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Natural History and Outcome of Optic Pathway Gliomas in Children

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Background. The optimal management of optic pathway gliomas (OPGs) is complicated by their variable natural history, the association with neurofibromatosis type 1 (NF1) and difficulties in defining progression and response to treatment. ***Methods.*** This study is a retrospective review of all children presenting to a single institution with an OPG between 1990 and 2004. ***Results.*** Of the 133 children included, 78 (59%) had NF1; 87 (71 NF1) were observed initially, of whom 23 (11 NF1) subsequently required treatment. Forty-six patients received immediate treatment. Initial treatment, without or with an observation period, comprised chemotherapy alone (32, 11 NF1); debulking + chemotherapy (15, 4 NF1); gross total resection (6); radiotherapy (2); debulking + radiotherapy (3); and debulking only (12, 3 NF1). Overall, 16 patients were irradiated during the study period. Four children died (overall survival at 5 and 10 years was 97.6% and 94.6% for those who required treatment). Progression-free survival (PFS) for the 69 patients who needed treatment was 48%. There was no difference in PFS between chemotherapy versus chemotherapy + debulking or debulking alone. PFS for the NF1 patients who required treatment was similar to that of non-NF1 patients. Mean follow-up time was 9.0 (range 0.6–18.0, median 8.6) years. ***Conclusions.*** The study confirms the complexity of OPGs and that NF1 is a major determinant of the resultant behavior of the tumor. Pediatr Blood Cancer 2009;53: 1231–1237.

Key words: diagnosis; low-grade gliomas; neurofibromatosis type 1; optic pathway; progression-free survival; treatment; visual outcome

INTRODUCTION

The optic pathway is a common site for low-grade gliomas in childhood. Despite this, optic pathway gliomas (OPGs) remain controversial in terms of what constitutes optimal management. Reasons for this include: difficulties with diagnosis often based on radiological characteristics rather than histology; the association with neurofibromatosis type 1 (NF1); the variable natural history ranging from prolonged periods of stability or even spontaneous regression to periods of slow or rapid progression; the ability to disseminate; and the difficulty in defining response to treatment or defining what constitutes progression. Treatment options in the past have included radiotherapy [1–4], surgery [5–8] and more commonly in recent years, chemotherapy [1,9–13]. These treatments may have been preceded by an initial period of observation.

In an attempt to better understand the natural history of OPGs and to describe the overall burden of these tumors on patients and clinicians, we report on all patients with OPG who were diagnosed and treated at a single institution. In this report, the optic pathway is taken to include the following: the optic nerves, optic chiasm, hypothalamus/suprasellar region, and optic radiations.

METHODS

This was a retrospective review of all consecutive patients who were diagnosed as having an OPG and were managed at the Hospital for Sick Children in Toronto, Canada, between the January 1, 1990, and December 31, 2004. Patient charts, radiology and pathology reports were reviewed for data relating to patient demographics, clinical presentation, diagnosis, treatment, outcome of treatment, visual and neuropsychological assessments, and follow-up. Patients were identified from a database of patients treated by the Pediatric Brain Tumor Program and a database of children seen at the Neurofibromatosis Clinic. Ethical approval for this study was granted by the Institutional Research Ethics Board.

One hundred thirty-three patients identified as having an OPG were diagnosed between January 1, 1990, and December 31, 2004. All of these patients had magnetic resonance imaging (MRI) performed before treatment commenced, except for six in whom treatment was started based on the findings of a computed tomography (CT) scan alone. All the latter six patients did receive subsequent MRI scans at some time during the study period.

Tumors were classified radiologically according to the location into groups as listed in Table I. In most cases, it is impossible to distinguish between low-grade gliomas that arise intrinsically from the optic chiasm and spread outwards or those that arise from hypothalamus and involve or compress the chiasm. Therefore, no attempt is made in this report to distinguish between chiasmatic and hypothalamic lesions. The diagnosis of optic nerve involvement usually involved consideration of the size (thickness), tortuosity, and contrast enhancement of the optic nerve. Patients whose imaging studies reported mild thickening of the optic nerves only were excluded unless the thickening was globular *and* associated with tortuosity and/or contrast enhancement.

