J Neurooncol (2016) 129:173–178
DOI 10.1007/s11060-016-2163-4

CLINICAL STUDY

Long-term visual outcomes of optic pathway gliomas in pediatric patients without neurofibromatosis type 1

Michael J. Wan[1] · Nicole J. Ullrich[2,3,4] · Peter E. Manley[3,4] · Mark W. Kieran[3,4] · Liliana C. Goumnerova[5] · Gena Heidary[1]

Received: 18 December 2015 / Accepted: 1 June 2016 / Published online: 16 June 2016

Abstract Sporadic optic pathway gliomas (OPGs) have been reported to cause more vision loss than OPGs associated with neurofibromatosis type-1, but long-term visual outcome data are limited. The purpose of this study was to report the visual outcomes of a cohort of pediatric patients with sporadic OPGs. This was a retrospective, cohort study at a tertiary care pediatric hospital and cancer institute. The study included all patients with sporadic OPGs evaluated from 1990 to 2014. The primary outcome was visual acuity at final follow-up. Secondary outcomes were risk factors for a poor visual outcome and the rate of progression. There were 59 pediatric patients included in the study. Median age at presentation was 2.5 years old and median follow-up was 5.2 years. In the worse eye at final follow-up, 16 patients (27%) were 20/30 or better, 9 patients (15%) were between 20/40 and 20/80, and 34 patients (58%) were 20/100 or worse. In the better eye at final follow-up, 33 patients (56%) were 20/30 or better, 11 patients (19%) were between 20/40 and 20/80, and 15 patients (25%) were 20/100 or worse. Risk factors for a poor visual outcome included younger age at presentation, optic nerve pallor, and tumor extent. Of the 54 patients (92%) who received treatment, 40 (74%) experienced disease progression during or after treatment. A majority of pediatric patients with sporadic OPGs had significant long-term visual impairment. In spite of treatment, tumor progression is common. Serial ophthalmic examinations with quantitative vision measurements are essential in the management of sporadic OPGs.

Keywords Glioma · Optic nerve glioma · Juvenile pilocytic astrocytoma · Neurofibromatosis 1 · Visual acuity · Visual pathways

Introduction

Optic pathway gliomas (OPGs) are an important subtype of low grade gliomas, the most common type of central nervous system tumor in childhood [1]. Although usually slowly progressive and uncommonly fatal, OPGs can be associated with significant visual impairment [2]. As a result, visual function has become a key outcome measure for OPGs to help guide treatment decisions, evaluate treatment effect, and assess for tumor progression [3].

It is important to differentiate patients with OPGs based on whether the tumor is sporadic or associated with an underlying diagnosis of neurofibromatosis type-1 (NF1). There is a substantial body of evidence suggesting that sporadic OPGs are associated with a higher risk of visual impairment [4–6]. However, long-term data on visual outcomes for sporadic OPGs is limited.

The purpose of this study was to report the long-term visual outcomes of a large cohort of pediatric patients with

✉ Gena Heidary
Gena.Heidary@childrens.harvard.edu

1 Department of Ophthalmology, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Fegan 4, Boston, MA 02115, USA

2 Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA

3 Department of Hematology/Oncology, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA

4 Pediatric Neuro-Oncology, Dana-Farber/Boston Children's Hospital Center for Cancer and Blood Disorders, Boston, MA 02115, USA

5 Department of Neurosurgery, Boston Children's Hospital, Harvard Medical School, Boston, MA 02115, USA

sporadic OPGs and to determine the risk factors for a poor visual outcome.

Methods

This study was approved by the Institutional Review Board at Boston Children's Hospital. The design of the study was a retrospective, observational cohort study at a tertiary care pediatric hospital and cancer institute. A search of the electronic medical records was conducted for all pediatric patients who were seen for OPGs from 1990 to 2014. Patients were excluded if they had (or later developed) NF1, if there was less than 1 year of follow-up, or if they were actively enrolled in primary treatment at the time of the last available follow-up.

For each patient, the clinical features at presentation, imaging characteristics of the tumor, type of treatment, evidence of tumor progression, and the results of all visual assessments were recorded. For the purpose of analysis, visual outcomes were grouped into an ordinal scale with three categories: (1) 20/30 or better, (2) 20/40 to 20/80, and (3) 20/100 or worse. The categories of visual outcomes were based on the standardized Pediatric Eye Disease Investigator Group (PEDIG) scale for visual impairment [7].

The primary outcome measure was visual acuity at final follow-up in the more severely affected eye. Secondary outcomes included visual acuity at final follow-up in the less severely affected eye, risk factors for a worse visual outcome (unilateral and bilateral) at final follow-up, median survival time, and 5-year progression free survival. Optotype visual was measured in all patients (unless vision was too poor) and no adjustment was made for age.

