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Optic Pathway Gliomas

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Background: Childhood optic pathway gliomas (OPGs) are low-grade neoplasms intrinsic to the optic nerve, optic chiasm, tracts, and radiations. The management of OPGs is still a highly controversial topic among neuro-ophthalmologists.
Evidence Acquisition: Authors' personal experience and literature review.
Results: This review describes our current understanding of the behavior of OPGs and discusses advances in their imaging, evaluation, and management. Patients with OPGs that progress are typically treated with chemotherapy using carboplatin and vincristine; however, newer approaches to therapy are being explored.
Conclusions: Although chemotherapy is the mainstay of treatment when indicated, multicenter collaborative studies involving oncologists and neuro-ophthalmologists, both retrospective and prospective, are still needed to establish evidence-based guidelines for the management of children with OPGs.

Journal of Neuro-Ophthalmology 2011;31:269–278
doi: 10.1097/WNO.0b013e31822aef82

We begin with 2 cases, both seen at the Children's Hospital of Philadelphia, that raise many of the controversial issues regarding OPGs. *What would you recommend in each case?* Our comments and recommendations regarding these cases appear at the end of the review.

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Dr. Avery was supported by the National Institutes of Health/National Eye Institute Pediatric Research Loan repayment program.

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The authors report no conflicts of interest.

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Case 1

A 5-year-old girl without neurofibromatosis type 1 (NF1) was found on a routine examination to have vision loss in her right eye. MRI showed enlargement of the right optic nerve (Fig. 1) and so she was referred to us. The girl saw 20/40, right eye, and 20/15, left eye, by HOTV acuity testing, had full fields to confrontation techniques, and had a right relative afferent pupillary defect (RAPD). There was no significant refractive error. Anterior segment examination was normal without Lisch nodules. Fundus examination demonstrated right optic disc pallor while the left optic disc appeared normal.

Case 2

A 3-year-old girl without NF1 developed progressive right proptosis over 3 months. Approximately 2 weeks prior to evaluation, she stated that her right eye "was not working." The referring ophthalmologist noted right proptosis that was not obvious on photographs taken 5 months earlier. MRI disclosed enlargement of the right optic nerve consistent with a glioma (Fig. 2). The patient's visual acuity (VA) was light perception, right eye, and 20/25, left eye, by HOTV and Lea figures, and the left visual field was full to confrontation techniques. She had a sluggishly reactive right pupil with right RAPD. Eye movements were normal. Anterior segment examination was normal without Lisch nodules. Dilated fundus examination demonstrated optic disc pallor and elevation in the right eye and a normal left disc.

Optic pathway gliomas (OPGs) are low-grade neoplasms intrinsic to the precortical visual pathway (optic nerve, optic chiasm, tracts, and radiations). They affect young children more than adolescents or adults and are important in the differential diagnosis of vision loss in children. They are also associated with NF1, a relatively common genetic condition with an incidence of 1:3,000 births (1). As evidenced by a spirited discussion following a platform presentation (2) at the 2010 North American Neuro-Ophthalmology Society meeting, the management of optic pathway gliomas remains a highly controversial topic among neuro-ophthalmologists.

For years, OPGs were thought to behave like hamartomas and not require treatment; however, aided by the

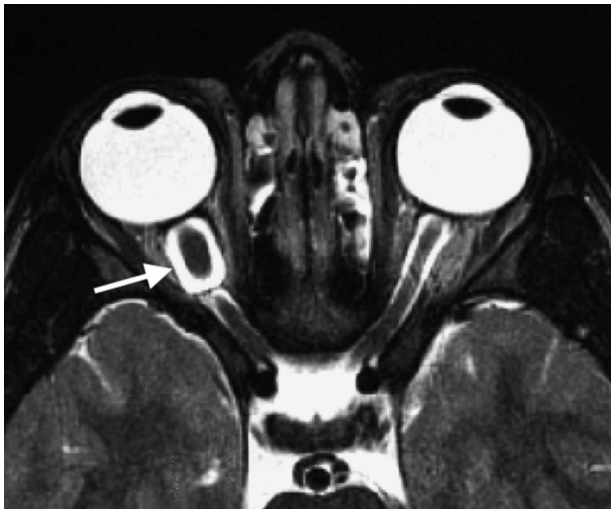

FIG. 1. T2 axial MRI demonstrating enlargement and kinking of the intraorbital portion of the right optic nerve (*arrow*), consistent with an optic nerve glioma. There was no extension beyond the optic canal, and the optic nerve did not enhance.

high-resolution MRI and careful serial observations, most clinicians who deal with these lesions realize that their growth patterns are varied and unpredictable. At institutions experienced in the care of children with OPGs, these lesions are considered to have the potential to behave as true neoplasms, and patients with documented clinical (visual) or neuroimaging progression are typically treated with chemotherapy (3,4).

