

## Optic pathway gliomas: a review

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✓ Optic pathway gliomas represent approximately 3–5% of childhood intracranial tumors. They usually occur in children during the first decade of life and are seen in 11–30% of patients with neurofibromatosis Type 1 (NF1). Although these tumors are typically low-grade gliomas, the clinical course and natural history are highly variable, making treatment paradigms difficult. Overall, however, they are often indolent tumors that can be observed over time for progression without initial treatment, especially in patients with NF1. Chemotherapy is the first-line treatment for progressive tumors, and radiation therapy is reserved for patients with progressive disease who are older than 5–7 years. Surgery is reserved for large tumors causing mass effect or hydrocephalus and tumors confined to the orbit or unilateral optic nerve. (DOI: 10.3171/FOC-07/11/E2)

**KEY WORDS** • hypothalamus glioma • neurofibromatosis Type 1 • optic pathway glioma

**O**PTIC pathway gliomas represent approximately 3–5% of childhood brain tumors<sup>11,12,15,25,28,33,35,74,75,83</sup> and affect 11–30% of children with NF1.<sup>3,28,48,56,64,75,79</sup> When associated with NF1, the tumors are more often benign, can be multifocal and bilateral,<sup>12,15</sup> and are usually found within the optic nerves<sup>74,83</sup> but can occur anywhere along the optic pathway, from the optic nerves to the visual cortex.<sup>54</sup> Chiasmatic gliomas are rarely associated with NF1, often have a more aggressive course, present with diencephalic syndrome (hypersomnia and cachexia), and typically progress.<sup>25,74,83</sup> Overall, 25% of OPGs are confined to the optic disc and nerve, whereas 40–75% involve the chiasm. Of the tumors involving the chiasm, 33–60% are considered posterior lesions that also involve the hypothalamus or third ventricle.<sup>15,22,30,33</sup> Approximately 75% of these tumors are diagnosed during the first decade of life and 60% are diagnosed before the age of 5 years, which also portends a less favorable prognosis.<sup>2,29,33,74,83</sup>

One of the most complete reviews of all cases of OPG was published in 1994 by Dutton,<sup>15</sup> who retrospectively reviewed all cases of OPG reported in the literature up to 1992, which included 2297 patients. Of those patients, age

data were available for 519 patients, and sex data were given for 594. The mean age at diagnosis was 8.8 years, although this included patients treated before the era of CT and MR imaging when diagnosis could be delayed. The mean age of diagnosis may be significantly lower, however, because of the advent and widespread use of CT and MR imaging. In addition, patients with OPGs that invade the hypothalamus typically present at a younger age (often by 1 year of age) with diencephalic syndrome.<sup>15,28</sup> Although their occurrence in younger patients is more common, OPGs have been reported in patients up to 79 years of age.<sup>15</sup> The male-to-female predilection is roughly equal,<sup>15,29</sup> although there are some data that suggest that OPGs limited to the optic nerves are more common in girls.<sup>15</sup> Although the incidence of OPGs in patients with NF1 is greater than that in the general population, not all patients with NF1 are screened for OPGs, and many OPGs can remain asymptomatic. Therefore, the incidence of OPGs in the NF1 population may, in fact, be underestimated.<sup>28</sup>

### Presentation

Patients with OPG may be asymptomatic or may present with symptoms that vary depending on location. For instance, patients with a tumor of the nerve within the orbit may have proptosis, strabismus, or visual loss, whereas patients with intracranial tumors can present with visual loss,

Abbreviations used in this paper: CSF = cerebrospinal fluid; CT = computed tomography; MR = magnetic resonance; NF1 = neurofibromatosis Type 1; OPG = optic pathway glioma; PFS = progression-free survival.

endocrine/hypothalamic disturbance, spasmus nutans, and obstructive hydrocephalus.<sup>3,28,48</sup> In addition, Grill et al.<sup>23</sup> found that the presentation depended on whether the patient had NF1. In their series, proptosis was significantly more frequent in patients with NF1 (21.5%) than in those without (5.5%), whereas patients without NF1 were more likely to present with nystagmus and hydrocephalus. These authors also found that diencephalic syndrome was seen only in children younger than 4 years of age, whereas precocious puberty was seen only in patients older than 4 years.

Overall, the most frequent clinical presentation of OPG is that of diminished vision and, in those cases in which tumor is confined to the optic nerve, proptosis.<sup>28</sup> The NF1 OPG Task Force recommends yearly eye examinations in children with asymptomatic NF1 through the age of 6 years,<sup>38,41–47,79</sup> whereas other authors recommend screening up to 10 years of age.<sup>19,34,41–47</sup> This is true even in patients with NF1 and no findings on imaging studies, given that OPGs can become apparent even though previously obtained images did not reveal any findings.<sup>53</sup> In addition, because children may present with precocious puberty and accelerated linear growth, accurate growth charts are essential in patients with NF1.<sup>45</sup>

### Monitoring of Visual Function

Patients with known OPGs are typically serially screened for progressive visual loss. Visual acuity is thought to be the most reliable test; however, in children younger than 6 years (the most common group to present with OPGs), this can be inaccurate. Visual evoked potentials have also been used to evaluate OPG progression.<sup>58,81</sup> Because visual evoked potentials measure the integrity of the visual pathway rather than actual visual function, however, they are difficult to interpret and are not recommended as a screening tool.<sup>45</sup>

### Diagnostic Imaging

Diagnosis is confirmed with modern imaging. Although once the standard of care, biopsy of suspected lesions is no longer warranted for lesions with characteristic imaging features, and it is now used only in cases with unusual clinical or imaging findings.<sup>40,65</sup> When imaging is not clearly indicative of OPG, biopsy may become a consideration for definitive diagnosis. The classic finding on plain radiographs is enlargement of the optic canals and a J-shaped sella turcica. This is seen in 65–85% of patients with tumors of the optic nerves.<sup>18</sup> When tumor is confined to the optic nerves, CT imaging demonstrates well-demarcated enlargement of the nerve, often with a tortuous or kinked appearance of the nerves.<sup>15,65</sup> Tumors of the chiasm exhibit a variety of appearances, from an enlargement of the chiasm to a suprasellar mass that may calcify.<sup>65</sup> The tumor is usually isodense to brain, and contrast enhancement is variable.

