Optic Nerve Gliomas

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Abstract

Objectives To describe the diagnostic and management features of optic nerve gliomas.

Design Literature review.

Results Optic nerve gliomas are generally benign in the pediatric age group although they are usually malignant and aggressive in adults. As such, the mechanisms by which these lesions are diagnosed, the systemic implications, the goals of intervention, and the nature of therapeutic management all differ between these tumors.

Conclusions This article addresses these lesions and discusses the diagnostic and therapeutic paradigms by which they may be approached.

Keywords
- glioma
- optic nerve glioma
- malignant optic nerve glioma

Introduction

Gliomas of the optic nerve and visual pathways occur in two distinct forms. In the pediatric population, these neoplasms are generally benign, and may be definitively detected on orbital imaging. Although they may not require intervention at all, medical management remains the standard of care; except in rare circumstances. Surgery is generally not indicated, and recent refinements in the comprehension of the cellular biology of these tumors have resulted in novel therapeutic interventions. Furthermore, well-designed trials have identified meaningful treatment strategies to address pediatric optic nerve gliomas. When these tumors recur, fail to respond, or progress despite appropriate management, emerging treatment protocols offer the promise of enhanced outcomes.

Alternatively, in adults, optic nerve gliomas carry a very poor prognosis. These lesions are rapidly progressive, and survival rates are poor. Surgical intervention is generally required to confirm the diagnosis in this age group. However, well-designed therapeutic protocols have not been developed for this disease, likely due to its rarity. Nonetheless, emerging evidence suggests that the nature of our treatments may have an impact on the duration of survival.

This review intends to carefully define the nature of these tumors and to discuss therapeutic options to address them.

Optic Pathway Gliomas: Pediatric Population

Optic nerve gliomas represent 2 to 5% of central nervous system neoplasms among children.[1–5] Furthermore, these lesions comprise 1% of all intracranial tumors[6] and 7% of all gliomas.[6,7] Seventy percent of optic nerve gliomas are detected within the first decade of life and 90% are identified by the second decade.[7]

These tumors may be associated with neurofibromatosis type 1 (NF-1) or may be sporadic. NF-1-related tumors are generally detected at a younger age (mean of 4.5 years) and may be either bilateral or unilateral.[2] In NF-1, reported rates of glioma development have ranged considerably, with incidences ranging from 20% overall to bilateral disease in 35%.[7–11]

Alternatively, sporadic optic nerve gliomas are generally detected at a slightly older age, although, when present, they are generally noted in the first decade of life.[2] These lesions carry a greater risk of vision loss.[12–14] Specifically, at least 50% of NF-1-associated gliomas are not associated with

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decreased vision, whereas 66 to 74% of sporadic tumors result in loss of vision and 74% progress radiographically.[7]

Histologically, pediatric optic nerve gliomas generally represent low-grade pilocytic astrocytomas, although fibrillary astrocytomas have been reported.[15] Furthermore, proliferation marker analysis indicates that sporadic gliomas demonstrate more aggressive histopathologic features.[16,17]

Recent scientific findings have shed light on the cellular biology of optic pathway gliomas. In NF-1, a tumor-suppressor gene that controls cellular proliferation, survival, and differentiation is inactivated. This control mechanism acts through the mitogen-activated kinase (MEK) and mammalian target of rapamycin (mTOR) pathways.[18] The product of the NF-1 gene (neurofibromin) normally binds to RAS, thereby inactivating it and controlling cellular division; consequently, inactivity of the NF-1 gene results in constitutive activation of RAS and unchecked cellular proliferation.[19] Alternatively, sporadic cases of optic nerve gliomas demonstrate a rearrangement of the serine-threonine protein kinase B-RAF gene.[7,18–22]

At presentation, the majority of optic nerve gliomas are asymptomatic and are thus detected either during screening evaluations or incidentally during imaging that is performed for other purposes.[3,10,23] Magnetic resonance imaging of the brain and orbits with and without gadolinium represents the preferred radiographic modality. Optic nerve gliomas are classically tubular or fusiform in nature and appear as isointense on T1 and iso- or hyperintense on T2 images.[2] In the light of the high risk of vision loss associated with biopsy,[24] surgical confirmation is rarely indicated, and the diagnosis may be made on radiographic features alone.[25]

The clinical course of optic nerve gliomas is highly variable; many of these tumors may be indolent for several years, whereas other are associated with marked, rapid growth. Ultimately, vision loss is the most critical determinant of the need to treat gliomas.[10,25–27] Perimetry may detect progression of vision loss more rapidly and with greater accuracy than simple acuity testing, although this evaluation may be difficult in children.

As such, optical coherence tomography (OCT) represents a powerful modality to assess the health of the optic nerve. Specifically, loss of the retinal nerve fiber layer is directly associated with loss of visual acuity and visual field and growth of the tumor.[28,29] Similarly, stability of the nerve fiber layer thickness on OCT correlates with the absence of vision loss in these patients.[30]

Recommendations for screening and repeat imaging are based on a given patient's specific features. Children with a known history of NF-1 and a documented history of an optic nerve glioma should be tested for visual acuity every 3 months for the first year after diagnosis. Assuming stable examinations, these children are advised to then undergo testing every 6 months until the age of 8 years, followed by annual examinations until the age of 18 years. Imaging is recommended every 3 months for the first year, every 6 months for 2 years, and annually for 3 to 5 years. Cases of NF-1 without a history of a glioma should receive an annual examination until the age of 8 years, and should then be assessed every other year until the age of 18 years.[2]

Pearls and Tips

- Whereas biopsy is generally not required in cases of suspected pediatric optic nerve gliomas and the diagnosis may be made on imaging features, surgical confirmation should take place in adult-onset malignant optic nerve gliomas.
- In pediatric patients with vision loss from optic nerve gliomas, chemotherapy is the standard of care. Newer agents and regimens offer hope in cases of recalcitrant or recurrent disease.
- Surgical debulking is generally reserved for disfiguring proptosis, severe pain, or progressive keratopathy in pediatric cases of optic nerve glioma.
- Combined chemotherapy and radiation therapy appear to extend the duration of survival in cases of malignant optic nerve glioma, although outcomes are generally poor.