We review our current understanding of the behavior of OPGs and discuss advances in their imaging, evaluation, and management. Because childhood OPGs are much more common (and controversial) than the malignant ones of adulthood, we will restrict our review primarily to OPGs in children.

DEFINITION AND EPIDEMIOLOGY

The most common brain tumors in children are low-grade gliomas (World Health Organization [WHO] grade I juvenile pilocytic astrocytomas and grade II diffuse fibrillary astrocytomas) (1). The term "optic pathway glioma" is reserved for those tumors confined to the precortical visual pathway, sometimes with the involvement of the hypothalamus. Because OPGs are intrinsic to the axons of the visual pathway, they are not easily amenable to biopsy or surgical resection without risking visual loss unless they have a sizable extrinsic component. This makes it difficult to obtain an exact incidence of each tumor type. In most cases, the typical MRI appearance (see below) and common association with NF1 obviate the need for diagnostic biopsy.

Most children diagnosed with OPGs have NF1 (5,6). Conversely, most case series report that about 20% of children with NF1 have an OPG (7,8). The term "sporadic OPG" is reserved for tumors in children without NF1.

CLINICAL PRESENTATION

Age at Presentation

Most OPGs in children with NF1 are diagnosed before 6 years of age (3,7). There is a considerable variability in the reported age of diagnosis for NF1-related OPGs, however, because some clinicians perform screening neuroimaging on all children with NF1, regardless of their ophthalmologic examination results. Others do not unless there is a specific indication. An older age at diagnosis and treatment would be expected at institutions where physicians forego screening MRIs and image only if ophthalmologic, neurologic, or behavioral symptoms are present. Although it is uncommon for NF1-associated OPGs to cause symptoms after 8 years of age (3), a number of reports have demonstrated newly symptomatic OPGs, even after previously normal neuroimaging, in children older than 8 years (9,10).

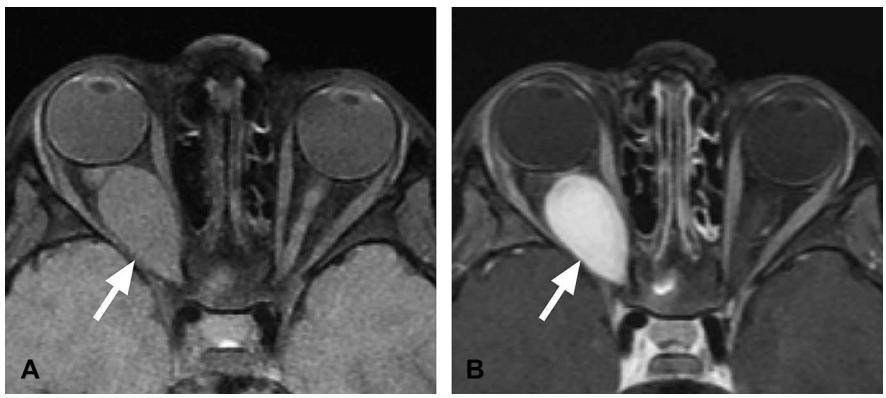

FIG. 2. Fat-suppressed T1 axial MRI, without (**A**) and with (**B**) gadolinium showing bulbous enlargement of the right optic nerve (*arrow*), consistent with an optic nerve glioma. The right eye is proptotic. Enhancement extended into the optic canal (not shown), but there was no enhancement or enlargement of the chiasm.

The typical age of presentation for sporadic OPGs typically is less than 8 years (6,11). Similar to NF1-associated OPGs, however, onset can occur in the second decade. Nearly 90% of all sporadic OPGs are discovered because the child has a new neurologic or ophthalmologic abnormality that prompts neuroimaging. Other reasons for the discovery include unexplained endocrinopathy or short stature or they are found incidentally (6). On occasion, older adults up to the fifth decade have been reported to have newly symptomatic sporadic OPGs (12–14).

