend to be slow-growing tumors and as a result the diagnosis can be delayed, especially in younger children not able to articulate the visual loss. The duration of symptoms prior to the obtaining of neuroimaging studies and an eventual diagnosis of OPG is typically several months to years.

Other presenting symptoms can include diplopia or increasing proptosis and other neuroophthalmic signs in addition to the visual acuity and visual field loss, including pupillary abnormalities (such as relative afferent pupillary defect or sluggishly reactive pupils), optic disc edema (35%) or atrophy (59%), choroidal folds, proptosis, ophthalmoplegia, or nystagmus (23%),³⁰ and spasmus-nutans-like movements.⁴ Neurological signs and symptoms may also be the result of hypothalamic involvement in patients with precocious puberty⁵⁰ and accelerated linear growth; or the result of hydrocephalus in patients with macrocephaly, headache (28%), nausea, vomiting, and diplopia.^{30,51} Lep-tomeningeal involvement is uncommon.^{17,22} Neuroophthalmologic surveillance of patients with OPGs is therefore recommended with age-appropriate evaluations of visual function (such as preferential looking testing, figure matching, Snellen visual acuity, formal visual field testing, color vision testing, and pupillary and dilated fundus examination).^{42,44,46,47}

Diagnosis of OPG

The diagnosis of OPG depends on clinical recognition of an optic nerve or chiasmal lesion followed by appropriate neuroimaging. The presence or absence of NF1 should be established. Orbital and cranial computed tomography scans of OPGs may show fusiform enlargement of the optic nerve, kinking of the optic nerve, or enlargement or enhancement of the optic nerve, chiasm, or retrochiasmal visual pathways.⁴³ Magnetic resonance imaging is usually superior for demonstrating these findings in OPGs and also

TABLE 2
*Summary of management considerations for OPGs**

<ul style="list-style-type: none"> • The growth rate of OPGs is unpredictable & variable, especially in children w/ NF1. • Clinical serial neuroophthalmic & radiographic follow-up exams including imaging studies of the brain are recommended for patients w/ OPGs. Observation is the recommended initial management. • Typically only symptomatic & clinically or radiographically progressive OPGs require consideration for treatment. • Although both chemotherapy & radiotherapy can decrease the size of or stabilize growth of OPGs, chemotherapy causes fewer side effects & should generally be considered first. • Tumor location defines prognosis in OPGs. Optic nerve gliomas have the fewest associated complications & deaths, & OCGs & HTGs have the highest. • The major complication is visual loss; the major cause of death is hypothalamic involvement. • Resection is an option for ONGs but is generally reserved for patients w/ poor or no vision, severe proptosis that is cosmetically unappealing or producing severe pain in a blind eye. • Resection is generally not an option for intrinsic chiasmal or retrochiasmal OPGs. Extrinsic or cystic components can be debulked surgically on a case-by-case basis. • Surgery for shunt placement can be performed to treat hydrocephalus in patients w/ OPGs.
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* Summary based on the findings of Dutton, 1994, and Lee & Dutton, 1999. Abbreviation: HTG = hypothalamic glioma.

TABLE 3

*Summary of progression rates, side effects and complications of treatment, and mortality rates based on two published literature review studies**

- The progression/recurrence rate for OPGs was ~37%, combining tumors in all locations.
- The overall mortality rate was 39%, but individual mortality rates vary based on the specific OPG location. Highest rates were seen in HTGs.
- The ONG progression/recurrence rate is 21.9%. Excision of an ONG can achieve a surgical “cure” w/ <1% mortality rate, but will cause complete blindness postoperatively. Excision may be considered in blind eyes w/ severe proptosis or for painful & blind eyes.
- The overall estimated response rate (stabilization) to chemotherapy for progressive ONGs is 48%. In OCGs managed w/ observation alone, the progression/recurrence rate was ~41% & mortality rate was ~29%. The risks associated w/ chemotherapy are uncommon but not trivial and include neutropenia or thrombocytopenia.
- For OCGs treated w/ RT, the progression rate was ~41% and mortality rate was 27%; 50% of RT-treated patients experienced radiation side effects.
- In HTGs the progression & mortality rates were both ~46%. In patients treated w/ RT for HTG, the progression rate was ~49% & the mortality rate was ~43%.