Several features correlate with increased tumor aggressiveness and worse visual outcomes. Younger age at diagnosis, sporadic tumors, and optic nerve pallor all represent clinical findings associated with worse prognoses.[26,31–34] Radiologically, greater degrees of enhancement and tumor extension beyond the chiasm suggest more aggressive oncologic behavior.[7]

Visual acuity and loss of vision remain the key features in determining whether or not optic nerve gliomas necessitate treatment. Clinically significant vision loss is conventionally defined as a decrease of 0.2 logMAR in acuity.[10,27] With progressive disease, chemotherapy has solidly emerged as the first-line therapy. Combination therapy consisting of vincristine and carboplatin results in 3- and 5-year rates of progression-free survival of 77 and 69%, respectively.[35] Although this regimen has not been associated with treatment-related mortality,[36] hypersensitivity reactions are quite common.[37,38]

Additionally, previous investigations revealed that therapy with thioguanine, procarbazine, lomustine (CCNU), and vincristine (TPCV) yielded outcomes that were similar to those seen with vincristine and carboplastin.[36] However, CCNU and procarbazine are associated with a risk of leukemia, and patients with NF-1 already carry a risk of this malignancy. As such, this regimen may be useful in sporadic cases of gliomas, but should be avoided with NF-1.[25] Cisplatin and etoposide chemotherapy yielded a 78% rate of progression-free survival in one study, but this combination carries risks of ototoxicity and secondary leukemia.[39] In cases of refractory and recalcitrant disease, monotherapy regimens that employ temozolomide, vinblastine, and vinorelbine have all demonstrated some evidence of success.[40–43]

Several caveats should be considered in the chemotherapeutic management of optic nerve gliomas. Specifically, clinicians should be aware that the correlation between

radiographic appearance and visual function is imperfect.[44–46] Additionally, the impact of this intervention on visual acuity may not be profound. In a large-scale investigation, the acuities of 24% of patients with NF-1 improved after chemotherapy, whereas 35% experienced stability and 41% worsened. Among sporadic gliomas, 18% improved, 43% achieved stability, and 39% worsened.[47]

Improved comprehension of the cellular features of gliomas and a broader arsenal of chemotherapeutic agents have resulted in new options to treat this disease. Given the role of MEK in the pathogenesis of these tumors, selumetinib, refametinib, trametinib, and cobimetinib have been employed in progressive and recurrent disease, and these agents resulted in 69% progression-free survival.[48]

Similarly, agents that target vascular endothelial growth factor may play an important role in the management of gliomas. Improved visual symptoms and a clinical response after bevacizumab treatment has been reported in 86% of patients.[49] A case series of four patients with initial treatment failures documented visual improvement after bevacizumab monotherapy in four patients,[50] and combination therapy of bevacizumab and irinotecan yielded a 47.8% rate of 2-year progression-free survival in patients with recurrent disease.[51]

Historically, radiation therapy carried high 10-year rates of progression-free survival, ranging from 90 to 100%.[52–56] Nonetheless, the complications associated with this modality are substantial, and include neurodevelopmental, visual, endocrinologic, neurovascular, and oncologic concerns.[25] As such, radiation is currently reserved for salvage therapy in older patients.

Finally, surgical intervention continues to play a role in the management of optic nerve gliomas. However, the risk of vision loss is substantial with surgical manipulation of the optic nerve. Furthermore, several authors contend that these lesions are unlikely to extend to the chiasm.[25,57] Given the multiple chemotherapeutic options for tumor control, surgery is generally not entertained to limit the growth of these neoplasms or to restore vision. Instead, debulking efforts are attempted to reduce disfiguring proptosis or heal significant exposure keratopathy. As such, these lesions may be approached through a standard lateral orbitotomy.

Malignant Optic Nerve Gliomas: Adult Population

Unlike the relatively less aggressive gliomas that occur in the pediatric population, these neoplasms represent a more nefarious disease. Classically, these tumors arise in middle-aged males who present with rapidly progressive vision loss. The visual deterioration tends to occur over several weeks, and tumor-related death typically occurs within several months of onset.[58]

Although pediatric gliomas are associated with a more bland histologic appearance, malignant optic nerve gliomas represent anaplastic astrocytomas (WHO grade III) or glioblastoma multiforme (WHO grade IV). Radiologically, these tumors appear quite similar to their pediatric counterparts, although the amount of contrast enhancement is generally more profound.[59–61] Conventionally, biopsy is recommended to rule out other causes of vision loss.

Despite the rarity of this disorder, a recent review analyzed the outcomes among 44 patients. The median age at diagnosis was 62.5 years. The median overall survivals for WHO grades III and IV were 11 and 10 months, respectively, and this difference was not statistically significant. Regardless of intervention, the outcomes were generally poor, although the nature of the treatment impacted the duration of survival. Without therapy, the median survival was 2 months, whereas chemotherapy resulted in a median survival of 4 months, and combined radiation therapy and chemotherapy yielded a median survival of 11 months. Due to the rarity of malignant optic nerve gliomas, well-designed prospective studies and treatment protocols have not been designed.[58]

Note

This study specifically focused upon sporadic OPG outlining their clinical characteristics, visual prognosis, and considerations for follow-up and treatment.

Conflict of Interest

None declared.

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