Signs and Symptoms

Ophthalmologic complaints and findings noted at diagnosis of OPGs include decreased VA, color vision loss, visual field defects, a RAPD, strabismus, nystagmus, proptosis, and optic disc pallor. In young children, visual field defects may not be readily apparent and are only infrequently a presenting symptom without associated VA loss. Nystagmus from an OPG can be horizontal or rotary, and asymmetric or monocular. High-frequency, low-amplitude, horizontal, "shimmering," asymmetric pendular nystagmus identical with or similar to the condition known as spasmus nutans can also be a presenting sign of an OPG (15,16). Other features of spasmus nutans (e.g., head nodding and torticollis) may or not be present. Signs and symptoms of increased intracranial pressure (headache and papilledema) and neurological findings are more often noted in larger, chiasmal-hypothalamic, sporadic OPGs (6). Precocious puberty, especially in a child with NF1, should raise the suspicion of an OPG. Many NF1-associated OPGs are discovered incidentally when a brain MRI is ordered. Impaired VA is more common at presentation in sporadic than in NF1-related OPGs (5,6,17) and is present in 50% or less of subjects with OPG and NF1 (3,18).

CLINICAL EVALUATION

Neuro-ophthalmic Evaluation

The neuro-ophthalmic examination is a key component in the diagnosis and management of OPGs. In children with NF1, examination guidelines have been developed by expert consensus (3). These guidelines can be adapted to children with sporadic OPG, especially once they become visually symptomatic or are undergoing treatment.

A quantitative assessment of VA is the single most important part of the examination. Qualitative measures of VA (e.g., fix and follow, constant-steady-maintained) are insufficient because subtle and even large changes in acuity may not be adequately detected or assessed by these methods. For example, a 2-year-old child with a VA of 20/40 that worsens to 20/80 or 20/100 will still fix and follow despite a substantial decrease in acuity. Teller grating acuity, assessed by a preferential looking test, can be attempted in children as young as 6 months of age and has an excellent relationship with Snellen acuity in children of 5 years (19) and matching with Lea figures or HOTV optotypes can be achieved in children as young as 3 years.

Accurate and reliable testing of VA is highly dependent on a child's cooperation. VA testing can be especially difficult in medically ill children or in young children with NF1 given their high incidence of developmental delay and attention deficit hyperactivity disorder; however, skilled pediatric examiners frequently can obtain reliable quantitative measures. For children who have difficulty cooperating, asking the parents to practice vision testing at home (i.e., identify the Lea figures or HOTV optotypes) while covering or patching one eye at a time can help reduce the testing anxiety at the next clinic visit.

In children with OPG, there is no agreed upon definition of clinically significant vision deterioration, yet experienced clinicians consider a VA decrease of 2 Snellen lines below the baseline VA as progression (3). Caution must be applied when children are transitioning between VA testing formats (e.g., Teller grating acuity to Lea or Lea to HOTV). When new visual loss is detected, refractive error, amblyopia, nonorganic visual loss, lack of cooperation, or ocular causes need to be considered before the clinical findings can be attributed to tumor progression. Tumor-related decreases in vision should be reconfirmed by repeat testing within 1–2 weeks before treatment decisions are made. Despite the effort required, VA remains the best clinical measure to monitor disease progression as it has been well studied (20), is relatively reproducible (21), and provides a quantitative, rather than qualitative, measure of visual function with increments that are easily understood as representing visual improvement or decline.

Visual field testing in children can be difficult, and the clinical significance of small field changes in this age group is often unclear (physiologic vs test variability vs lack of cooperation). Nevertheless, testing by confrontation should be attempted at all visits, with transition of more objective methods, such as kinetic or static perimetry, when age-appropriate (typically at least age 10 years in our experience).

When a child is age-appropriate, color vision testing should be performed and is helpful for differentiating amblyopic vision loss from vision loss due to optic neuropathy secondary to OPG progression. Children with amblyopia may have excellent color vision in the amblyopic eye unless VA is extremely poor (e.g., $<$20/400), whereas optic nerve dysfunction from OPG may be characterized by very poor color vision despite reasonably good visual acuity. Pupillary reactivity, ocular ductions, ocular alignment, and the fundi should be evaluated at every visit.

Once a child is diagnosed with an OPG and a decision has been made to observe the child, the frequency of complete neuro-ophthalmologic examinations is guided by age, clinical findings, and presence or absence of NF1 (3). At our institutions, children with a new diagnosis of OPG are examined every 3 months for the first year, then every

6 months. Children with NF1 and an OPG who remain asymptomatic until 8 years of age can then be examined yearly. New or progressive visual loss, an increase in the size and/or enhancement pattern of the presumed OPG, and potential changes in therapy generally warrant an increase in the frequency of examinations.

