Visual Loss in Children With Neurofibromatosis Type 1 and Optic Pathway Gliomas: Relation to Tumor Location by Magnetic Resonance Imaging

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• PURPOSE: To examine the potential for visual acuity loss, and its relation to extent and location of optic pathway gliomas in a cohort of children with neurofibromatosis type 1 studied with magnetic resonance imaging.
• METHODS: We reviewed the neuro-ophthalmologic records and brain/orbital magnetic resonance imaging scans for 43 consecutive pediatric patients with neurofibromatosis type 1 and optic pathway gliomas who were followed at the Children's Hospital of Philadelphia. The presence of visual loss, defined as abnormal visual acuity for age in one or both eyes, was determined. Optic pathway gliomas were classified by tumor extent and location according to involvement of the optic nerves, chiasm, and postchiasmal structures by magnetic resonance imaging.
• RESULTS: Involvement of the optic tracts and other postchiasmal structures at tumor diagnosis was associated with a significantly higher probability of visual acuity loss ($P = .048$, chi-square test). Visual loss was noted in 20 of 43 patients (47%) at a median age of 4 years; however, three patients developed visual acuity loss for the first time during adolescence.
• CONCLUSIONS: In pediatric patients with neurofibromatosis type 1 and optic pathway gliomas, the likelihood of visual loss is dependent on the extent and location of the tumor by magnetic resonance imaging and is particularly associated with involvement of postchiasmal structures. Furthermore, older age during childhood (adolescence) does not preclude the occurrence of visual loss. Close follow-up beyond the early childhood years, particularly for those with postchiasmal tumor, is recommended. (Am J Ophthalmol 2001;131:442–445. © 2001 by Elsevier Science Inc. All rights reserved.)

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OPTIC PATHWAY GLIOMAS OCCUR IN 15% TO 20% of patients with neurofibromatosis type-1.[1,2] These tumors are juvenile pilocytic astrocytomas, which arise in the afferent visual pathways.[3] Visual loss is the most worrisome complication; greater than one third of patients with these tumors may develop visual acuity loss or optic atrophy.[1–4]

Modern magnetic resonance imaging techniques with thin slices, high resolution, and gadolinium have allowed for more definitive diagnosis, assessment of size, and localization of optic pathway gliomas.[3] In most previous series,[1–6] neuroimaging has been limited to computed tomographic scanning or other techniques available before the widespread use of magnetic resonance imaging.

The relation of visual loss to tumor extent and location in children with neurofibromatosis type 1 and optic pathway gliomas has not yet been established in a cohort of patients studied uniformly with magnetic resonance imaging. The purpose of this investigation was to examine the prevalence of visual loss in children with neurofibromatosis type 1 and optic pathway gliomas according to tumor extent and location within the afferent visual pathways at initial diagnosis.

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METHODS

THE NEURO-OPHTHALMOLOGIC EXAMINATION RECORDS and magnetic resonance imaging scans of all children with neurofibromatosis type 1[7] and optic pathway gliomas followed at the Children's Hospital of Philadelphia between 1992 and 1999 were reviewed. Since 1992, children with neurofibromatosis type 1 have been routinely examined and followed by the neuro-ophthalmology and neuro-oncology services at Children's Hospital of Philadelphia. Cranial and orbital magnetic resonance imaging has also been performed routinely for children with neurofibromatosis type 1, both as a screening tool and to evaluate new symptoms. Characteristic magnetic resonance imaging findings of enlargement and enhancement have been used to establish the diagnosis of optic pathway glioma in patients with neurofibromatosis type 1[3]; all gliomas in this series were diagnosed and followed using magnetic resonance imaging. Only those children initially examined at Children's Hospital of Philadelphia before age 18 years were included in this study. Approval from the Children's Hospital of Philadelphia Institutional Review Board was obtained for all study protocols.