For the purpose of this study, the extent of surgical resection is divided into: (1) no surgical procedure; (2) biopsy (<10% tumor removed); (3) debulking surgery >10% tumor removed; and (4) gross total resection (no residual tumor visible by surgeon or

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TABLE I. Demographic, Clinical, and Pathology Data

	Non-NF1	NF1	Overall
Number of patients	55 (42%)	78 (58%)	133
Gender	Male: 25 (45%)	Male: 47 (61%)	Male: 72 (54%)
	Female: 30 (55%)	Female: 31 (39%)	Female: 61 (46%)
Age at diagnosis (years)	Mean: 7.21	Mean: 5.09	Mean: 5.89
	Range: 0.34–17	Range: 0.39–14.6	Range: 0.34–16.8
0–1 years	9	1	10
1–4 years	13	50	63
5–9 years	15	20	35
>10 years	18	7	25
Reasons for 1st imaging			
Eye problems			61 (46%)
Decreased visual acuity	11	5	16
Nystagmus	12	2	14
Proptosis	7	5	12
Papilloedema	8	0	8
Optic atrophy	3	4	7
Squint	2	2	4
Field defect	2	0	2
Diplopia	1	0	1
NOS	5	4	9
Screening imaging	0	52	52 (39%)
Neurological problems			
Headaches ± vomiting	17	5	22
Seizures	1	1	2
Motor deficit	5	1	6
Cranial nerve palsy	2	0	2
Ataxia	1	1	2
Altered behavior	1	1	2
Losing development milestones	1	0	1
Head bobbing	0	1	1
Endocrinopathy			6
Precocious puberty	3	2	5
Short stature	1	0	1
Others	2	1	3
Incidental finding on head imaging	2	1	3
Increasing head circumference	1	1	2
Diencephalic syndrome	1	1	2
Intracranial bleed	1	0	1
Stiff neck	1	0	1
Back pain	1	0	1
Tumor location			
Hypothalamic/chiasmatic (HC)	35	15	50
Unilateral optic nerve	7	22	29
HC + bilateral optic nerves	3	16	19
HC + unilateral optic nerve	1	9	10
Bilateral optic nerves	0	10	10
HC + optic nerves + optic radiations	3	6	9
HC + extension to thalamus	3	0	3
HC + optic radiations	1	0	1
HC + dissemination	2	0	2
Diagnosis			
Imaging only	7	68	75 (59%)
Low-grade astrocytoma (NOS)	22	6	28
Pilocytic astrocytoma	22	2	24
Pilomyxoid astrocytoma	1	2	3
Fibrillary astrocytoma	1		1
Ganglioglioma	1		1
Oligodendroglioma	1		1

NF1, neurofibromatosis type 1; NOS, not otherwise specified.

on imaging). The distinction between biopsy and debulking was made taking into account the surgeons' interpretation of the outcome of the surgical procedure and radiological imaging post procedure.

The majority of children had their vision checked regularly. Visual data collected included clinical features, visual acuity, and visual fields. Data were analyzed in terms of best eye and worse eye. Visual acuity was assessed using a variety of methods adapted to the child's developmental age. Most patients >3 years were assessed using a Snellen linear chart method. In children who were not able to cooperate with this method (usually <3 years of age), visual acuity was assessed as accurately as possible using single optotype symbols, the preferential looking method using Cardiff cards, or pattern visual-evoked potentials. Peripheral visual field data were assessed clinically by confrontation testing and in those children who were old enough to cooperate, the findings were confirmed by formal Goldmann perimetry. In only three patients no visual assessments were obtainable for review at any stage of their management.

For comparison purposes, Snellen visual acuities were converted to the nomenclature using logarithm of the minimal angle of resolution (log MAR) [14]. A Snellen score of 20/20 converts to a log MAR of 0.0, 20/40 to a log MAR of 0.30, 20/100 to a log MAR of 0.69, 20/200 to a log MAR of 1, and 20/400 to a log MAR of 1.3. Log MAR results were clustered into the following groups: <0.0–0.0 (normal vision), 0.01–0.29 (mild impairment of vision), 0.3–0.69 (moderate visual impairment—the World Health Organization (WHO) definition of low vision [15] starts at 0.3 log MAR), 0.7–1.69 (severe visual impairment), and then 1.7 (counting fingers), 1.8 (hand movements), 1.9 (light perception), and 2.0 (no light perception). Legal blindness is defined in most countries in terms of a visual acuity value of 1.0 log MAR or worse.