Although OPGs may be readily apparent on CT scanning, MR imaging is the preferred method of imaging. Typical MR imaging findings include the appearance of an iso- to hypointense lesion on T1-weighted images, with hyperintensity seen on T2-weighted sequences and homog-

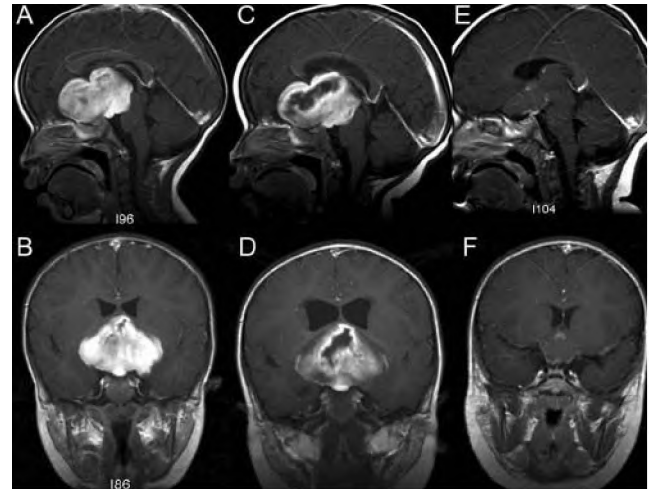


FIG. 1. Magnetic resonance images obtained in a 19-month-old girl who presented with failure to thrive, visual loss, and horizontal rotatory and pendular nystagmus from a biopsy-proven optic pathway juvenile pilocytic astrocytoma. Sagittal (A) and coronal (B) Gd-enhanced T1-weighted images. The patient was started on chemotherapy treatment. Follow-up sagittal (C) and coronal (D) T1-weighted Gd-enhanced images demonstrating decreased central enhancement of the tumor and increased hydrocephalus requiring a ventriculoperitoneal shunt to be placed on the left side. Two more courses of chemotherapy were administered. Follow-up sagittal (E) and coronal (F) images obtained 15 months post-chemotherapy, showing a significant decrease in tumor size and minimal tumor enhancement with resolution of hydrocephalus.

eneous enhancement with Gd administration (Figs. 1–3).<sup>15,28,68,72</sup> Some authors have described detailed MR imaging findings in patients with NF1, including bilateral tumors with circumferential growth and downward kinking of the intraorbital segment of the optic nerve.<sup>15,65</sup> In addition, the double intensity or pseudo-CSF signal is characteristic in NF1.<sup>15,65</sup> This consists of a hyperintense core on T1-weighted images, surrounded by lower signal intensity. On T2-weighted images, the inverse is seen. Furthermore, patients with NF1 are more likely to demonstrate glioma extension along the optic tracts into the lateral geniculate ganglia and temporal lobes<sup>18,73</sup> as well as infiltrating lesions.<sup>25</sup> Hydrocephalus may be apparent for large tumors that obstruct CSF outflow (Figs. 1 and 3).

Magnetic resonance imaging is also the modality of choice for monitoring progression or treatment response. Positron emission tomography technology has also been shown to be useful for monitoring progression and treatment response in OPGs and may actually be found to change more quickly than MR imaging.<sup>64</sup>

### Pathological Findings

Histologically, OPGs are typically low-grade gliomas; both pilocytic and fibrillary astrocytomas have been reported,<sup>25,74,83</sup> although the majority of tumors are pilocytic.<sup>15</sup> Pilocytic astrocytomas classically have a biphasic pattern with characteristic Rosenthal fibers and eosinophilic granular bodies. In contrast, a relatively new subgroup of OPGs has been defined: pilomyxoid astrocytomas (Fig. 4). These tumors demonstrate piloid cells in a loose fibrillary and

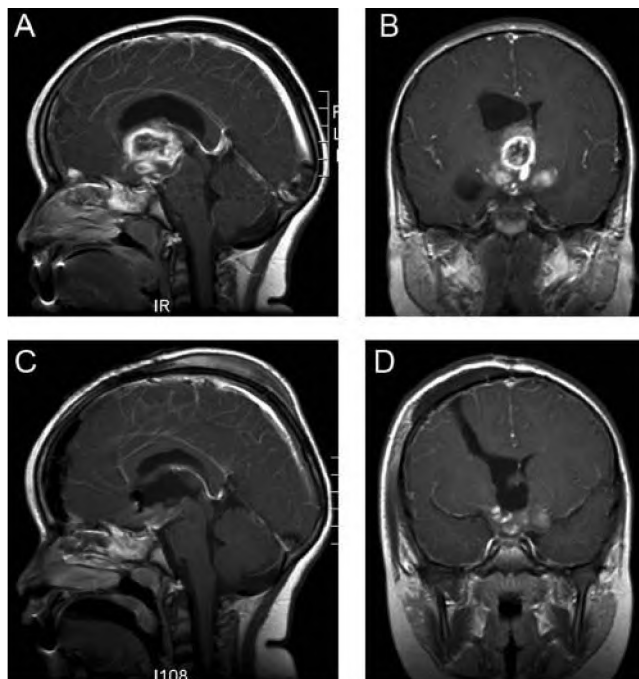


FIG. 2. Magnetic resonance images. Two years after the final images in Fig. 1 were obtained, the same patient presented with headaches and worsening vision. Sagittal (A) and coronal (B) T1-weighted Gd-enhanced images demonstrating recurrent tumor growth and enhancement obstructing the third ventricle resulting in unilateral right-sided hydrocephalus. A right frontal transventricular approach to the lateral and third ventricle was performed. Tumor debulking was performed to open the CSF pathways, thus avoiding a second shunt placement (see Video Clip). Sagittal (C) and coronal (D) postoperative images showing removal of the third ventricular portion of tumor and resolution of hydrocephalus. There is residual tumor in the optic apparatus and hypothalamus. [Click here for Windows and here for Real Player.]

myxoid background. They lack Rosenthal fibers and reveal only rare eosinophilic granular bodies.<sup>35</sup> Pilomyxoid astrocytomas were once classified with pilocytic astrocytomas but are a distinct entity with more aggressive behavior.<sup>35,36</sup> In the series reported by Komotar et al.,<sup>35</sup> 14% of patients with pilomyxoid astrocytomas presented with CSF dissemination, whereas no patients with pilocytic astrocytomas had CSF spread. The mean age at presentation for pilomyxoid astrocytoma is also much younger (18 months).<sup>35</sup> Tumors can exhibit either a perineural or an intraneural growth pattern. Patients with NF1 are more likely to have a perineural pattern, whereas patients without NF1 predominantly have an intraneural growth pattern.<sup>15</sup> Although in the past some authors advocated that OPGs are little more than hamartomatous growths of the optic nerves, this theory has fallen out of favor based on histological features, invasion, and ability to undergo malignant transformation.<sup>15</sup> Enlargement is usually the result of cystic degeneration, hemorrhage, or accumulation of mucus.