The age in years at which each patient was first documented to have visual loss, defined as uncorrectable abnormal visual acuity for age in one or both eyes, was recorded. Criteria for abnormality were based on published norms for Teller visual acuity (applicable to infants and children younger than 3 years)[8] and for letter acuity testing (applicable to children 3 years and older).[9] Acuity testing methods used in children 3 years and older included "HOTV" letter matching, Allen figures (pictures), and Snellen letters; methods were selected for each child based on ability and cooperation. Visual acuities were considered abnormal based on the following criteria: age 3 years, worse than 20/40; age 4 years, worse than 20/30; age 5 years, worse than 20/25; and age 6 years and older, worse than 20/20.[9]

Cranial and orbital magnetic resonance imaging scans were reviewed by one neuroradiologist to determine the extent and location of tumor within the afferent visual pathways; both signal abnormality and enhancement were used to indicate the presence of tumor. The neuroradiologist was not masked to the presence of NF or visual loss, but was not aware of the level of visual loss. Patients were divided into three groups based on tumor extent and location by magnetic resonance imaging at the time of initial diagnosis of the optic glioma: the optic nerve(s) group, involvement of one or both optic nerves only; the chiasm group, involvement of optic chiasm with or without involvement of optic nerve(s); the postchiasm group, involvement of postchiasmal visual pathways (including hypothalamus) with or without involvement of the chiasm and optic nerve(s).

The relation between visual loss and tumor location/extent by magnetic resonance imaging at diagnosis was examined using the chi-square test. The optic nerve(s) and chiasm groups were combined for purposes of analysis given the small sample size of the optic nerve(s) group (n = 4). A logistic regression model was used to assess the status of age at diagnosis as a potential confounder in the relation between visual loss and tumor location. Statistical analyses were performed using Stata 5.0 Statistical Software (StataCorp, College Station, Texas).

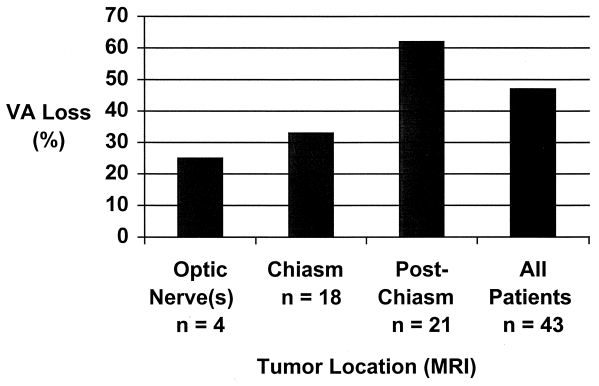

FIGURE 1. Percentages of patients with visual acuity (VA) loss according to location/extent of optic pathway glioma by magnetic resonance imaging (MRI; n = 43). Optic Nerve(s) indicates the group with involvement of optic nerve(s) only (n = 4); Chiasm indicates involvement of optic chiasm with or without optic nerve(s) (n = 18); Post-Chiasm indicates involvement of optic tracts or other postchiasmal structures in addition to the chiasm and optic nerve(s) (n = 21).

RESULTS

FORTY-THREE CHILDREN WITH OPTIC PATHWAY GLIOMAS fulfilled diagnostic criteria for neurofibromatosis type 1[7] within the study period. Patient characteristics, including age at diagnosis of optic pathway glioma, proportions with visual acuity loss, and age at first discovery of visual loss, are presented in Table 1. Nearly half of the patients, 21 of 43 (49%), had involvement of postchiasmal structures by tumor on magnetic resonance imaging (all patients in the postchiasm group also had involvement of the optic chiasm and one or both optic nerves).

Visual acuity loss was noted in 20 of 43 (47%) of the entire cohort of patients during a median follow-up of 3 years (range, 0–8 years; median, 2 years for patients without visual loss) (Fig. 1). However, as shown in Table 2, the proportion of patients with visual loss was significantly higher among those with involvement of postchiasmal structures by magnetic resonance imaging (postchiasm group, visual loss in 62%), compared with patients with chiasmal and/or optic nerve involvement alone (optic nerve(s) and chiasm groups combined, visual loss in 32%; $P = .048$, chi-square test). Whereas age at diagnosis of the optic pathway glioma demonstrated an effect on the