Statistical Considerations

Treatments were assessed in terms of progression-free survival (PFS). PFS was measured from the date of diagnosis to the date of progression, death or last contact and was estimated using the Kaplan–Meier method [16]. When patients experienced tumor progression, the exact date of progression was difficult to record because diagnosis of progression was often based on a combination of clinical, visual, and imaging assessments, not all of which occurred at exactly the same time. Date of progression was therefore recorded as the date on which treatment was changed in response to the progression.

Follow-up data were analyzed to the end of December 2008. Comparisons of subgroups were by log-rank analysis.

RESULTS

Demographics

Of the 133 patients identified with OPG, 78 (58%) had NF1. There were 72 males (48 NF1) and 61 females (30 NF1). Patients were much more likely to be male if they had NF1 ($P = 0.028$). Mean age at diagnosis was 5.89 (range 0.34–16.8) years for the whole group; 7.09 (range 0.34–16.8) years for those without NF1 (NNF1); and 5.05 (range 0.39–14.6) years for the NF1 group. This difference in age at presentation for the latter two groups was statistically significant ($P = 0.0008$). These findings are summarized in Table I.

Clinical Presentation

Clinical presentation was variable. Reasons for the first imaging being performed are presented in Table I. Fifty-two patients (all NF1) were diagnosed following a screening scan which was the policy in the neurofibromatosis clinic at various times during the study period. Seventeen patients (15 NNF1 + 2 NF1) had hydrocephalus at diagnosis that required a ventriculoperitoneal shunt. Visual acuities at diagnosis and before treatment commenced were available in 107 patients.

Diagnosis

Seventy-five patients (67 NF1) were diagnosed as having an OPG by imaging characteristics only. The rest of the patients (58, 10 of whom had NF1) had their diagnosis confirmed histologically. This includes 9 patients who had delayed surgery 5–110 months after initial diagnosis by imaging only. Histological subtypes are listed in Table I.

Tumor Location

Tumor locations on imaging are listed in Table I. Patients with NF1 were more likely to have lesions involving one or both optic nerves, whereas chiasmatic/hypothalamic involvement was more common among NNF1 patients. Two NNF1 patients presented with disseminated disease, both involving leptomeningeal spread including the spine. Both patients underwent a diagnostic biopsy at the spinal level.

Treatment

Following the initial diagnosis of OPG, patients were managed as follows. In 87 patients (16 NNF1, 71 NF1), a decision was made to observe the patient only with follow-up imaging. Sixteen non-NF1 patients were observed because of mild visual symptoms (four nystagmus, five reduced visual acuity or visual field), presenting hydrocephalus that was treated with ventriculoperitoneal shunt (four patients), proptosis, precocious puberty, or incidental diagnosis (one patient each) that allowed an observation strategy. In five of these NNF1 patients, a biopsy was performed before the period of observation. For the remaining 46 patients (7 NF1), treatment was started immediately. The rationale for starting treatment was multifactorial and included consideration of the age of the child, NF1 status, tumor size, duration and severity of symptoms and visual status. Treatment for these 46 patients included: chemotherapy (16 NNF1 + 2 NF1, 12 of these NNF1 patients had a biopsy before chemotherapy); debulking + chemo-chemotherapy (8 NNF1 + 4 NF1); gross total resection (5 NNF1); debulking + radiotherapy (2 NNF1); and debulking only (8 NNF1 + 1 NF1). Of the 87 patients who were observed initially, 23 (12 NNF1 + 11 NF1) progressed and required treatment. The mean time from diagnosis to start of treatment in those who failed the initial period of observation was 10.6 (range 2.5–177) months (5.6 months for NNF1 patients vs. 15.4 months for NF1 patients). First treatment in those who failed initial observation included: chemotherapy (5 NNF1 + 9 NF1); debulking + chemotherapy (3 NNF1); debulking only (1 NNF1 + 2 NF1); radiotherapy (2 NNF1); and gross total resection (1 NNF1).