### Treatment of OPGs

The treatment of OPG is divided into observation, chemotherapy, radiation therapy, and surgery. In patients who

are asymptomatic and have smaller tumors, careful observation may be considered. However, patients presenting with symptoms of visual loss, endocrine disturbance, hydrocephalus, or mass effect may require aggressive intervention. Historically, radiation therapy was the treatment of choice for OPGs, but this modality has fallen out of favor as first-line therapy for OPGs in young children because of the cognitive and endocrine disturbances, as well as radiation-induced complications such as secondary tumors and moyamoya disease in patients with NF1.<sup>9,14,32,70,71</sup> Astrup<sup>5</sup> advocated observation for newly diagnosed OPG, resection for progressive intraorbital tumors, radiotherapy for progressive chiasmatic tumors in older children, and chemotherapy in children younger than 5 years. He also advocated surgery for some exophytic chiasmatic tumors.

### Surgery for OPGs

The role of surgery in the treatment of OPG is controversial. Complete tumor resection is only realistic when the tumor is limited to one optic nerve because the procedure causes blindness. Although surgical debulking of the tumor has not been found to affect overall survival, partial debulking may be useful in some cases in which the tumor causes mass effect or obstructive hydrocephalus. In the latter case, the goal of surgical debulking is to open up CSF pathways, thereby avoiding shunt placement (Fig. 2; see Video Clip). Therefore, contemporary indications for surgery include single nerve involvement causing progressive, disfiguring proptosis, blindness, or both, or exophytic chiasmatic tumors causing mass effect or hydrocephalus.<sup>2,5,54,55</sup> Surgery is contraindicated in patients with infiltrative tumors. Although authors of numerous case reports have described spontaneous regression of OPG after surgical debulking or biopsy without additional postoperative adjuvant therapy,<sup>25,28,54,55,84,85</sup> it is unclear whether spontaneous regression might have occurred without any treatment at all, which has also been well-reported.<sup>63,66</sup> In 2006, Ahn et al.<sup>2</sup> retrospectively reviewed a series of 33 patients with OPGs who had undergone surgery over a 17-year period. They found that radical removal of OPGs was of no survival benefit and that it did not reduce endocrine complications. They found it to be a benefit, however, in controlling hydrocephalus and in postponing radiation treatment in younger children. Wisoff<sup>83</sup> also advocated surgery if feasible to postpone radiation therapy in young children to limit radiation-induced side effects; however, the usefulness of surgery to postpone radiation is also questionable. For example, the authors of one study found no advantage to partial resection over chemotherapy alone in patients younger than 3 years of age.<sup>73</sup> In addition, the cognitive effects of open craniotomy for tumor must be considered.<sup>10</sup>

The extent of resection and type of adjuvant therapy do not seem to influence PFS or overall survival in patients with pilomyxoid astrocytoma compared with survival of patients with pilocytic astrocytoma. The less favorable prognosis of the pilomyxoid astrocytoma tumor type seems related to the pathological features rather than type of treatment.<sup>35</sup>

Patients with NF1 represent a different subgroup of patients with OPGs. Patients with NF1 tend to have more diffuse disease, and surgical intervention tends to fail in them at a rate almost twice that of their counterparts without

