Optic Pathway Gliomas

Neoplasms, Not Hamartomas

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Importance: Optic pathway gliomas are an important neuro-ophthalmic cause of vision loss in children. Their management depends on whether they are considered neoplasms or hamartomas.

Objective: To outline the evidence that optic pathway gliomas are slowly growing neoplasms and not hamartomas.

Design: Review of relevant studies in the literature.

Setting: The authors are from a pediatric tertiary referral center.

Results: The growth patterns and histopathology of optic pathway gliomas are more consistent with those of neoplasms. Spontaneous regression, thought to be a characteristic of hamartomas, can be seen in neoplasms of other types as well as in optic pathway gliomas. Chemotherapy used in low-grade gliomas has been shown to halt or improve vision loss in optic pathway gliomas in many cases.

Conclusions and Relevance: Optic pathway gliomas are not hamartomas but truly are neoplasms. Thus, patients should be followed up closely, and chemotherapies should be used when clinical progression occurs. Other more directed therapies will certainly be used in the future.


But when something is shouted loudly enough, often enough, and to enough people, with no checking of the accuracy of what’s being shouted, a downright silly claim can come to sound like a long-suppressed truth.

Sarah Beckwith

HOYT AND BAGHDASSARIAN popularized the notion that optic pathway gliomas are hamartomas. Parsa and Givrad have continued to argue extensively that optic pathway gliomas are congenital developmental lesions, not neoplastic, and therefore should not be treated, even when there is evidence of clinical or radiographic progression. In his latest article on this topic, without data to support his stance, Parsa attempts to explain why visual deterioration in optic pathway gliomas may not be a sign of tumor progression. These claims, which may mislead concerned parents because they virtually advocate therapeutic nihilism, have frightening implications for the follow-up and treatment of children with optic pathway gliomas.

In fact, more recently, magnetic resonance imaging techniques have provided clinicians with a more detailed method for observing the natural history of optic pathway gliomas that was not available decades ago. In addition, many children with optic pathway gliomas today are followed up serially by dedicated pediatric ophthalmologists or neuro-ophthalmologists working closely with pediatric neuro-oncologists. Now, most clinicians dealing with optic pathway gliomas have realized that the growth patterns are varied and unpredictable.

The question boils down to this: are optic pathway gliomas hamartomas or slowly growing neoplasms? This article outlines the evidence to support our opinion that optic pathway gliomas are slowly growing neoplasms and not hamartomas, in contrast to Parsa’s stance.

OPTIC PATHWAY GLIOMAS DO NOT SATISFY THE DEFINITION OF HAMARTOMAS

A hamartoma is a “focal malformation that resembles a neoplasm, grossly and even microscopically, but results from faulty de-
velopment in an organ; it is composed of an abnormal mixture of tissue elements, or an abnormal proportion of a single element, normally present in that site which develop and grow at virtually the same rate as normal components, and are not likely to result in compression of adjacent tissue.\(^{10}\)

Opitz and Jorde wrote, "Hamartomata are localized overgrowths of a single tissue or combination of tissues, indigenous to the affected body part or organ, usually growing at the same rate as the normal components and causing little pain or functional impairment.\(^{11}\)

Optic gliomas, on the other hand, can destroy the structures within and around which they are growing (Figure 1). They can demonstrate growth at rates more rapid than that of the visual pathways or brain (Figure 2). Optic gliomas are also often symptomatic.

While many are asymptomatic, up to 50% of patients with neurofibromatosis type 1 (NF1) and optic pathway gliomas exhibit vision loss to some degree.\(^{12}\) Hypothalamic gliomas can cause obstructive hydrocephalus and endocrinopathy such as diencephalic syndrome or precocious puberty. Finally, optic gliomas can metastasize in the absence of shunt manipulation,\(^{9,13}\) a behavior not characteristic of hamartomas.

**HISTOPATHOLOGICALLY AND BIOLOGICALLY, OPTIC PATHWAY GLIOMAS ARE NEOPLASMS**

A neoplasm is defined as a "new growth; tumor(s); an abnormal tissue that grows by cellular proliferation more rapidly than normal and continues to grow after the stimuli that initiated the new growth cease. Neoplasms show partial or complete lack of structural organization and functional coordination with the normal tissue, and usually form a distinct mass of tissue which may either be benign (benign tumor) or malignant (cancer).\(^{14}\) Neoplasms may grow at different rates and have varying potential for metastases.

For several reasons, the histopathologic and biological characteristics of optic pathway gliomas make them neoplasms. First, many are grade 1 juvenile pilocytic astrocytomas,\(^{15}\) just like the childhood cerebellar juvenile pilocytic astrocytomas, which are not hamartomas. These tumors do not appear at all like normal cerebellum as a hamartoma would.

Second, some optic pathway gliomas are grade 2 fibrillary astrocytomas, and it is artificial to separate those that might be predominantly grade 1 from those with grade 2 components, particularly in cases not undergoing biopsy. The uncertainty arises because most optic pathway gliomas, particularly those associated with NF1, are

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**Figure 1.** Axial (A) and coronal (B) magnetic resonance images with gadolinium enhancement demonstrating chiasmal-hypothalamic glioma (thick arrows) with involvement of surrounding brain (thin arrows).

**Figure 2.** Axial magnetic resonance imaging with gadolinium enhancement (2 slices, A and B) revealed a large chiasmal glioma with bilateral optic tract involvement, left more than right, in January 2008. In April 2009 (2 slices, C and D), the left optic tract component enlarged significantly, leading to obstructive hydrocephalus.
not biopsied (when the radiographic appearance is typical, the risk associated with biopsy is deemed unwarranted), and sampling error may occur.