Other Ophthalmic Testing

Attempts have been made to detect vision loss or correlate VA with visual evoked potentials (VEP) in children with OPGs (22–24); however, in children with visual field loss confirmed by kinetic or automated perimetry, VEP findings frequently overlap between patients with hemianopia and healthy control subjects without visual field defects (22). Median 1F and 2F VEP amplitudes have been correlated to loss of VA in children with OPGs, but in the same subjects also are well correlated to the degree of optic disc pallor on clinical examination (24), suggesting that a careful clinical examination may be just as sensitive as VEP in a majority of children with an OPG. Some authors have suggested that VEPs can be used to detect an OPG in children with (25) and without vision loss (23). Unfortunately, the sensitivity and specificity of this testing technique do not support its use as a screening tool (23,25). It is not certain how much of a change, and in what VEP parameter, defines "worsening" when patients are followed longitudinally (3,26). Therefore, a number of experts recommend against the use of VEPs in this population (3,26).

A recent study from our institution (27) demonstrated a strong relationship between visual function and peripapillary retinal nerve fiber layer (PRNFL) thickness, as measured by optical coherence tomography, in children of 6 years and older with sporadic or NF1-associated OPG. PRNFL thickness was decreased in an overwhelming majority of children who had either abnormal VA and or a visual field defect. Other investigators also have found decreased PRNFL in children with NF1-associated OPGs (28); however, longitudinal studies of younger children with OPGs are needed before PRNFL thickness can be considered a surrogate marker of visual function (29).

NEUROIMAGING FEATURES

MRI of the brain and orbits with thin slices through the optic nerves and chiasm is the standard imaging technique for evaluating the extent of an OPG as well as monitoring for progression. OPGs are typified by diffuse enlargement of the optic nerves (Fig. 2) and/or the chiasm (Fig. 3), sometimes with optic tract (Fig. 4) or optic radiation (Fig. 5) involvement. Optic nerve gliomas usually have a fusiform appearance and can have a downward kink in mid orbit (Fig. 1). In some cases, not only is the nerve itself enlarged but there may be abnormal tissue surrounding the nerve but confined within the nerve sheath due to either extension of the tumor through the pia-arachnoid or arachnoid hypoplasia. In the former instance, the extra-axial intradural tissue may have magnetic resonance characteristics of cerebrospinal fluid ("pseudo-CSF" sign) (30). Chiasmal gliomas, best seen on coronal images, appear as enlargement of the chiasm (Fig. 3) or as a suprasellar mass, occasionally with a cystic component (Fig. 5). They usually are isointense on T1 and isointense to hyperintense on T2 sequences. Gadolinium enhancement and the presence of a cystic component within the tumor are more common in sporadic than in NF1-associated OPGs (17).

To date, there is no correlation between imaging features, including enhancement, and likelihood of tumor progression (5,31). Standard MRI assessment can identify and delineate the extent of tumor but cannot be used to predict the likelihood of tumor progression or change in visual function. Newer imaging techniques, such as perfusion and diffusion-weighted MRI, are being used to evaluate brain tumors for grading, treatment response, and prognosis (32). Diffusion tensor imaging (DTI) assesses the integrity of white matter tracts, including the optic radiations (33). DTI of the optic nerves is challenging, given their small size and risk for patient and eye movements during data acquisition. Despite these limitations, studies in mice and humans have revealed abnormalities in DTI parameters associated with OPGs (34,35).

Although there is extensive literature on the use of positron emission tomography in the management of brain tumors, there is comparatively little on pediatric brain tumors and even less about OPGs (36). One retrospective series (37) reported a correlation between [^{18}F] fluorodeoxyglucose (FDG) uptake and clinical outcome. Another study (38) revealed an association between FDG uptake and the likelihood of an OPG being symptomatic. The authors also reported a decrease in FDG uptake associated with clinical response following treatment in 2 patients. Prospective studies of these newer imaging techniques are needed to evaluate their utility in predicting the clinical behavior of OPGs.