The statistical analysis was conducted using STATA Statistical Software Version 13 [8]. For independent variables with two categories, univariate analysis was conducted using the Wilcoxon rank-sum test. For independent variables with more than two categories, univariate analysis was conducted using the Kruskal–Wallis test. If a statistically significant relationship was discovered, individual categories were compared using Dunn's test with the Bonferroni adjustment for multiple comparisons [9, 10]. Multivariate analysis was conducted using an ordered logistic regression. Variables were included in the multivariate analysis if the p value was <0.20 in the univariate analysis. The proportional odds assumption was tested using the Brant test.

Results

There were a total of 74 patients identified with sporadic OPGs during the study period. Of these, 15 were excluded: 5 because they were receiving primary treatment at last follow-up, 5 because they lacked ophthalmologic follow-up, 3 because of uncertainty about the diagnosis, and 2 because of missing information. The final cohort included 59 pediatric patients with sporadic OPGs. The baseline characteristics of the patients are summarized in Table 1. Of the 59 patients included in the study, 54 (92%) patients received treatment (Table 2). All but three of the patients received primary chemotherapy with a median treatment duration of 14 months (range 5–26 months). There were five patients who did not receive treatment; of these, four had normal vision at presentation and no evidence of progression during follow-up and one had poor vision (unilateral) vision at presentation and no progression or involvement of the other eye.

Of the 54 patients who received treatment, 40 (74%) had evidence of progression, which was defined as a change in visual function or neuro-imaging which necessitated a change or re-initiation of therapy (Table 2). Disease progression was defined by vision changes in 24% of the patients, MRI changes in 54% of the patients, and both vision and MRI changes in 22% of the patients. A survival analysis

Table 1 Baseline features of pediatric patients with sporadic optic pathway gliomas

Characteristic	n (%)
Gender	
Female	24 (41)
Male	35 (59)
Age at presentation (years)	
Median	2.5
Range	0.3–16.1
Clinical presenting features (patients could have more than one presenting feature)	
Nystagmus	16
Vision loss	15
Neurological finding	14
Strabismus	8
Headache	7
Failure to thrive	6
Proptosis	5
Precocious puberty	4
Incidental finding	3
Other	6
Tumor location[a]	
Optic nerve	5 (9)
Optic chiasm	13 (22)
Hypothalamus	16 (27)
Optic tract	20 (34)
Optic radiations	5 (9)

[a]Tumor location refers to the most posterior extent of the tumor along the visual pathways

showed a 5-year progression free survival of 23.5 % and a median progression-free survival time of 2.6 years (Fig. 1).

The median follow-up was 5.2 years (range 1.2–26.6 years) from presentation. In the more severely affected eye at final follow-up, 16 patients (27 %) had vision of 20/30 or better, 9 patients (15 %) had vision between between 20/40 and 20/80, and 34 patients (58 %) had vision of 20/100 or worse. In the less severely affected eye, 33 patients (56 %) had vision of 20/30 or better, 11 patients (19 %) had vision between 20/40 and 20/80, and 15 patients (25 %) had vision of 20/100 or worse (Fig. 2).

To determine the risk factors associated with a poor visual outcome, univariate and multivariate analyses were performed. For the more severely affected eye, younger age at diagnosis and optic nerve pallor at presentation were associated with a worse visual outcome (Table 3). For the less severely affected eye, younger age at presentation, optic nerve pallor, and post-chiasmal tumor extent were associated with a worse visual outcome (Table 3). The Brant test confirmed that the proportional odds assumption was not violated.

Table 2 Primary and secondary treatments for pediatric patients with sporadic optic pathway glioma

Treatment	Number of patients
Primary treatment	**54**
Chemotherapy	51
Carboplatin/vincristine	44
Carboplatin/vincristine/temozolomide	2
Vincristine/actinomycin	2
Vincristine	1
TPCV (thioguanine, procarbazine, CCNU, vincristine)	1
Missing data	1
Combined with biopsy	7
Combined with subtotal resection	21
Subtotal resection alone	3
Second treatment (for disease progression or recurrence)	**40**
Chemotherapy	26
Radiotherapy	6
Resection	6
Chemotherapy and subtotal resection	2
Third treatment	**23**
Chemotherapy	15
Radiotherapy	5
Subtotal resection	3
Fourth treatment	**8**
Chemotherapy	8
Fifth treatment	**3**
Chemotherapy	3