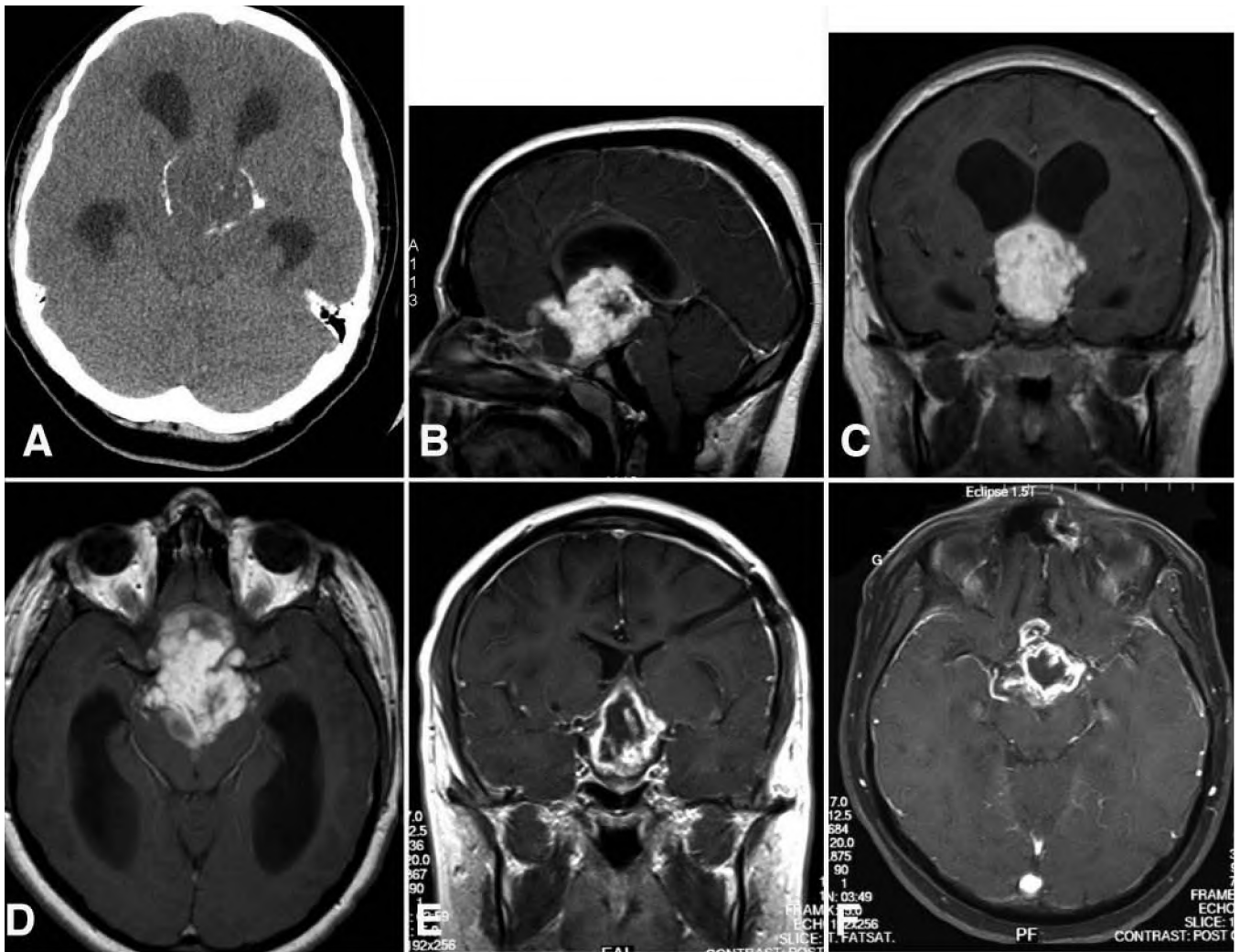


FIG. 3. A 5-year-old boy presented with visual loss and hydrocephalus. A CT scan (A) demonstrating a suprasellar mass with peripheral rim of calcification suggestive of a craniopharyngioma. Sagittal (B), coronal (C), and axial (D) T1-weighted Gd-enhanced MR images demonstrating a brightly enhancing OPG involving the optic chiasm and hypothalamus filling the third ventricle. A ventriculoperitoneal shunt was placed for hydrocephalus and chemotherapy was initiated for the tumor. Coronal (E) and axial (F) MR images obtained 15 months after treatment, showing a decrease in tumor size and central enhancement.

NF1.<sup>4,13,28,78</sup> In addition, although they may develop sizable lesions, the tumors rarely progress after the patient is 6 years old.<sup>23,28</sup> Therefore, surgery is typically not warranted in patients with NF1. However, in patients with NF1 who have only optic nerve involvement, Jenkin et al.<sup>30</sup> reported 92% survival at 15 years after complete resection. Lesions posterior to the chiasm had a much lower relapse-free survival rate of 41% at 10 years.

#### *Chemotherapy for OPGs*

Although no single chemotherapeutic agent has been identified as primary treatment, chemotherapy is considered first-line therapy for OPGs that are symptomatic (such as visual loss, pituitary dysfunction, and hypothalamic dysfunction). It can treat tumors that have gone beyond the observation stage, even in young children, without the long-term cognitive and neuroendocrine sequelae seen with

surgery and radiation therapy.<sup>7,28</sup> Because of this, chemotherapy is the primary treatment modality in children younger than 3 years of age with progressive or symptomatic disease.<sup>28</sup> Agents including carboplatin, cisplatin, vincristine, vinblastine, actinomycin D, lomustine, thioguanine, procarbazine, etoposide, tamoxifen, and temozolomide either as first-line treatment or adjuvant treatment have all been used;<sup>24,28</sup> however, the most widely used regimens stems from reports published by Packer and colleagues.<sup>61,62</sup> They treated patients who had newly diagnosed low-grade gliomas and patients with recurrent disease. Their regimen of concurrent carboplatin and vincristine in a 10-week induction phase, followed by 48 weeks of maintenance carboplatin/vincristine, resulted in a PFS of 75% at 2 years and 50% at 5 years. In addition, they reported imaging evidence of tumor shrinkage in 63% of patients. Children 5 years of age or younger had a notably more favorable rate of response.

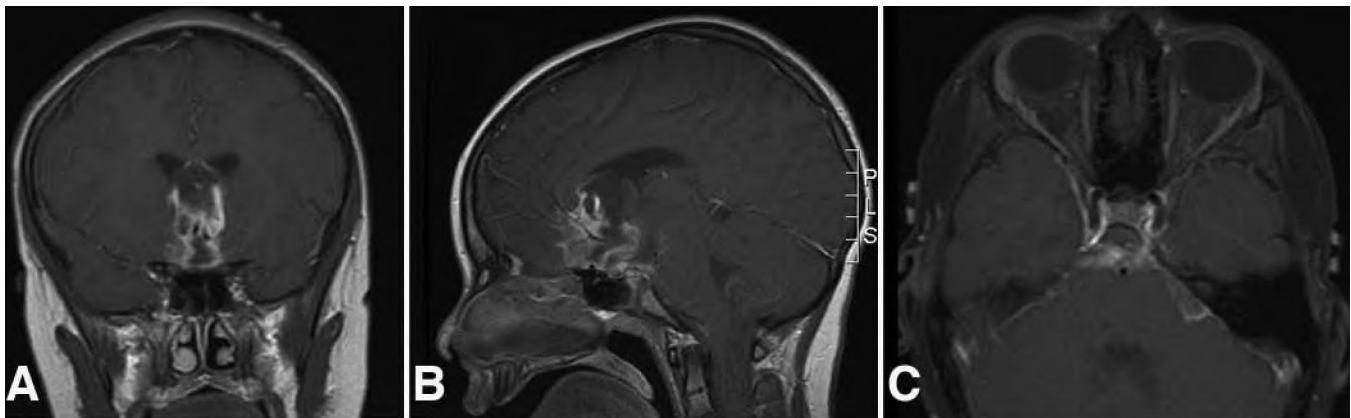


FIG. 4. A 9-year-old boy presented with precocious puberty, headaches, and diabetes insipidus. Magnetic resonance images reveal a poorly circumscribed, partially hemorrhagic mass centered in the hypothalamus. A and B: Prominent seeding of the basilar cisterns is noted. C: A biopsy revealed pilomyxoid astrocytoma.