TABLE 1. Patient Characteristics According to Extent and Location of Optic Pathway Glioma by Magnetic Resonance Imaging (at Tumor Diagnosis)

	Optic Nerve(s)	Chiasm	Postchiasm	All Patients
Number of patients, n (%)	4 (9%)	18 (42%)	21 (49%)	43 (100%)
Median age at diagnosis, n (range)	2 (1–10)	5.5 (1–17)	3 (1–10)	3 (1–17)
Visual acuity loss, n (%)	1 (25%)	6 (33%)	13 (62%)	20 (47%)
Median age at visual acuity loss, years (range)	4.5 (2–7)	7 (1–17)	3 (1–6)	4 (1–17)

Chiasm = involvement of optic chiasm with or without optic nerve(s); optic nerve(s) = involvement of optic nerve(s) only; postchiasm = involvement of optic tracts or other postchiasmal structures (including hypothalamus) in addition to the chiasm with or without optic nerve(s).

TABLE 2. Numbers and Percentages of Patients With Visual Loss According to Location/Extent of Glioma by Magnetic Resonance Imaging (Postchiasmal vs Anterior Visual Pathway Involvement)

	Postchiasm	Optic Nerve(s) + Chiasm	All Patients
Visual acuity loss, n (%)*	13 (62%)	7 (32%)	20 (47%)
No visual acuity loss, n (%)	8 (38%)	15 (68%)	23 (53%)
Total, n	21	22	43

Chiasm = involvement of optic chiasm with or without optic nerve(s); optic nerve(s) = involvement of optic nerve(s) only; postchiasm = involvement of optic tracts or other postchiasmal structures (including hypothalamus) in addition to the chiasm with or without optic nerve(s).

*A significant association between visual acuity loss and involvement of postchiasmal structures by tumor was demonstrated by the chi-square test ($P = .048$).

probability of visual loss when included in a logistic regression model ($P = .051$), the relation between visual loss and tumor location [postchiasm vs optic nerve(s) and chiasm combined] remained significant ($P = .041$). This indicates that age at glioma diagnosis was not a confounding factor.

Although visual acuity loss was first noted in most children before the age of 10 years (median, 4 years), three patients developed visual loss for the first time during adolescence (two patients at age 11, one at age 17). Importantly, all three of these patients (and 17 of the 20 patients with visual loss) had normal visual acuities documented within the previous year. Progression of tumor by magnetic resonance imaging was also noted within 6 months of the first documentation of visual loss in six of 20 patients. Abnormal visual acuities were detected at the time of diagnosis or within 1 year after magnetic resonance imaging diagnosis of the glioma in eight of 20 patients with visual loss. Therefore, among all patients, 12 of 43 (28%) developed visual acuity loss at least 1 year after diagnosis. Those children who did not develop visual acuity loss during the follow-up period ranged in age from 3 to 18 years at the time of their most recent neuro-ophthalmologic examinations.

Possible causes for visual loss other than optic pathway glioma were detected in only one patient (with glaucoma), although some patients with asymmetric acuity abnormalities were thought to have amblyopia in addition to their tumor-related visual loss. Optic disk pallor was noted in 24 of 43 patients (56%). Fourteen patients had both optic disk pallor and visual acuity loss; in all of these cases the pallor preceded visual loss or was noted at the same time. Six patients with visual acuity loss were not noted to have disk pallor.

DISCUSSION

THE RESULTS OF THIS INVESTIGATION PROVIDE EVIDENCE, based on a cohort studied uniformly with magnetic resonance imaging, that the likelihood of visual loss in children with neurofibromatosis type 1 and optic pathway gliomas is dependent on tumor extent and location. A significantly higher proportion of children with involvement of the postchiasmal visual pathways developed visual loss, compared with those with chiasmal and/or optic nerve involvement alone. The possible association of postchiasmal tumor with a greater prevalence of visual loss should be a consideration for neuroimaging follow-up. Larger studies with prospective visual assessment and magnetic resonance imaging are needed; such investigations will demonstrate how involvement of the chiasm vs optic nerve(s) may affect the likelihood of visual loss.