Details of initial treatments are provided in Figure 1. Chemotherapy regimens used as first-line treatment varied during the

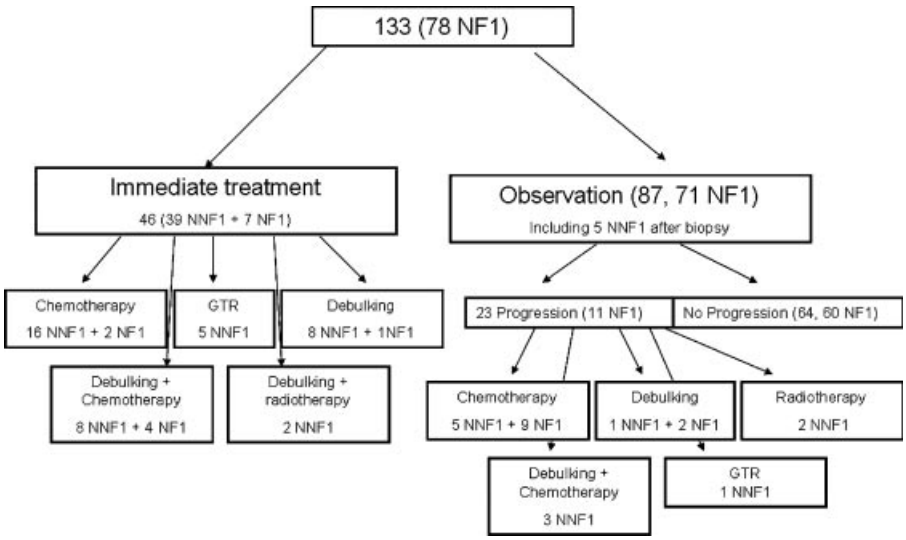

Fig. 1. Details of the initial management for the 133 patients (NF1, neurofibromatosis type 1; NNF1, patient without neurofibromatosis; GTR, gross total resection).

15 years of the study period. Details of chemotherapies used are summarized in Table II. When more than one chemotherapy regimen was used in an individual patient, 47 changes were due to tumor progression, 15 changes were due to carboplatin allergy, 1 was due to hearing loss, and 1 was due to delays caused by myelosuppression.

Outcome

Median follow-up time for patients in this study was 8.6 years (range 0.56–18.0) years. Four patients died during the study period; one after widespread dissemination of her disease; two patients who were severely neurologically disabled from the effects of their tumor, hydrocephalus, or debulking surgery, progressed after completing one and three courses of chemotherapy, respectively, and no further treatment was attempted. The fourth patient who had NF1 died from a radiotherapy-induced secondary PNET which did not respond to treatment.

Twenty-six of 51 (55%) patients without NF1 and 8 of 18 (44%) with NF1 who required treatment progressed after their first-line treatment. Twenty patients (6 with NF1) progressed only once; 8 (1 with NF1) progressed twice; 4 (1 NF1) progressed thrice; 2 progressed eight times. Mean time to first progression for all patients was 28.4 months (range 2.5–117.5, median 23.4). Mean time to second progression was 29.4 months (range 3.9–109.2, median 15.7). Figure 2 illustrates age distribution at time of progression. Most progressions occurred early in childhood with a peak between 2 and 4 years of age. It would appear that there may a smaller peak around the time of puberty between 9 and 14 years of age. Overall, 16 children including 3 children with NF1 received radiotherapy at some time during their treatment, although it was the part of the initial treatment in only 4 patients. Median age at the time of irradiation was 11.3 years (range 3–17). Out of the 16 patients, radiotherapy was the final treatment used in 10 children. The other six patients progressed after their radiotherapy and required further treatment with chemotherapy (five patients) or surgery (one patient). No child with NF1 was irradiated since 1994 and only four patients diagnosed between 1998 and 2004 received radiotherapy compared to 12 diagnosed during the period 1990–1997. The 5-year radiation-free estimate for treated patients was $67.6 + 8.1\%$ for patients diagnosed between 1990 and 1997 compared to $90.9 + 5.0\%$ for patients diagnosed in 1998 and after ($P = 0.071$).

Overall survival for the whole group of patients was $97.6 + 1.4\%$ at 5 and 10 years and $94.6 + 3.1\%$ at 5 and 10 years for treated patients. PFS was $89.5 \pm 15\%$ for the NF1 patients and $47 \pm 7\%$ for the non-NF1 group ($P < 0.0001$). PFS at 5 and 10 years for those 67 patients who needed treatment was 48.3% (CI 30.5–57.5) and 45.6% (CI 33–57.6), respectively. There was no significant difference in PFS when compared among those who underwent chemotherapy alone, debulking, and chemotherapy or debulking alone as first-line treatment. Salvage treatment patients received were decided according to what they received as first-line treatment and existing protocols at the institution.