More recently, Massimino et al.<sup>52</sup> reported a 78% PFS over 3 years with cisplatin and etoposide, with improved visual acuity in most patients and acceptable toxicity profiles. Temozolomide has also been shown to be useful in stabilizing disease in more than 50% of patients without significant toxicity<sup>26</sup> and is considered an option in patients with progressive OPG in whom first-line therapy has failed. Petronio et al.<sup>67</sup> addressed the use of a 5-drug regimen consisting of 6-thioguanine, procarbazine, dibromodulcitol, lomustine, and vincristine for treatment of OPG, and they obtained favorable results. A similar regimen in which dibromodulcitol was excluded was compared with the standard regimen of carboplatin and vincristine in 2003 and was deemed a reasonable second-line therapy for patients with OPG.<sup>39</sup> Although other chemotherapy regimens have demonstrated efficacy against low-grade gliomas, the Packer regimen remains the most commonly used course of therapy.<sup>31,37,50,57,60</sup>

#### Radiotherapy for OPGs

In 1956, Taveras et al.<sup>77</sup> cited a role for radiation therapy for treatment of OPG, based on the results from 34 patients treated primarily with radiotherapy. As a result, radiation has played a major role in the management of OPGs. Currently, however, radiation therapy is reserved for treatment of progressive OPG in children older than 5–7 years of age,<sup>45,82</sup> despite the lack of randomized trials comparing radiation therapy with other treatment modalities. Authors of many studies have demonstrated no benefit of radiation therapy over observation or surgery on 10-year progression rates, long-term survival, or preservation of sight.<sup>15,20,30,69</sup> However, external-beam radiation therapy has been associated with good visual outcomes and tumor-free progression rates in other series.<sup>17,76</sup> In addition, new techniques of delivering radiation, including stereotactic radiosurgery and proton beam radiotherapy, have been developed.<sup>18</sup> Stereotactic conformal radiotherapy has been associated with a 79% 5-year survival rate without the cognitive or endocrine disturbances associated with traditional external-beam radiation therapy.<sup>11,51,65</sup> Proton beam therapy is an attractive option for radiation therapy, as it is able to provide high doses of radiation to the lesion with sharp fall-off of ener-

gy within millimeters of the treatment area. In small series, it has been found to be well tolerated; however, it is not widely available to patients and has not proven to be superior to standard techniques.<sup>27,65</sup> Current recommendations state that children younger than 7 years of age should receive chemotherapy as first-line treatment. Children between the ages of 7 and 10 years fit into a gray zone of patients who may or may not warrant radiation therapy, and patients older than 10 years should be treated with 45–50 Gy in fractions of 160–200 cGy each.<sup>16,21,26,28</sup>

#### Prognosis

The natural history of OPGs is highly variable based not only on the histological findings but also on the presence or absence of NF1 and also differences in each patient. Most series investigating this topic have been retrospective, have covered large time frames in which treatment modalities change, or have involved small numbers of patients because of the infrequency of the lesion. Overall, however, OPGs tend to be low-grade and slow-growing with long patient survival.<sup>35,65</sup> In addition, the presence of NF1 and an anterior location are associated with a more favorable prognosis,<sup>23,80</sup> whereas younger age at presentation is associated with a poorer prognosis.<sup>2,29,33,59,74,83</sup>

Most patients with OPG have an indolent or even asymptomatic course. Survival for OPGs confined to the optic nerve is close to 100%. Chiasm involvement and particularly hypothalamic involvement are associated with a decreased rate of survival, although survival is still > 90% for treated and untreated tumors.<sup>65,80</sup> Even patients with progressive disease have good survival rates.<sup>1,8,65</sup> In 2003, Tow et al.<sup>80</sup> studied the morbidity and mortality rates in a cohort of OPG patients with and without NF1, both treated and untreated, who were observed for at least 10 years. Most of the patients who were not treated had NF1 and survived, and they had better visual outcomes than their treated counterparts.<sup>80</sup> This guided the recommendation that OPGs should not be treated unless they demonstrate clear disease progression. Another argument for observing patients with newly diagnosed OPGs is the fact that spontaneous regression without treatment has been well documented in patients with and those without NF1.<sup>25,48,49,63,65,66</sup>

In a major review of 1136 cases for which treatment data were available, Dutton<sup>15</sup> found that 40% of patients with OPGs of the anterior visual pathway experienced progression or recurrence. Over a 12-year follow-up period, 33% of patients died. The authors of other series have found mortality rates up to 50% with 20-year follow-up. In addition, Dutton found that 21% of patients presented with 20/40 or better vision and 45% with 20/200 or better vision. Accordingly, only 21% of patients experience progressive visual loss, and some patients improve.<sup>15</sup>

For patients with tumor confined to the optic nerve who underwent tumor resection, with or without radiation therapy, Dutton<sup>15</sup> found a 0% tumor-related mortality rate. Of patients with tumor confined to the optic nerve who were observed without treatment, 21% exhibited progression, 5% died of tumor-related causes, and 91% maintained stable vision.<sup>15</sup>

Patients with chiasmatic gliomas evaluated in the review by Dutton<sup>15</sup> demonstrated a 42% rate of progression, 29% tumor-related mortality, and a rate of stable visual acuity of 77%. Treatment did not seem to change these percentages. Dutton found that patients who presented with hypothalamic or third ventricle involvement fared much worse than other patients, especially if hydrocephalus was present. The tumor-related mortality rate in this group was 43%, with a 51% rate of recurrence/progression, although the prognosis for vision was similar to that of the chiasmatic tumor group, with 71% exhibiting stable vision.<sup>15</sup>

The subgroup of patients with pilomyxoid astrocytoma typically demonstrates a higher rate of local tumor recurrence (75% compared with 50%) and CSF dissemination (14% compared with 0% in this series) than patients with pilocytic astrocytoma.<sup>35</sup> In the series by Komotar et al.,<sup>35</sup> overall survival for patients with pilomyxoid astrocytoma was 63 months compared with 213 months in patients with pilocytic astrocytoma.

Finally, there is some evidence that increased microvessel density as a marker of vascularity and angiogenesis is associated with shorter PFS in patients with OPGs.<sup>6</sup>

## Conclusions

Optic pathway gliomas are true neoplasms found anywhere along the optic pathway, and they occur primarily in children. These tumors are typically slow growing, usually present with visual decline that stabilizes over time, and can often be observed clinically without treatment. However, the natural history is often unpredictable. When tumor is confined to one optic nerve, surgery is often the treatment of choice. Chemotherapy is first-line treatment for most other OPGs, followed by radiation treatment for older children with progressive disease. The overall prognosis is variable but typically favorable in children with pilocytic histology. Patients with pilomyxoid histology may have a more aggressive course.