As emphasized previously,[2–4] the diagnosis of optic pathway gliomas in patients with neurofibromatosis type 1, and the detection of visual loss related to these tumors, is most likely to occur during the early childhood years. The emergence of optic pathway gliomas in children with previously normal neuroimaging, conversely, has been reported.[10] The median age at glioma diagnosis in our series was 3 years (4 years in previous studies),[2,6] and visual

loss was first detected at a median age of 4 years. However, three patients developed visual loss for the first time during adolescence, two of whom had involvement of postchiasmal structures by tumor. Consequently, there appears to be no absolute age during childhood beyond which the likelihood of visual loss becomes insignificant. Furthermore, because neuro-ophthalmologic screenings have been performed routinely on all children with neurofibromatosis type 1 at Children's Hospital of Philadelphia, the likelihood that our results reflect selective referral for visual symptoms has been minimized. The prevalence of visual acuity loss in our cohort (47%: Table 1) was within the range observed in previous series (20%–70%).[2]

Although previous studies of children with neurofibromatosis type 1[2] have suggested that progression of visual loss after the initial diagnosis of optic pathway gliomas is uncommon, a high proportion of our patients (28%) developed visual loss between 1 and 6 years after diagnosis of optic pathway glioma. The results of this study thus emphasize the crucial importance of close neuro-ophthalmologic as well as radiologic follow-up in children with neurofibromatosis type 1 throughout adolescence, especially for children with known optic pathway gliomas and for those with postchiasmal involvement. Such follow-up is also important given the association of postchiasmal tumor with mortality in addition to visual morbidity.[1–3]

The Neurofibromatosis Type 1 Optic Pathway Glioma Task Force[6] has recommended yearly screening ophthalmologic or neuro-ophthalmologic examinations for children with asymptomatic neurofibromatosis type 1 through age 6 years, with examinations every 2 to 4 years thereafter. At the Children's Hospital of Philadelphia, current practice for the follow-up of children with neurofibromatosis type 1 and known optic pathway gliomas includes neuro-ophthalmologic examinations at 3 month intervals for the first 12 months following diagnosis. If stable, patients are then followed at 6-month intervals for five years, then annually through adolescence. In addition to visual acuity measurements, visual field testing should be performed as appropriate for the patient's age and abilities. Our results, based on magnetic resonance imaging in a large cohort of children with neurofibromatosis type 1, provide further evidence in favor of such close follow-up of patients with known optic pathway gliomas.

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REFERENCES

1. Lewis RA, Gerson LP, Axelson KA, Riccardi VM, Whitford RP. Von Recklinghausen neurofibromatosis. II. Incidence of optic gliomata. Ophthalmology 1984;91:929–935.
2. 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 1994;125:63–66.
3. Dutton JJ. Gliomas of the anterior visual pathway. Surv Ophthalmol 1994;38:427–452.
4. Hoyt WF, Baghdassarian SA. Optic glioma of childhood: natural history and rationale for conservative management. Br J Ophthalmol 1969;53:793–798.
5. Alvord EC, Lofton S. Gliomas of the optic nerve or chiasm: outcome by patients' age, tumor site, and treatment. J Neurosurg 1988;68:85–98.
6. 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 1997;41:143–149.
7. National Institutes of Health Consensus Development Conference. Neurofibromatosis. Conference statement. Arch Neurol 1988;45:575–578.
8. Salomão SR, Ventura DF. Large sample population age norms for visual acuities obtained with Vistech-Teller Acuity Cards. Invest Ophthalmol Vis Sci 1995;36:657–670.
9. Myers VS, Gidlewski N, Quinn GE, Miller D, Dobson V. Distance and near visual acuity, contrast sensitivity, and visual fields of 10-year-old children. Arch Ophthalmol 1999;117:94–99.
10. Listernick R, Charrow J, Greenwald M. Emergence of optic pathway gliomas in children with neurofibromatosis type 1 after normal neuroimaging results. J Pediatr 1993;121:584–587.