PATHOLOGY/BIOLOGY

Although some authors have suggested that OPGs are hamartomas (39), numerous cases and series that have included histopathology from biopsies or resections clearly demonstrate that OPGs are low-grade gliomas (neoplasms). Juvenile pilocytic astrocytoma is the predominant histology (Fig. 6); however, fibrillary astrocytoma (grade II, WHO) and other low-grade glioma variants are reported as well (40–42). In addition, measurements of proliferation using MIB-1, an antibody to the Ki-67 antigen, reveal that like pilocytic astrocytomas in other brain locations (4,43–45), some OPGs have increased proliferative activity (MIB-1 labeling index of 2%–3%) (46), and this is associated with more aggressive tumor behavior (45,46). High-grade malignant OPGs are rarely seen in childhood. Despite the indolent nature of a large portion of OPGs, particularly in the setting of NF1, and the potential for some of these lesions to regress

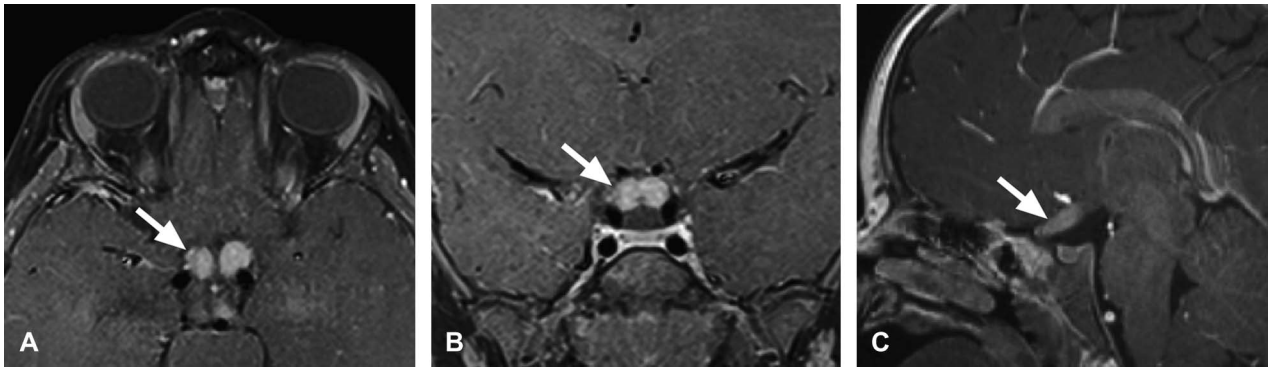

FIG. 3. Contrast-enhanced axial (**A**), coronal (**B**), and sagittal (**C**) MRI demonstrates thickening and enhancement of the junction of the chiasm and intracranial optic nerves (*arrows*) consistent with an OPG.

spontaneously (47), large series with longitudinal follow-up demonstrate clinical and neuroimaging progression of many OPGs, and temporal responses to treatment that far exceed the reported spontaneous regression rate.

Our understanding of the tumorigenesis of low-grade gliomas has only recently begun to emerge. The NF1 gene product neurofibromin is a tumor suppressor and negative regulator of RAS, a protein that promotes cell division. It accelerates the conversion of active guanosine triphosphate bound RAS to inactive guanosine diphosphate bound RAS (48). Lack of functional neurofibromin results in dysregulated RAS signaling with resultant increased cell proliferation and tumor formation. Inactivation of the NF1 gene also results in hyperactivation of the mammalian target of rapamycin (mTOR) via the RAS/PI3K/AKT signaling pathway (49). mTOR is a serine/threonine protein kinase that regulates multiple cell functions, including cell growth and proliferation. Inhibition of mTOR in a mouse model of NF1-related OPG results in a decrease in tumor volume (50). Although activation of mTOR has also been noted in sporadic low-grade gliomas (49), an alternative RAS effector pathway (RAS/RAF/MEK/MAPK) is more likely involved. Through the use of high-throughput, whole genome, single-nucleotide polymorphism microarrays, a small nonrandom duplication in the 7q34 region has been identified in the majority of sporadic pilocytic astrocytomas (51,52). This duplication involves BRAF, a known oncogene that has been implicated in a wide variety of cancers (53), and causes upregulation of the RAS/RAF/MEK/MAPK pathway. BRAF mutations or rearrangements have not been reported in pilocytic astrocytomas from NF1 patients (54).