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## References

1. Aarabi B, Long DM, Miller NR: Enlarging optic chiasmal glioma with stable visual acuity. *Surg Neurol* **10**:175–177, 1978
2. Ahn Y, Cho BK, Kim SK, Chung YN, Lee CS, Kim IH, et al: Optic pathway glioma: outcome and prognostic factors in a surgical series. *Childs Nerv Syst* **22**:1136–1142, 2006
3. Allen JC: Initial management of children with hypothalamic and thalamic tumors and the modifying role of neurofibromatosis-1. *Pediatr Neurosurg* **32**:154–162, 2000
4. Alvord EC Jr, Lofton S: Gliomas of the optic nerve or chiasm. Outcome by patients' age, tumor site, and treatment. *J Neurosurg* **68**:85–98, 1988
5. Astrup J: Natural history and clinical management of optic pathway glioma. *Br J Neurosurg* **17**:327–335, 2003
6. Bartels U, Hawkins C, Jing M, Ho M, Dirks P, Rutka J, et al: Vascularity and angiogenesis as predictors of growth in optic pathway/hypothalamic gliomas. *J Neurosurg* **104** (5 Suppl):314–320, 2006
7. Bianchi-Marzoli S, Brancato R: Tumors of the optic nerve and chiasm. *Curr Opin Ophthalmol* **5**:11–17, 1994
8. Borit A, Richardson EP Jr: The biological and clinical behaviour of pilocytic astrocytomas of the optic pathways. *Brain* **105**:161–187, 1982
9. Capo H, Kupersmith MJ: Efficacy and complications of radiotherapy of anterior visual pathway tumors. *Neurol Clin* **9**:179–203, 1991
10. Carpentieri SC, Waber DP, Pomeroy SL, Scott RM, Goumnerova LC, Kieran MW, et al: Neuropsychological functioning after surgery in children treated for brain tumor. *Neurosurgery* **52**:1348–1357, 2003
11. Combs SE, Schulz-Ertner D, Moschos D, Thilmann C, Huber PE, Debus J: Fractionated stereotactic radiotherapy of optic pathway gliomas: tolerance and long-term outcome. *Int J Radiat Oncol Biol Phys* **62**:814–819, 2005
12. Czyzyk E, Józwiak S, Roszkowski M, Schwartz RA: Optic pathway gliomas in children with and without neurofibromatosis 1. *J Child Neurol* **18**:471–478, 2003
13. Deliganis AV, Geyer JR, Berger MS: Prognostic significance of type 1 neurofibromatosis (von Recklinghausen Disease) in childhood optic glioma. *Neurosurgery* **38**:1114–1119, 1996
14. Desai SS, Paulino AC, Mai WY, Teh BS: Radiation-induced moyamoya syndrome. *Int J Radiat Oncol Biol Phys* **65**:1222–1227, 2006
15. Dutton JJ: Gliomas of the anterior visual pathway. *Surv Ophthalmol* **38**:427–452, 1994
16. Erkal HS, Serin M, Cakmak A: Management of optic pathway and chiasmatic-hypothalamic gliomas in children with radiation therapy. *Radiother Oncol* **45**:11–15, 1997
17. Flickinger JC, Torres C, Deutsch M: Management of low-grade gliomas of the optic nerve and chiasm. *Cancer* **61**:635–642, 1988
18. Fuss M, Hug EB, Schaefer RA, Nevinny-Stickel M, Miller DW, Slater JM, et al: Proton radiation therapy (PRT) for pediatric optic pathway gliomas: comparison with 3D planned conventional photons and a standard photon technique. *Int J Radiat Oncol Biol Phys* **45**:1117–1126, 1999
19. Gayre GS, Scott IU, Feuer W, Saunders TG, Siatkowski RM: Long-term visual outcome in patients with anterior visual pathway gliomas. *J Neuroophthalmol* **21**:1–7, 2001
20. Glaser JS, Hoyt WF, Corbett J: Visual morbidity with chiasmatic glioma. Long-term studies of visual fields in untreated and irradiated cases. *Arch Ophthalmol* **85**:3–12, 1971
21. Grabenbauer GG, Schuchardt U, Buchfelder M, Rodel CM, Gusek G, Marx M, et al: Radiation therapy of optico-hypothalamic gliomas (OHG)—radiographic response, vision and late toxicity. *Radiother Oncol* **54**:239–245, 2000
22. Grill J, Couanet D, Cappelli C, Habrand JL, Rodriguez D, Sainte-Rose C, et al: Radiation-induced cerebral vasculopathy in children