Third, the fact that optic pathway gliomas, like subependymal giant cell tumors and craniopharyngiomas, do not generally undergo malignant transformation does not make them hamartomas.

In addition, as Walrath et al8 and Miller16 have discussed, some optic pathway gliomas may exhibit markers of cellular proliferation identified by techniques such as those using MIB-1, an antibody to the Ki-67 antigen,17 and silver nuclear organizing region (AgNOR),18 a measure of mitotic activity. Like pilocytic astrocytomas in other locations in the brain,19-21 a portion of optic pathway gliomas have elevated proliferative activity (MIB-1 labeling index of 2%-3%),17 which is associated with more aggressive tumor behavior.7,17,21 Parsa5 has countered that apoptosis should be considered when assessing MIB-1 positivity. However, apoptosis is not typically seen histopathologically in optic pathway and other low-grade gliomas.

Finally, advances in our understanding of the biology of optic pathway gliomas are consistent with the notion that they are neoplasms. Neurofibromin, the NF1 gene product, is a tumor suppressor and negative regulator of RAS, a protein that promotes cell division. When neurofibromin is dysfunctional, RAS is upregulated, leading to cell proliferation and tumor formation.7 Hyperactivation of the mammalian target of rapamycin (mTOR) via the RAS/phosphatidylinositol 3'-kinase (PI3K)/AKT signaling pathway can also result from inactivation of NF1.22 In fact, NF1-related optic pathway gliomas have high levels of mTOR pathway activation.23 In sporadic low-grade gliomas, similar activation of mTOR may occur via an alternative RAS effector pathway (RAS/RAF/mitogen-activated protein kinase [MEK]/mitogen-activated protein kinase [MAPK]), which is upregulated by the oncogene BRAF.22 Thus, the growth characteristics and pathology of optic pathway gliomas are more consistent with those of neoplasms.

**SPONTANEOUS IMPROVEMENT AND RESOLUTION CAN BE SEEN IN NEOPLASMS**

Parsa has also argued that spontaneous improvement seen uncommonly in optic pathway gliomas24,25 supports the concept that these are benign hamartomas. However, this behavior is not a characteristic of just hamartomas as it occurs in some high-grade neoplasms as well. For instance, neuroblastomas, which are bona fide malignant neoplasms with cure rates less than 40%, may also demonstrate spontaneous regression in a specific subset of patients. In one study,26 of 53 six-month-old infants found to have neuroblastoma on screening, 17 (32%) exhibited complete spontaneous regression. Even a subset of cases with stage IV neuroblastoma with metastases have demonstrated spontaneous regression.
There is proof that antimitotic therapies are effective in optic pathway gliomas

Several studies have been published that counter Parsa's claim that the use of “antimitotic and genotoxic nostrums” for optic pathway gliomas is an “example of faith-based, rather than evidence-based, medicine.” At most centers, chemotherapy has been used when radiographic and/or clinical progression is documented. Using radiologic data primarily as the outcome measure, the combination of carboplatin and vincristine sulfate, the most common regimen, was associated with a 3-year progression-free survival (<25% growth) rate of 77% and a 5-year progression-free survival rate of 69% in patients with NF1.

Figure 3 depicts examples of radiographic improvement following chemotherapy. Although allergic reactions may occur, this regimen is generally tolerated very well in children.

Data regarding visual outcomes following chemotherapy for optic pathway gliomas now exist. One recent study showed that chemotherapy halted the progression of visual acuity loss. In a retrospective, international, multicenter review of 115 patients with NF1 treated with chemotherapy during a 10-year period, at the completion of therapy, visual acuity improved (32% of subjects), remained stable (40%), or declined (28%). In a meta-analysis, 14% improved and 47% stabilized. These rates of improvement (14%-32%) with chemotherapy cannot be explained by the occasional phenomenon of spontaneous regression.

Radiation therapy, again using radiologic data, has been shown to be effective for optic pathway gliomas, with reported 10-year progression-free survival rates of 66% to 90%. However, radiation is no longer used as a first-line therapy because of the risks of cognitive decline, endocrinopathies, cerebrovascular disease, and secondary malignancies. These risks are higher in the setting of NF1.

Newer therapies are being explored. Based on the developing understanding of the biology of these tumors, inhibitors of BRAF, MEK, and mTOR are already in clinical trials. In addition, drugs targeting tumor angiogenesis such as bevacizumab have demonstrated responses in recurrent or refractory optic pathway gliomas and are being evaluated in larger studies.

Deleterious Implication of Designating Optic Pathway Gliomas as Hamartomas

It is a disservice to and potentially dangerous for patients with optic pathway gliomas and their families to label these lesions hamartomas not requiring treatment or to suggest that visual deterioration may actually mean the glioma is improving. Some optic pathway gliomas are clearly life threatening (Figure 2). Families may get the false impression that if treatments are ineffective or unnecessary, clinical follow-up, consultation with a neuro-oncologist, and serial imaging are also unnecessary.

Conclusions

In summary, based on their growth patterns and histopathology, optic pathway gliomas are not hamartomas but truly are neoplasms. Spontaneous regression can be seen in neoplasms of other types as well as in optic pathway gliomas. Chemotherapies should be used when clinical progression occurs. Other more directed therapies will certainly be used in the future.


Congratulations to the winner of our December quiz, Dilraj Singh Grewal, MD, Department of Ophthalmology, Northwestern University, Chicago, Illinois. The correct answer to our December challenge was Churg-Strauss syndrome vasculitis. For a complete discussion of this case, see the Research Letters section in the January issue (Harris Nwananywu KM, De Lott LB, Cornblath WT, Elmer VM. Transient monocular vision loss due to Churg-Strauss syndrome vasculitis. *JAMA Ophthalmol*. 2013;131[1]:117-119).