GROWTH PATTERNS AND PROGNOSIS

The natural history of OPGs is unpredictable because stabilization, progression, and even spontaneous improvement have been documented; however, the following growth patterns and prognostic features have been observed (55):

1. In general, optic nerve gliomas without chiasmal involvement at presentation do not later extend into the chiasm. Reported cases of this phenomenon are rare (56). Removal of an optic nerve glioma to prevent "spread" to the chiasm usually is unnecessary.
2. Anterior gliomas (involving the chiasm and nerve only) likely have a better clinical and neuroimaging prognosis than posterior gliomas involving the chiasm

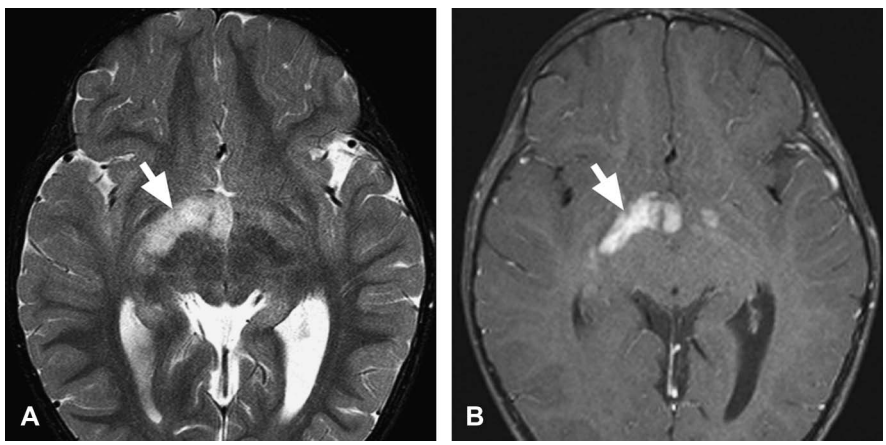

FIG. 4. OPG involving the right optic tract (*arrow*) on T2 axial (**A**) and contrast-enhanced T1 (**B**) MRI.

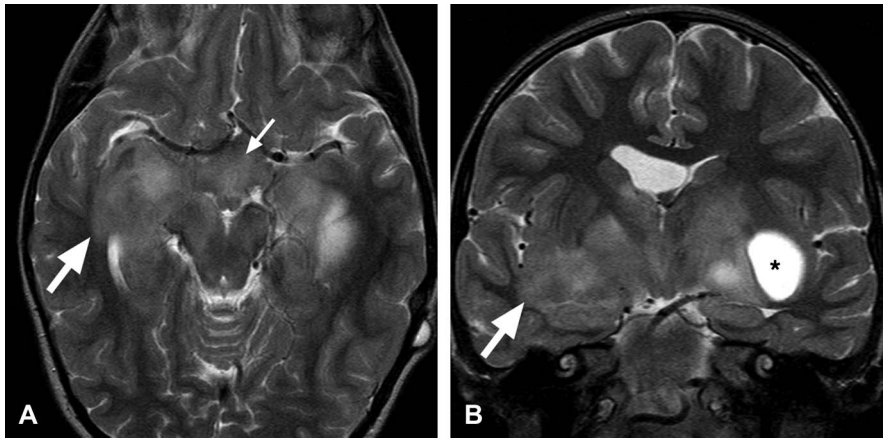

FIG. 5. T2 axial (**A**) and coronal (**B**) MRI in a child with NF1 and a chiasmal glioma (*small arrow*) revealing extension into the optic radiations in the temporal lobes, worse on the right (*large arrows*), and a cyst in the left optic tract (asterisk). Note the compressed temporal horn of the left lateral ventricle can be seen below the cyst.

along with the optic tract or radiation and/or hypothalamus (18).

3. Although uncommon, significant optic radiation involvement can occur in OPGs associated with NF1 (57) (Fig. 5).
4. Compared with sporadic OPGs, NF1-related gliomas are less likely to have visual impairment at diagnosis and are more likely to remain stable over time (5,17,31). In addition, isolated unilateral optic nerve glioma is more commonly associated with NF1 (5,6,17,58), whereas non–NF-1 patients have a higher proportion of tumors involving the chiasm and posterior optic pathway (5,6,17,18,58). Bilateral optic nerve gliomas without chiasmal involvement are virtually diagnostic of NF-1.
5. Younger age was associated with poorer outcome in several studies of OPGs. The age cutoff reported in these studies varied from 1 to 5 years (41,59–61).