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- with neurofibromatosis and optic pathway glioma. **Ann Neurol** **45**:393–396, 1999
23. Grill J, Laithier V, Rodriguez D, Raquin MA, Pierre-Kahn A, Kalifa C: When do children with optic pathway tumors need treatment? An oncological perspective in 106 patients treated in a single centre. **Eur J Pediatr** **159**:692–696, 2000
  24. Gururangan S, Fisher MJ, Allen JC, Hemdon JE II, Quinn JA, Reardon DA, et al: Temozolomide in children with progressive low-grade glioma. **Neuro Oncol** **9**:161–168, 2007
  25. Hoffman HJ, Humphreys RP, Drake JM, Rutka JT, Becker LE, Jenkin D, et al: Optic pathway/hypothalamic gliomas: a dilemma in management. **Pediatr Neurosurg** **19**:186–195, 1993
  26. Horwich A, Bloom HJ: Optic gliomas: radiation therapy and prognosis. **Int J Radiat Oncol Biol Phys** **11**:1067–1079, 1985
  27. Hug EB, Muenter MW, Archambeau JO, DeVries A, Liwnicz B, Loredon LN, et al: Conformal proton radiation therapy for pediatric low-grade astrocytomas. **Strahlenther Onkol** **178**:10–17, 2002
  28. Jahraus CD, Tarbell NJ: Optic pathway gliomas. **Pediatr Blood Cancer** **46**:586–596, 2006
  29. Janss AJ, Grundy R, Cnaan A, Savino PJ, Packer RJ, Zackai EH, et al: Optic pathway and hypothalamic/chiasmatic gliomas in children younger than age 5 years with a 6-year follow-up. **Cancer** **75**:1051–1059, 1995
  30. Jenkin D, Angyalfi S, Becker L, Berry M, Buncic R, Chan H, et al: Optic glioma in children: surveillance, resection, or irradiation? **Int J Radiat Oncol Biol Phys** **25**:215–225, 1993
  31. Kadota RP, Kun LE, Langston JW, Burger PC, Cohen ME, Mahoney DH, et al: Cyclophosphamide for the treatment of progressive low-grade astrocytoma: a Pediatric Oncology Group phase II Study. **J Pediatr Hematol Oncol** **21**:198–202, 1999
  32. Kestle JR, Hoffman HJ, Mock AR: Moyamoya phenomenon after radiation for optic glioma. **J Neurosurg** **79**:32–35, 1993
  33. Khafaga Y, Hassounah M, Kandil A, Kanaan I, Allam A, El Hussein G, et al: Optic gliomas: a retrospective analysis of 50 cases. **Int J Radiat Oncol Biol Phys** **56**:807–812, 2003
  34. King A, Listernick R, Charrow J, Piersall L, Gutmann DH: Optic pathway gliomas in neurofibromatosis type 1: the effect of presenting symptoms on outcome. **Am J Med Genet A** **122**:95–99, 2003
  35. Komotar RJ, Burger PC, Carson BS, Brem H, Olivi A, Goldthwaite PT, et al: Pilocytic and pilomyxoid hypothalamic/chiasmatic astrocytomas. **Neurosurgery** **54**:72–80, 2004
  36. Komotar RJ, Mocco J, Jones JE, Zacharia BE, Tihan T, Feldstein NA, et al: Pilomyxoid astrocytoma: diagnosis, prognosis, and management. **Neurosurg Focus** **18(6A)**:E7, 2005
  37. Lacaze E, Kieffer V, Streri A, Lorenzi C, Gentaz E, Habrand JL, et al: Neuropsychological outcome in children with optic pathway tumors when first-line treatment is chemotherapy. **Br J Cancer** **89**:2038–2044, 2003
  38. Lama G, Esposito Salsano M, Grassia C, Calabrese E, Grassia MG, Bismuto R, et al: Neurofibromatosis type 1 and optic pathway glioma. A long-term follow-up. **Minerva Pediatr** **59**:13–21, 2007
  39. Lancaster DL, Hoddes JA, Michalski A: Tolerance of nitrosurea-based multiagent chemotherapy regime for low-grade pediatric gliomas. **J Neurooncol** **63**:289–294, 2003
  40. Leonard JR, Perry A, Rubin JB, King AA, Chicoine MR, Gutmann DH: The role of surgical biopsy in the diagnosis of glioma in individuals with neurofibromatosis-1. **Neurology** **67**:1509–1512, 2006
  41. Listernick R, Charrow J, Greenwald M, Mets M: Natural history of optic pathway tumors in children with neurofibromatosis type 1: a longitudinal study. **J Pediatr** **125**:63–66, 1994
  42. Listernick R, Charrow J, Gutmann DH: Comments on neurofibromatosis 1 and optic pathway tumors. **Am J Med Genet** **102**:105, 2001
  43. Listernick R, Charrow J, Gutmann DH: Intracranial gliomas in neurofibromatosis type 1. **Am J Med Genet** **89**:38–44, 1999
  44. Listernick R, Darling C, Greenwald M, Strauss L, Charrow J: Optic pathway tumors in children: the effect of neurofibromatosis type 1 on clinical manifestations and natural history. **J Pediatr** **127**:718–722, 1995
  45. Listernick R, Ferner RE, Liu GT, Gutmann DH: Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. **Ann Neurol** **61**:189–198, 2007
  46. Listernick R, Ferner RE, Piersall L, Sharif S, Gutmann DH, Charrow J: Late-onset optic pathway tumors in children with neurofibromatosis 1. **Neurology** **63**:1944–1946, 2004
  47. Listernick R, Louis DN, Packer RJ, Gutmann DH: Optic pathway gliomas in children with neurofibromatosis 1: consensus statement from the NF1 Optic Pathway Glioma Task Force. **Ann Neurol** **41**:143–149, 1997
  48. Liu GT: Optic gliomas of the anterior visual pathway. **Curr Opin Ophthalmol** **17**:427–431, 2006
  49. Liu GT, Brodsky MC, Phillips PC, Belasco J, Janss A, Golden JC, et al: Optic radiation involvement in optic pathway gliomas in neurofibromatosis. **Am J Ophthalmol** **137**:407–414, 2004
  50. Mahoney DH Jr, Cohen ME, Friedman HS, Kepner JL, Gerner L, Langston JW, et al: Carboplatin is effective therapy for young children with progressive optic pathway tumors: a Pediatric Oncology Group phase II study. **Neuro Oncol** **2**:213–220, 2000
  51. Marcus KJ, Goumnerova L, Billett AL, Lavally B, Scott RM, Bishop K, et al: Stereotactic radiotherapy for localized low-grade gliomas in children: final results of a prospective trial. **Int J Radiat Oncol Biol Phys** **61**:374–379, 2005
  52. Massimino M, Spreafico F, Cefalo G, Riccardi R, Tesoro-Tess JD, Gandola L, et al: High response rate to cisplatin/etoposide regimen in childhood low-grade glioma. **J Clin Oncol** **20**:4209–4216, 2002
  53. Massry GG, Morgan CF, Chung SM: Evidence of optic pathway gliomas after previously negative neuroimaging. **Ophthalmology** **104**:930–935, 1997
  54. Medlock MD, Madsen JR, Barnes PD, Anthony DS, Cohen LE, Scott RM: Optic chiasm astrocytomas of childhood. 1. Long-term follow-up. **Pediatr Neurosurg** **27**:121–128, 1997
  55. Medlock MD, Scott RM: Optic chiasm astrocytomas of childhood. 2. Surgical management. **Pediatr Neurosurg** **27**:129–136, 1997
  56. Menor F, Martí-Bonmatí L, Mulas F, Cortina H, Olagüe R: Imaging considerations of central nervous system manifestations in pediatric patients with neurofibromatosis type 1. **Pediatr Radiol** **21**:389–394, 1991
  57. Moghrabi A, Friedman HS, Ashley DM, Bottom KS, Kerby T, Stewart E, et al: Phase II study of carboplatin (CBDCA) in progressive low-grade gliomas. **Neurosurg Focus** **4(4)**:E3, 1998
  58. Ng YT, North KN: Visual-evoked potentials in the assessment of optic gliomas. **Pediatr Neurol** **24**:44–48, 2001
  59. Opocher E, Kremer LC, Da Dalt L, van de Wetering MD, Viscardi E, Caron HN, et al: Prognostic factors for progression of childhood optic pathway glioma: a systematic review. **Eur J Cancer** **42**:1807–1816, 2006
  60. Osztie E, Várallyay P, Doolittle ND, Lacy C, Jones G, Nickolson HS, et al: Combined intraarterial carboplatin, intraarterial etoposide phosphate, and IV Cytosan chemotherapy for progressive optic-hypothalamic gliomas in young children. **AJNR Am J Neuroradiol** **22**:818–823, 2001
  61. Packer RJ, Bilaniuk LT, Cohen BH, Braffman BH, Obringer AC, Zimmerman RA, et al: Intracranial visual pathway gliomas in children with neurofibromatosis. **Neurofibromatosis** **1**:212–222, 1988
  62. Packer RJ, Savino PJ, Bilaniuk LT, Zimmerman RA, Schatz NJ, Rosenstock JG, et al: Chiasmatic gliomas of childhood. A reappraisal of natural history and effectiveness of cranial irradiation. **Childs Brain** **10**:393–403, 1983
  63. Parsa CF, Hoyt CS, Lesser RL, Weinstein JM, Strother CM, Muci-Mendoza R, et al: Spontaneous regression of optic gliomas: thir-