TABLE II. Chemotherapy Protocols Used as First-Line Treatment

Chemotherapy protocol	Number of patients
Chemotherapy alone	
Weekly carboplatin + vincristine[a]	15
Monthly carboplatin + vincristine[b]	10
Monthly carboplatin alone[c]	5
Vincristine + CCNU + procarbazine	1
Vinblastine	1
Debulking + chemotherapy	
Monthly carboplatin alone[c]	9
Monthly carboplatin + vincristine[b]	3
Weekly carboplatin + vincristine[a]	1
Vincristine + etoposide	1
Thioguanine + procarbazine + CCNU + vincristine	1

[a]Induction: carboplatin 175 mg/m^2 weekly at weeks 0, 1–3, 6–9. Vincristine 1.5 mg/m^2 weekly for weeks 0–9. Maintenance: carboplatin 175 mg/m^2 weekly × 4 in 6-week cycles. Vincristine 1.5 mg/m^2 weekly × 3 in 6-week cycles; [b]Carboplatin 560 mg/m^2 and vincristine 1.5 mg/m^2 monthly; [c]Carboplatin 560 mg/m^2 monthly × 1 year.

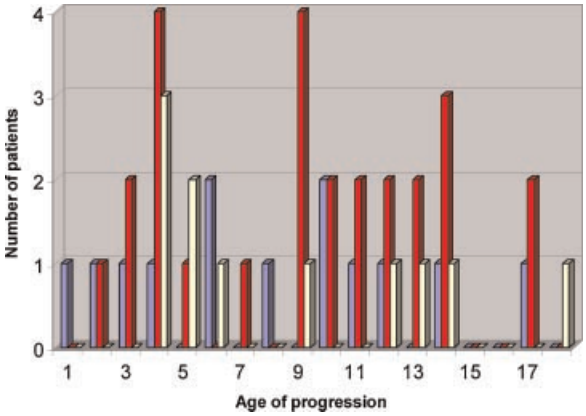

Fig. 2. Age distribution and progression. The blue histograms show the age of progression after an initial period of observation. The red histograms show the age of progression after an initial treatment. The yellow histograms show the age of progression after two initial treatments. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Visual acuities before both treatment commenced and after all treatment were completed were available in only 31 of the 66 patients who received treatment. Visual outcome data are illustrated in Tables III and IV. There were insufficient data collected at diagnosis or prior to treatment (often because the patient was too young for accurate assessment) to be able to make any comparisons between peripheral field findings before and after treatment. Ten patients had severe neurological deficits at the time they were last seen; five of these patients suffered the damage immediately after their debulking procedure. Six patients had seizures, including two NF1 patients who were never treated.

Data regarding intellectual outcome were available for 35 patients referred for neuropsychological assessment. Thirty-four of these patients received treatment including chemotherapy, debulking, and/or radiation with only one patient being monitored without therapy. Table V shows the characteristics of this sample). Mean Full, Verbal, and Visual-spatial scale IQ scores for the entire sample were 81, 77, and 95, respectively. Overall, the Full scale and Verbal scores are >1 standard deviation below normative means (mean = 100, SD = 15), indicating generally poor outcome. Quantitative comparisons were not conducted due to small and unequal subject numbers but IQ scores for children who received radiation therapy at any time in their treatment were not lower than the overall group means (Full scale = 95, Verbal = 96, Visual-spatial = 87). Patients with NF1 displayed IQ scores similar to the overall means (Full scale = 85; Verbal = 83; Visual-spatial = 87). Patients treated with debulking and chemotherapy displayed lower Full and Verbal scale IQ than those treated with chemotherapy only (Full scale = 76 vs. 85; Verbal = 76 vs. 84), but no difference for Visual-spatial IQ (87 vs. 87). Further, patients treated with shunt insertion for hydrocephalus displayed lower Full, Verbal, and Visual-spatial scale IQ relative to those not requiring shunt insertion (FIQ = 68 vs. 81; VIQ = 69 vs. 77; PIQ = 87 vs. 95).