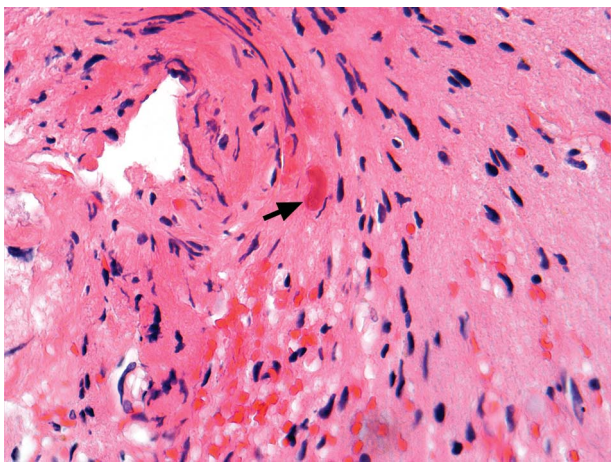

FIG. 6. Biopsy specimen from an OPG demonstrating a Rosenthal fiber (*arrow*) consistent with a juvenile pilocytic astrocytoma (hematoxylin and eosin, ×200).

6. On rare occasions, both NF1-associated and sporadic OPGs have demonstrated spontaneous clinical and neuroimaging improvement (47,62–65). Unfortunately, improvement in the neuroimaging findings is not always associated with an improvement in visual function (47).
7. Only extremely rarely do OPGs metastasize to the subarachnoid space (66,67).
8. Although most children with OPGs who lose vision do so at an early age, typically before 8 years of age, visual deterioration can occur in adolescence and later (9,18).

MANAGEMENT AND TREATMENT

Given the variable natural history of OPGs, initial management in most cases is close observation with serial neuro-ophthalmic and MRI evaluations. Initiating treatment at diagnosis is rarely necessary but may be considered in patients who present with severe visual impairment along with poor prognostic factors (e.g., sporadic OPG, involvement of the optic tracts/radiations).

Treatment usually is reserved for patients with documented progression; however, what constitutes meaningful progression warranting treatment is controversial. A myriad of other treatment indications have been suggested including visual field loss; progressive proptosis; presence of or worsening of optic disc pallor; and tumor location, size, extent, and degree of or increase in enhancement. A recent, large, international, multicenter retrospective study (2) suggests that a decline in VA and tumor progression on MRI are the most common and accepted indications for treatment. As discussed above, an operational definition proposed for the former is a 2-line decrease in VA compared with the prior examination (3). Neuroimaging progression is defined by an increase in tumor size or extension along the optic pathway. Although an increase in tumor enhancement may warrant close monitoring, this finding alone is not an indication for treatment. Optic disc swelling or pallor, as

either may occur without visual loss, is also not by itself an indication for treatment. Several studies reveal a poor correlation between neuroimaging evidence of progression and visual function as well as neuroimaging response to treatment and visual improvement (2,68,69).

Surgery is the primary therapy for pediatric low-grade astrocytomas in most other brain locations (70), and radical resection can result in prolonged stable disease in a majority of OPGs (40,59), yet surgery is rarely appropriate for OPGs because of the risks of further visual compromise as well as the possibility of endocrine deficits and cerebrovascular events associated with surgical removal of chiasmal/hypothalamic tumors. Indications for surgery include resection of large intraorbital optic nerve gliomas for painful or disfiguring proptosis or corneal exposure in patients whose eye has severe impairment of vision. Debulking surgery also may be warranted for large chiasmal/hypothalamic gliomas that exert mass effect on surrounding structures with or without hydrocephalus due to compression of the third ventricle.

Radiotherapy is potentially efficacious for OPGs with reported 10-year progression-free survival (PFS) rates of 66%–90% (71–75); however, in more modern treatment algorithms for OPGs, radiotherapy is avoided in most patients because of the risks of further visual decline (71,72, 74,75), hormone deficits (71,75,76), cerebrovascular disease (77,78), neurocognitive deficits when young children with developing brains are treated (42,74,79), and secondary malignant neoplasms (80). Patients with NF1 are particularly at an increased risk for both cerebrovascular disease and secondary malignant neoplasms (77,78,80,81). Radiation is therefore reserved for children who are older (teenagers) and for younger children who have exhausted chemotherapy options. It is a therapy of last resort for patients with NF1. Newer radiation techniques, including fractionated stereotactic, intensity modulated, and proton beam radiotherapy, are being pursued. Initial reports of these modalities are encouraging (82–84), but long-term follow-up data are required to determine if they mitigate the toxicity of conventional radiotherapy.