- teen cases documented by serial neuroimaging. **Arch Ophthalmol** **119**:516–529, 2001
64. Peng F, Juhasz C, Bhambhani K, Wu D, Chugani DC, Chugani HT: Assessment of progression and treatment response of optic pathway glioma with positron emission tomography using alpha-[(11)C]methyl-L-tryptophan. **Mol Imaging Biol** **9**:106–109, 2007
  65. Pepin SM, Lessell S: Anterior visual pathway gliomas: the last 30 years. **Semin Ophthalmol** **21**:117–124, 2006
  66. Perilongo G, Moras P, Carollo C, Battistella A, Clementi M, Laverda A, et al: Spontaneous partial regression of low-grade glioma in children with neurofibromatosis-1: a real possibility. **J Child Neurol** **14**:352–356, 1999
  67. Petronio J, Edwards MS, Prados M, Freyberger S, Rabbitt J, Silver P, et al: Management of chiasmal and hypothalamic gliomas of infancy and childhood with chemotherapy. **J Neurosurg** **74**:701–708, 1991
  68. Pungavkar SA, Lawande MA, Patkar DP, Agrawal NV, Gadani S: Bilateral optic pathway glioma with intracranial calcification: magnetic resonance imaging and magnetic resonance spectroscopy findings. **Australas Radiol** **49**:489–492, 2005
  69. Rush JA, Younge BR, Campbell RJ, MacCarty CS: Optic glioma. Long-term follow-up of 85 histopathologically verified cases. **Ophthalmology** **89**:1213–1219, 1982
  70. Serdaroglu A, Simsek F, Gücüyener K, Oguz A, Karadeniz C, Balibey M: Moyamoya syndrome after radiation therapy for optic pathway glioma: case report. **J Child Neurol** **15**:765–767, 2000
  71. Sharif S, Ferner R, Birch JM, Gillespie JE, Gattamaneni HR, Baser ME, et al: Second primary tumors in neurofibromatosis 1 patients treated for optic glioma: substantial risks after radiotherapy. **J Clin Oncol** **24**:2570–2575, 2006
  72. Shen TT, Sakai O, Curtin HD, Rizzo JF III: Magnetic resonance imaging of primary anterior visual pathway tumors. **Int Ophthalmol Clin** **41**:171–180, 2001
  73. Silva MM, Goldman S, Keating G, Marymont MA, Kalapurakal J, Tomita T: Optic pathway hypothalamic gliomas in children under three years of age: the role of chemotherapy. **Pediatr Neurosurg** **33**:151–158, 2000
  74. Suárez JC, Viano JC, Zunino S, Herrera EJ, Gomez J, Tramunt B, et al: Management of child optic pathway gliomas: new therapeutic option. **Childs Nerv Syst** **22**:679–684, 2006
  75. Sylvester CL, Drohan LA, Sergott RC: Optic-nerve gliomas, chiasmal gliomas and neurofibromatosis type 1. **Curr Opin Ophthalmol** **17**:7–11, 2006
  76. Tao ML, Barnes PD, Billett AL, Leong T, Shrieve DC, Scott RM, et al: Childhood optic chiasm gliomas: radiographic response following radiotherapy and long-term clinical outcome. **Int J Radiat Oncol Biol Phys** **39**:579–587, 1997
  77. Taveras JM, Mount LA, Wood EH: The value of radiation therapy in the management of glioma of the optic nerves and chiasm. **Radiology** **66**:518–528, 1956
  78. Tenny RT, Laws ER Jr, Younge BR, Rush JA: The neurosurgical management of optic glioma. Results in 104 patients. **J Neurosurg** **57**:452–458, 1982
  79. Thiagalingam S, Flaherty M, Billson F, North K: Neurofibromatosis type 1 and optic pathway gliomas: follow-up of 54 patients. **Ophthalmology** **111**:568–577, 2004
  80. Tow SL, Chandela S, Miller NR, Avellino AM: Long-term outcome in children with gliomas of the anterior visual pathway. **Pediatr Neurol** **28**:262–270, 2003
  81. Trisciuzzi MT, Riccardi R, Piccardi M, Iarossi G, Buzzonetti L, Dickmann A, et al: A fast visual evoked potential method for functional assessment and follow-up of childhood optic gliomas. **Clin Neurophysiol** **115**:217–226, 2004
  82. Walker D: Recent advances in optic nerve glioma with a focus on the young patient. **Curr Opin Neurol** **16**:657–664, 2003
  83. Wisoff JH: Management of optic pathway tumors of childhood. **Neurosurg Clin N Am** **3**:791–802, 1992
  84. Yoshikawa G, Nagata K, Kawamoto S, Tsutsumi K: Remarkable regression of optic glioma in an infant. Case illustration. **J Neurosurg** **98**:1134, 2003
  85. Zizka J, Eliás P, Jakubec J: Spontaneous regression of low-grade astrocytomas: an underrecognized condition? **Eur Radiol** **11**:2638–2640, 2001

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