TABLE IV. Peripheral Visual Fields at Least 6 Months After Completion of Treatment or at Last Assessment for Those Not Receiving Treatment

Peripheral visual field finding	Number of patients
Normal in both eyes	67
Light perception only or worse in one eye and normal in other eye	9
Light perception only or worse in both eyes	6
Unilateral constriction and other eye normal	5
Bilateral constriction	4
Bilateral constriction and bitemporal hemianopsia	4
Homonymous hemianopia	2
Unilateral hemianopia and other eye normal	1
Bitemporal hemianopia	1
Unilateral hemianopia and other eye light perception only or worse	1
Unilateral constriction and other eye light perception only or worse	1
Junctional scotoma	1
Unilateral constriction and unilateral hemianopia in same eye	1
Bilateral constriction and unilateral hemianopia	1

DISCUSSION

Demographics and Association With Neurofibromatosis Type 1 (NF1)

The incidence of associated NF1 varies in studies of OPG from 18% to 58% [1,2,5,9–13,17,18]. This reflects the selection of patients in those studies, some of which only reported patients who

TABLE III. Change in Visual Acuities in Patients Before and After Initial Treatment and at Diagnosis and Date When Last Seen for Those Not Receiving Treatment

	Best eye at diagnosis				Worse eye at diagnosis			
	No change	Better[a]	Worse[a]	Insufficient data	No change	Better[a]	Worse[a]	Insufficient data
Observation only	25 (38%)	17 (26%)	13 (20%)	11 (17%)	22 (33%)	23 (35%)	10 (15%)	11 (17%)
Chemotherapy	8	3	1	18	5	4	3	18
Debulking and chemotherapy	4	4	0	9	5	1	2	9
Radiotherapy	1	0	0	1	1	0	0	1
Debulking and radiotherapy	1	1	0	1	1	1	0	1
Gross total resection	2	0	0	4	0	0	2	4
Debulking only	5	0	1	3	4	0	2	3

[a]Better or worse indicates any decrease or increase in log MAR score, respectively.

TABLE V. Medical and Demographic Characteristics of Sample of Patients Seen for Clinical Neuropsychological Assessment

	Patient characteristics
Age at diagnosis (years)	5.57
Age at assessment (years)	10.49
Time since diagnosis (years)	4.92
NF status	
NF diagnosis	11
Non-NF	24
Radiation therapy	
Yes	9
No	26
Treatment	
Chemotherapy and debulking	13
Chemotherapy only	22
Shunt insertion	
Yes	13
No	22

were being treated, others reported all patients. The incidence of NF1 in our study was 58% in all patients but only 25% in those who were actually treated. The mean age at diagnosis was significantly less in the NF1 patients than the non-NF1 patients ($P = 0.0008$). Other studies have not shown any significant difference in age at presentation [2]. It is probable that OPG in NF1 patients are over-diagnosed when a policy of radiological screening is in effect.

Progression After Initial Period of Observation

Twelve out of 16 non-NF1 (69%) and 11 out of 71 NF1 (13%) patients initially observed demonstrated evidence of progression after an initial period of observation following diagnosis. The mean time to progression was similar to other studies [1,18]. Only four non-NF1 patients therefore did not receive any treatment at all throughout the study period. All four had tumors affecting the hypothalamic/chiasmatic region with mild visual symptoms allowing careful observation. One had concomitant hydrocephalus that required ventriculoperitoneal shunt. Three patients were teenagers at diagnosis (13, 14, and 15 years) and one was 5 years old. Follow-up time was 26, 54, 68, and 158 months.

Treatment

The management of our patients varied throughout the 15-year period of this study, but was increasingly characterized by an emphasis on avoiding the use of radiotherapy. Surgery played more of a role in the earlier period. All patients who underwent debulking as part of their initial treatment were treated before the end of 2000—no debulking was done as primary treatment thereafter. In keeping with trends reported in the literature [1,9–13], chemotherapy was increasingly used to control disease initially, but in our program, most of our patients who progressed more than once were often treated with multiple different chemotherapy regimens. The reasons for commencing treatment were multifactorial in most cases and involved a consideration of the following: age of the child, presence or absence of NF1, size of tumor, duration and severity of symptoms, and visual status. This was difficult to assess retrospectively and is one of the weaknesses of this study.