Discussion

In this study, we report the clinical characteristics and long-term visual outcomes of a cohort of 59 pediatric patients with sporadic OPGs. To our knowledge, this is the largest cohort of pediatric patients with long-term visual outcomes for sporadic OPGs. Overall, there was a significant burden of long-term visual impairment, as more than two thirds of the patients had evidence of long-term vision loss, more than half had severe vision loss in at least one eye, and a quarter had severe bilateral vision loss. These results are comparable to the one existing study on long-term visual outcomes in sporadic OPGs. Campagna et al. [11] published a study of 32 patients with sporadic OPGs and reported that, after a median follow-up of 6 years, 74 % of the patients had evidence of significant vision loss and 16 % had severe

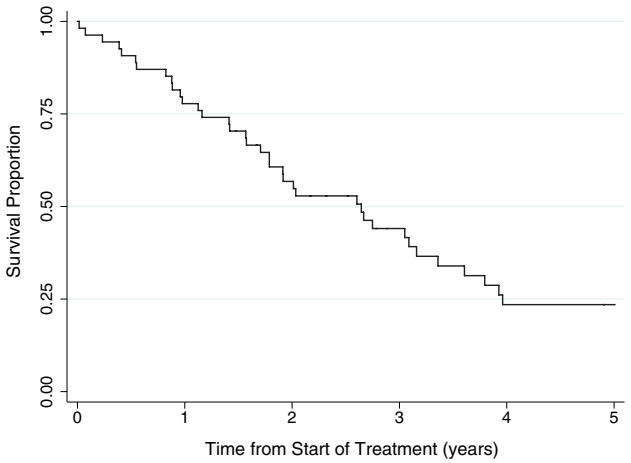

Fig. 1 Progression-free survival analysis for pediatric patients with sporadic optic pathway glioma

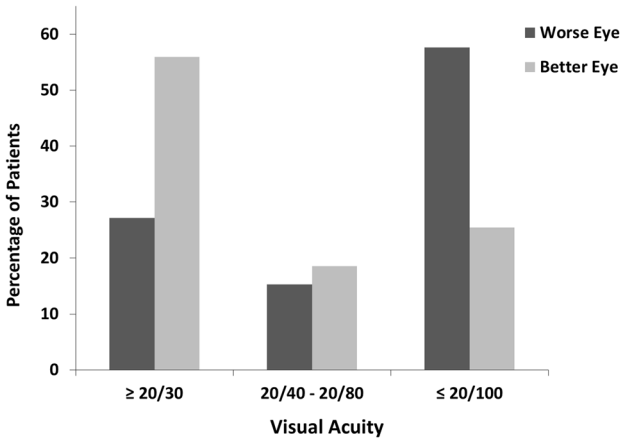

Fig. 2 Visual outcomes of the worse eye and better eye at last follow-up for pediatric patients with sporadic optic pathway glioma

Table 3 Risk factors for poor visual outcome

Eye	Risk factor at presentation	Univariate, P value	Multivariate	
			Odds ratio (95 % CI)	P value
More severely affected eye	Younger age	<0.01	2.9 (1.4–6.0)	<0.01
	Gender	0.70		
	Optic nerve pallor	0.01	4.8 (1.5–16.1)	0.01
	Optic nerve edema	0.94		
	Shunted hydrocephalus	0.41		
	Posterior extent of tumor	0.93		
Less severely affected eye	Younger age	<0.01	4.0 (1.9–8.6)	<0.01
	Gender	0.22		
	Optic nerve pallor	0.05	4.8 (1.3–18.1)	0.02
	Optic nerve edema	0.73		
	Shunted hydrocephalus	0.34		
	Posterior extent of tumor	0.01	5.8 (1.8–19.0)	<0.01

bilateral vision loss. Of note, 53 % of the patients in the study received radiotherapy, which is no longer considered first line therapy at our institution due to the secondary effects of radiation [12].

In comparison to sporadic OPGs, existing studies on the long-term visual outcomes NF1-associated OPGs suggest a more favorable prognosis. Thiagalingam et al. [13] studied 54 patients with NF1-associated OPGs and reported that 54 % had no evidence of significant vision loss and only 4 % had severe bilateral vision loss after a mean follow-up of 8.6 years. Balcer et al. [14] looked at 43 patients with NF1-associated OPGs and reported that 23 patients (53 %) had no evidence of vision loss after a median follow-up of 3 years. Segal et al. [15] reported visual acuity outcomes for 44 patients with NF1-associated OPGs and found that only four patients (9 %) had significant OPG-related vision loss after a mean follow-up of 7 years. Finally, Fisher et al. found that 72 % of children with NF1-associated OPGs had stable or improved vision after treatment with chemotherapy [16]. The current study adds further evidence that patients with sporadic OPGs have more severe long-term visual impairment in comparison to patients with NF1-associated OPGs. However, it should be noted that patients with NF1 are routinely screened for OPGs and many diagnosed NF1-associated OPGs do not require treatment. Therefore, it may be worthwhile for future studies to compare visual outcomes in NF1 and non NF1-associated OPGs which require therapy.