* Summary based on the findings of Dutton, 1994, and Lee & Dutton, 1999.

for documenting intracranial involvement (hypothalamic and retrochiasmal involvement and hydrocephalus). In some cases there is a hemorrhagic, cystic, or exophytic (extrinsic) component to the lesion.¹⁹ Magnetic resonance images are superior to computed tomography scans for defining the extent of intracranial or intracranial involvement (in the hypothalamus and along the optic tract for example) and also may be useful in the identification of other intracranial lesions suggestive of NF1.^{38,401,45} In most cases, typical neuroimaging in the appropriate clinical presentation is sufficiently diagnostic to obviate the need for tissue confirmation via biopsy sampling, but some atypical cases still require pathological confirmation.^{30,51}

Management of OPG

Despite extensive literature on the subject, the best management for OPGs remains controversial.^{30,51} The major limitations for all of the studies conducted to date include incomplete or noncomparable data; combined reports from before and after the advent of MR imaging; a lack of histological diagnosis in all cases (especially after the introduction of MR imaging); lack of, short, or poor follow-up; poor documentation of the pretreatment tumor location; lack of or poor documentation of the presence or absence of NF1; small sample sizes, referral, selection, ascertainment, and recall bias; and uncontrolled retrospective data.^{30,51} Despite these limitations, some recommendations can be made. Tables 2 and 3 summarize the key management points.^{30,51}

Neuroophthalmic Management Guidelines for OPGs

In the 1994 and updated 1999 reviews of the literature on OPGs (including 1136 and 1364 cases, respectively) the overall long-term prognosis for visual function (> 11 years) was good (“stable or improved”) in 78%, but poor (worsening vision) in 22%. Likewise, 80% had stable visual fields over the same period of time.³⁰ Unfortunately, the rate of recurrence or clinical or radiographic progression was moderately high at 38–40%, and the overall mortality rate in patients with OPGs was 30–33%. In their systematic review, Opocher et al.⁶⁴ reported two studies with multivariate analysis supporting tumor site as a prognostic factor

(albeit with some methodological limitations).^{42,44} Because the major goal in managing cases of OPG is to preserve vision for as long as possible, initial observation is recommended for all patients harboring OPGs. Continued observation is generally recommended for OPGs that do not progress clinically or radiographically. In addition, some OPGs actually spontaneously regress.⁵⁵ The management of OPGs thus requires an individualized approach, but tumor location is a major factor in the decision making.^{50,57,58}

Management of ONG

In prior literature reviews, stable or improved vision was demonstrated in 91% of ONGs that were observed rather than treated (114 cases), and recurrence or progression was seen in 21%. The tumor-related mortality rate for ONGs is low (probably < 6%) and presumably occurs from intracranial extension.^{30,51} Although there could be progression to the other eye or the optic chiasm from an ONG, many authors believe this to be a theoretical risk only.^{52–54,62}

Patients with ONGs treated with either complete or partial excision and then by RT (200 reported cases) suffered vision loss as a complication.³⁰ Thus, surgery alone is probably counterproductive in ONG if the goal is to preserve vision. Patients with no useful vision, severe eye-threatening proptosis, or a blind, painful eye might benefit from gross-total resection. In the literature reviews, there were no tumor-related deaths in patients who underwent complete resection of the ONG, but most authors would not recommend resection in a seeing eye.^{30,51}

Unlike OPGs confined to the optic nerve alone (ONGs), OCGs are not generally amenable to complete excision without incurring unacceptable complications such as bilateral visual loss. Debulking of the exophytic or cystic component of the OCG can be considered in individual cases (especially in those with rapid progression), but the indications for surgery are not well defined.⁷⁹ However, patients with OCGs or hypothalamic gliomas who develop hydrocephalus may benefit from shunt placement. As in ONGs, the general recommendation for both OCGs and hypothalamic gliomas is initial clinical and radiographic observation for evidence of progression.

Optic pathway gliomas with progressive disease can be treated with RT.^{11,12,15,25,32,34,37,39,41,49,66,69} However, RT may

TABLE 4
Summary of the literature concerning response to chemotherapy in optic pathway gliomas*

Authors, Year	Chemotherapy Regimen	Median FU Duration	Response to Tx
Packer et al., 1988 (24)	vinc/AD	4 yrs	stable disease (14)
Petronio et al., 1991 (15)	TPDVL	67.3 wks	stable disease (3)
Packer et al., 1993 (30)	car/vinc	14 mos	stable disease (10)
Janss et al., 1995 (32)	AD/vinc (31), VP16/vinc (1)	72 mos	stable disease (9)
Sutton et al., 1995 (10)	AD/vinc	3 yrs	stable disease (10)
Aquino et al., 1999 (12)	car	38.6 mos	stable disease (6), partial response (4)
Mahoney et al., 2000 (50)	car	18 mos	39/50 stable or better
Silva et al., 2000 (14)	car (8), car & vinc (4), other (2)	15 mos to 8 yrs	5-year progression-free survival 63%
Mitchell et al., 2001 (12)	monthly car	not applicable	stable radiologic disease (9)
Gnekow et al., 2004 (123)†	vinc/car	22.5 mos	progression-free survival 61%

* All numbers in parentheses are numbers of patients. Abbreviations: AD = actinomycin-D; car = carboplatin; FU = follow-up; TPDVL = 6-thioguanine, procarbazine, dibromodulol, vincristine, lomustine; Tx = treatment; vinc = vincristine; VP16 = etoposide.