The Role of Debulking Surgery

Gross total resection is clearly an effective treatment for those cases in which it is feasible. Six patients, all with non-NF1, unilateral optic nerve gliomas, and no useful vision in the affected eye, had their tumors completely excised primarily for cosmetic reasons. One further NF1 patient with a growing unilateral OPG progressed after a trial of chemotherapy such that she lost any useful vision also subsequently underwent gross total resection. None of these patients had a recurrence of their tumor. However, can surgery that results in less than a gross total resection be considered a treatment in its own right? Twelve patients (nine non-NF1 and three NF1) had debulking surgery only as their initial treatment (including three patients after a period of observation). All had tumors in the hypothalamic/chiasmatic region. Six out of nine non-NF1 patients and the three NF1 patients subsequently progressed and required further treatment. Mean time to progression was 17.7 months (range 3.3–59.5). There were therefore three, all of whom have obvious residual tumor on imaging, who have not progressed after 73, 108, and 132 months follow-up. There was no significant difference, however, in PFS between patients who received chemotherapy alone ($n = 32$) and those who had debulking followed by chemotherapy ($n = 15$) as their initial treatment ($P = 0.65$).

Outcome

Four patients died during the period of this study. The OS of 97.6% at 5 and 10 years for the whole group and 94.6% for that group of patients who required treatment compare favorably with other large studies. However, comparing results is difficult since many studies originate from oncology centers or oncology groups. Fouladi et al. [1] report on a group of 73 children with hypothalamic/chiasmatic tumors receiving radiotherapy or chemotherapy whose 6-year OS was 86%. Laithier et al. [10] report on a prospective French Society of Pediatric Oncology (SFOP) study using chemotherapy as first-line therapy in 85 children and their 5-year OS was 89%. Cappelli et al. [2] report an OS at 10 years of 83% for 69 children treated with radiotherapy before the chemotherapy era. Because of these good OS results, most studies report on PFS which is a more useful parameter. Our PFS at 5 years for patients who required treatment was 48.0% (CI 36–60). By comparison, Fouladi et al. [1] report a 6-year PFS of 36% for their whole cohort, 69% for those treated with radiotherapy, and 12% for those treated with chemotherapy. Cappelli et al. [2] report a 10-year PFS of 65.5% for patients treated with radiotherapy and Grabenbauer et al. report a similar 69% at 10 years for their group of 25 patients treated with radiotherapy. The SFOP study mentioned previously reported a 5-year PFS of 34% with chemotherapy [10].

Radiotherapy Versus Chemotherapy

Sixteen children received radiotherapy at some time during their treatment including three patients with NF1 who were treated in the early period of this study. It is worth noting that one child with NF1 who received radiotherapy as salvage treatment subsequently died from a secondary malignant tumor confirming the widely held belief that radiotherapy should be avoided in this group because of the increased risk of second cancer and vasculopathies [19,20]. The role of chemotherapy in the management of OPG has increased over the last two decades [21]. Our experience confirms this trend and the

present report contrasts with a previous publication from our institution in which radiation was the treatment of choice [22].

As we have found in our study, it is difficult to study visual outcomes in children with OPG in a retrospective manner. Many studies report visual outcome in a non-standard manner and make comparison of results between treatments difficult. Gayre et al. [23] attempted to describe the long-term visual outcome of patients with OPG but did not go in to any detail on the methods used in assessing children's vision. OPGs impact on visual acuity and visual fields and these are difficult to test reliably and accurately in the young children who comprise a large proportion of these patients at diagnosis. Because any comparisons of treatments, for example, chemotherapy versus radiotherapy will need to take visual outcome into account, vision assessment is an area of research that will require dedication and cooperation between oncologists and ophthalmologists. Hopes for the use of extended visual-evoked potentials have been raised [24] but have not met universal agreement. It is possible that more detailed studies comparing tumor location on MRI with visual defects may allow better prediction of visual problems.

CONCLUSIONS

This report confirms the complexity of the natural history of OPG and suggests that current chemotherapy-based strategies are not associated with decreased outcomes compared to previous radiation-based strategies. The coexistence of neurofibromatosis is a major determinant of the resultant behavior of the tumor. However, once a patient with NF1 has been shown to have a tumor which needs treatment, the PFS is not too dissimilar to patients without NF1 in our study. Our findings suggest that the role of surgery in OPG is beneficial when the object is biopsy, decompression of a tumor causing hydrocephalus, or gross total resection of a unilateral optic nerve glioma in which there is no useful residual vision in the affected eye. The role of debulking as an adjunct to other therapies is unclear but may be associated with more long-term side effects.

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