In the analysis of risk factors for a poor visual outcome, we identified post-chiasmal involvement, younger age, and optic nerve pallor at presentation as statistically significant risk factors for long-term vision loss. Although not a universally consistent finding [15], posterior tumor involvement at presentation has been associated with poor visual outcomes in several studies [14, 16–18]. Younger age at diagnosis was identified as a risk factor by Fisher et al. [16] and Thiagalingam et al. [13] for NF1-associated OPGs. Campagna et al. [11] suggested that both younger age and optic nerve pallor were poor prognostic factors for sporadic OPGs, but did not statistically test these assertions. This study adds evidence that posterior tumor involvement, younger age, and optic nerve pallor at presentation are risk factors for a poor visual outcome in sporadic OPGs. Further research is needed, for both NF1-associated and sporadic OPGs, to further define and quantify the impact of such prognostic factors.

The risk of disease progression with sporadic OPGs and the need for monitoring are central issues in the care of affected patients. At our institution, patients are monitored with serial MRIs and frequent ophthalmic examinations. The overall rate of progression in the study was high at 74 %, adding to the accumulating body of evidence that sporadic OPGs have a greater risk of progression compared to NF1-associated tumors [6, 19–24]. At present, there is no universally accepted definition of progression and existing studies have used variable radiological and clinical criteria to define progression [16, 25]. One thing that has become clear is that radiological changes and changes in visual function are not always correlated [16, 26–28]. Indeed, in our study, only 22 % of the patients with progression had concurrent changes in vision and imaging, while 24 % had vision changes only, and 54 % had MRI changes with stable visual function. Therefore, we believe that it is crucial that patients with sporadic OPGs are monitored with serial MRIs and ophthalmic examinations by an ophthalmology service that is able to quantify and follow visual function in children.

Another central issue for patients OPGs is the lack of clear treatment indications. Treatment decisions are not always straightforward and can hinge upon several factors including patient age, tumour location and size, and visual symptoms [29]. In our cohort, over 90 % of the patients received treatment, most commonly a weekly chemotherapy regimen of vincristine and carboplatin [30]. Fisher et

al. [16] demonstrated convincingly that chemotherapy can stabilize, and sometimes improve, the vision of patients with NF1 associated OPGs. Since the majority of patients in our study (59 %) were unable to perform letter recognition visual acuity at presentation, we were unable to address this question directly. Therefore, whether treatment of sporadic OPGs results in improved visual outcomes remains an open question [31].

In the future, the management of pediatric gliomas may be transformed by emerging research in molecular and cell biology. In patients with NF1-associated OPGs, there is a mutational inactivation of the NF1 tumor suppressor gene [32]. In contrast, many cases of sporadic OPGs are associated with a somatic rearrangement, in which the kinase domain of the BRAF gene is fused to gene KIAA1549 (KIAA1549:BRAF) [33]. The presence or absence of the KIAA1549:BRAF fusion and the prognostic significance is currently under investigation. In our study, we were unable perform a meaningful analysis on the molecular data because only a minority of patients had biopsy tissue available for molecular testing. However, as new evidence continues to emerge, molecular factors will likely play an increasingly important role in the diagnosis, prognosis, and treatment of OPGs.

There are several limitations to this study. Due to the retrospective nature of the study, the follow-up was variable in terms of frequency and overall duration. In addition, the definition of progression and the treatment indications and regimen were not standardized and there was some variation between patients over the course of the study.

Finally, although this is the largest reported cohort of sporadic OPGs, there were too few patients who were untreated (8 %) to perform any meaningful comparative analysis of treatment efficacy.

In this cohort of pediatric patients with sporadic OPGs, there was a large burden of visual impairment. Treatment was initiated for the majority of the patients, but there was still a high propensity for disease progression. The results of this study suggest that the long-term visual outcomes for sporadic OPGs remain poor despite high rates of therapy, and more research is needed to better define treatment indications, standardize criteria for progression, and assess treatment efficacy and durability. In addition to neuro-imaging, serial ophthalmic assessments with quantitative measures of visual function are crucial in a multidisciplinary approach to the management of sporadic OPGs in children.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedure performed in studies involving human participants were in accordance with the ethical standards of Boston Children's Hospital and Harvard University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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