Given the risks of surgery and radiotherapy, chemotherapy is the initial treatment for most OPGs. The combination of carboplatin and vincristine is the most common regimen with a 3-year PFS of 77% (85) and 5-year PFS of 69% in patients with NF1 (86). Although carboplatin generally is well tolerated with few serious side effects, hypersensitivity reactions to this drug occur in up to 40% of patients (87,88); fortunately, most of these are mild. In addition, in a large study (>250 subjects) of this regimen, treatment-related mortality and second malignant neoplasms were not seen (86).

The combination of thioguanine, procarbazine, lomustine (CCNU), and vincristine (“TPCV”) is also efficacious. In a direct comparison with carboplatin/vincristine for low-grade gliomas in subjects without NF1, TPCV had a non-significant trend for improved event-free survival (86). TPCV is avoided in patients with NF1 because of the risk of secondary leukemia associated with lomustine and procarbazine as well as an NF1-related underlying predisposition to leukemia (70). Other promising therapies that have been evaluated in smaller studies include cisplatin plus etoposide, the use of which is associated with a 3-year PFS of 73% (89). Given the risk of ototoxicity with cisplatin and the risk of secondary leukemia with etoposide, this regimen should be pursued cautiously in children with OPGs. Temozolomide (90) and vinblastine (91) are both promising as single agents for recurrent/refractory low-grade OPGs and are being evaluated in combination with other agents.

The literature on the efficacy of chemotherapy is dominated by neuroimaging response data rather than visual outcome. Very little is known about neuro-ophthalmic outcomes following chemotherapy. A large, multicenter, retrospective study (2) examined this issue and found that at the completion of chemotherapy (carboplatin/vincristine for most subjects), VA had improved in one third and remained stable in 40% of the subjects. Tumor involvement of the optic tracts and radiations was associated with a significantly worse visual response to chemotherapy, and there was a poor correlation between MRI and visual outcomes.

CONTROVERSIES AND FUTURE DIRECTIONS

MRI screening for OPG in all children with NF1 currently is not recommended. Neuroimaging usually is reserved for those with symptoms or abnormal findings on examination. If it is not possible to obtain a reliable and accurate VA, neuroimaging should be considered.

There has been little progress in therapy for OPGs since Packer et al (85) published their prospective study of carboplatin/vincristine in 1997. However, our developing understanding of the biology of these tumors carries the promise of improved outcomes for this tumor as newer approaches to therapy are being explored. Inhibitors of BRAF, MEK, and mTOR are already in clinical trials. Drugs targeting tumor angiogenesis, such as bevacizumab, have been shown to yield objective responses in recurrent/refractory OPG (92) and are being evaluated in larger studies.

There continues to be little agreement about the indications for initiating treatment of an OPG beyond a decline in VA. This is underlined by the obvious differences in indications for treatment among centers in a retrospective review (2). Although neuroimaging progression is cited frequently, there still are many who believe that this should not drive treatment in the absence of changes in vision. Whether factors such as tumor extent, tumor size, tumor location, visual field deficits, and others should influence the decision to treat remains to be elucidated.

Symptomatic OPGs requiring treatment are relatively uncommon, and the treatment with chemotherapy is considered standard of care at most oncology centers. Therefore, there may never be a natural history study of these tumors, nor will there likely be a masked, controlled, randomized trial

comparing treatment vs no treatment. On the other hand, given the clinical and molecular heterogeneity of OPGs, multicenter collaborative studies, both retrospective and prospective, are still needed to establish evidence-based guidelines for the management of children with these lesions. Oncologists and neuro-ophthalmologists should work more closely so that patients with OPGs may benefit from the combined expertise of physicians in both disciplines.

COMMENTS AND RECOMMENDATIONS

Case 1

The MRI was consistent with an optic nerve glioma, and a biopsy was thought not to be necessary. The patient's VA was mildly reduced, but it was not certain when the vision loss had occurred. She was observed without intervention. Repeat vision testing and neuroimaging 3 months later was unchanged, and the patient will be followed on a regular basis.

Case 2

The MRI characteristics made an optic nerve glioma most likely, so a biopsy was not necessary. The new-onset proptosis, patient history, and moderate rather than severe optic disc pallor suggested a subacute but relatively recent progression of the glioma. Chemotherapy with vincristine and carboplatin was recommended; the goal of treatment was to offer the child a small chance of visual recovery and improvement in proptosis. Shatterproof protective eyewear also was prescribed. Surgical removal to prevent "spread" to the chiasm was not recommended because this growth pattern is rare. If the proptosis worsens and becomes disfiguring or associated with a significant corneal exposure, removal of the intraorbital portion of the optic nerve, but not the eye, would be recommended.

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