† Patients had a median age of 3.7 years.

result in significant complications in children with OPGs, such as cerebrovascular disease, Moyamoya disease, cerebral atrophy, secondary malignancies, mental retardation, cataracts, radiation retinopathy, endocrinopathy, and radiation necrosis of the optic pathways or hypothalamus.^{11,12,15,32,63} Although abnormally low intelligence or learning disabilities after RT is relatively common and may be debilitating, the development of secondary tumors after RT can be life threatening. Jenkin et al.⁴⁹ reported that 5 (10%) of 48 patients treated with RT (median follow-up period of 11 years) developed a second malignant tumor (fatal in all cases) compared with the 49 patients who did not receive RT and did not develop subsequent tumors.

Sharif and associates⁷¹ reviewed 80 NF1-related OPGs treated with and without RT. In this cohort, 9 (50%) of 18 patients with OPGs developed 12 second tumors after RT (in 308 person-years of follow-up) compared with only 8 (20%) of 40 patients who were not treated with RT who developed 9 tumors in 721 person-years of follow-up. The relative risk of a second nervous system tumor after RT was 3.04 (95% confidence interval, 1.29–7.15), and the authors concluded that there is a “significantly increased risk” of a second tumor in patients with NF1 who are treated with RT for OPGs. New and emerging RT modalities and techniques such as fractionated stereotactic RT may reduce the risks of RT but have not completely eliminated them.²³

In previous literature reviews, the visual outcome in patients with OPGs (mean follow-up of 10 years) indicated stable vision in 68% of patients who received RT compared with 81% of those who were simply observed.^{30,51} The recurrence or progression rate was 41% in both the RT-treated group and the observation group, and the mortality rate in both groups was 27%. Many authors believe that although RT may have short-term benefits in delaying OPG progression, it has little influence on final visual outcome or survival.^{30,51}

Chemotherapy is useful for delaying the need for RT in progressive OPGs and has been used with variable success (67–90% stabilization).^{62,65,67,70} Carboplatin-based regimens such as carboplatin and vincristine have been the most commonly studied, but other regimens (with or without carboplatin) have been reported as well (Table 4). Chemotherapy is considered the first-line therapy advocated by many authors, and has significantly fewer associated

complications than RT. The carboplatin regimens also appear to be relatively well tolerated, but neutropenia, thrombocytopenia, and allergic reactions may occur. Although chemotherapy may delay progression or stabilize visual function in patients with progressive OPGs, there remains a significant rate of progression or recurrence after chemotherapy.

Conclusions

Optic pathway gliomas are typically childhood tumors. The growth rates of OPGs are variable but unpredictable, and their management should be individualized on a case-by-case basis. Close clinical neuroophthalmic follow-up and serial radiography (preferably MR imaging of the brain) are recommended for OPGs. Observation is the recommended initial management. Typically only symptomatic and radiographically progressing OPGs require strong consideration for treatment. Although both chemotherapy and RT can decrease the size or growth of an OPG and stabilize visual loss, chemotherapy, especially in patients younger than 5 years of age, causes fewer side effects than RT and should be considered as a first-line therapy for progressive lesions. Radiation therapy can produce significant neurocognitive and endocrinological complications and carries a significant risk of secondary tumor development, especially in patients with OPGs due to NF1.⁶⁶ Tumor location defines prognosis, as ONGs have the lowest morbidity and mortality followed by OPGs and then hypothalamic glioma. The major symptom of OPG is visual loss, but the major cause of systemic complications or death is typically hypothalamic involvement (causing electrolyte abnormalities) or hydrocephalus. Resection is an option for ONG, but is generally reserved for patients with poor or no vision, patients with cosmetically unappealing severe proptosis, or for ONGs producing severe pain or exposure keratopathy in a blind eye. Resection is generally not an option for intrinsic OPGs, hypothalamic gliomas, or retrochiasmal OPGs. Extrinsic (exophytic or cystic) components can be debulked surgically, but the indications for this treatment are controversial. Future work and emerging therapies such as endoscopic techniques, brachytherapy, and stereotactic fractionated conformal RT⁷⁴ may improve our strategies for managing cases of OPG. Currently, however, the recommendation remains for case-by-case decision making.^{77,78}

Acknowledgment

This work was supported in part by an unrestricted grant from Research to Prevent Blindness, Inc., New York, New York.

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Manuscript submitted August 27, 2007.

Accepted September 14, 2007.

Address correspondence to: Andrew G. Lee, M.D., Department of Ophthalmology, University of Iowa Hospitals and Clinics, 200 Hawkins Drive PFP, Iowa City, Iowa 52242. email: Andrew-lee@uiowa.edu.