Optic Pathway and Hypothalamic/ Chiasmatic Gliomas in Children Younger than Age 5 Years with a 6-Year Follow-Up

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Background. **Gliomas of the hypothalamus and optic pathways (H/OPG) comprise 5% of pediatric intracranial tumors, present most frequently in patients younger than age 5 years, and may have a more aggressive course in younger children. This study examined clinical characteristics and consequences of treatment of young children diagnosed with H/OPG.**

Methods. **The authors reviewed the course, treatment, and outcomes of 46 children diagnosed with H/OPG younger than age 5 years; the median follow-up was 72 months. The median age at diagnosis was 27 months.**

Results. **Fifteen (33%) of 46 patients had neurofibromatosis-1 (NF-1).Forty children (87%) had tumor progression in the follow-up period, and tumor growth was less common in children with NF-1.**

Initial therapy was limited to surgical resection in three and radiation in five children. To postpone radiation until after the age of 5 years, initial therapy was limited to chemotherapy in 32 patients. Radiation was not required in 9 of these patients and was postponed for 40 months (mean) in 17.

Of the 46 children, 5 died of tumor progression, 4 became blind, and 20 of 34 evaluable patients had endocrine abnormalities. Endocrinopathy did not correlate with therapy. Ten of 17 children evaluated by questionnaire required special education. There was a trend for educational problems to occur in children who were irradiated before the age of 5 years.

Conclusions. **Gliomas of the hypothalamus and optic pathways and their treatment cause long term morbidity in young children. Chemotherapy postpones radiation effectively, and this delay may reduce neurologic morbidity; however, 60% of children eventually relapse. By contrast, patients with NF-1 have indolent disease. *Cancer* 1995;75:1051–9.**

Key words: hypothalamic gliomas, optic pathway gliomas, chiasmatic gliomas, neurofibromatosis type 1, radiation injury, endocrinopathy, chemotherapy.

Histologically benign optic pathway gliomas with or without contiguous involvement of the hypothalamus (H/OPG) comprise 2–5% of intracranial tumors in children. Of these tumors, 65% occur in the first 5 years of life.[1–4] The behavior of these tumors is highly variable. Large globular tumors may remain quiescent for years, and small chiasmatic tumors may cause rapid visual loss. Most H/OPGs, however, eventually progress, leading to visual disability, endocrine or intellectual impairment, and, in up to 20–30% of patients, death.[1–11] There are no clinical, histologic, or neuroimaging characteristics that distinguish aggressive from indolent tumors. Recent reports, however, suggest that these tumors are more aggressive in the very young.[12–14]

Management strategies for visual pathway gliomas include observation, surgery, irradiation, chemotherapy, and a combination of these modalities.[1–12,15–25] Radiation has been the standard therapy for progressive H/OPGs. The late effects of radiation therapy, however, including endocrinopathy, vasculopathy, optic nerve injury, and radiation-induced second neoplasms, are important considerations of H/OPG management strategies, because most patients with H/OPGs survive longer than 10 years. These issues have stimulated in-

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vestigation of alternative treatment approaches, including chemotherapy, that are associated with little risk of second malignancy, surgery, and reduced doses of radiation.[2,4–7,10,11,15,17–25]

Investigation of new management strategies of H/OPGs in children younger than 5 years of age assumes a high priority because this is the most common age of initial diagnosis, H/OPGs may be more aggressive at this age (see above), and progressive radiation-associated cognitive dysfunction is more severe in young children.[3,20–27] Phase II chemotherapy trials produce objective response rates (comparable to those of radiation therapy), providing important evidence that these agents are active against low grade astrocytic tumors and suggest that some cytotoxic drugs may delay or obviate the need for radiation therapy in children younger than 5.[3,20,27] These and other studies in young children suggest that chemotherapy may have little or no significant adverse effect on cognitive or endocrine function. The limited duration of follow-up for H/OPG Phase II studies, however, does not permit an accurate assessment of the duration of the response or the proportion of children for whom radiation therapy is delayed successfully beyond 5 years.

To address these questions, we retrospectively evaluated the medical records of 46 children treated at The Children's Hospital of Philadelphia (Philadelphia, PA) for H/OPG who were younger than 5 at the time of initial tumor diagnosis. The present report describes the clinical presentation, management strategies, outcome, and long term functional status of these patients.

Patients and Methods

Patients

Between 1977 and 1990, 76 children with H/OPGs were diagnosed or treated at The Children's Hospital of Philadelphia. These include gliomas of the optic chiasm, posterior extension of tumor along the optic radiations, and/or contiguous involvement of the hypothalamus. Isolated optic nerve tumors anterior to but not invading the optic chiasm were not included. Forty-six of these children (65%) were younger than 5 years of age at initial diagnosis and constituted the study population. Previous reports from The Children's Hospital of Philadelphia focusing on response of H/OPGs to therapy included 25 of these 46 children.[10,16] The present study significantly expands both the period of follow-up and the size of the study population, evaluates the efficacy of multiple treatment modalities, and characterizes the long term sequelae of H/OPGs and therapy in young children.

All patients were evaluated serially by neurologic and ophthalmologic examinations. Children with neurofibromatosis Type 1 (NF-1) met the National Institutes of Health consensus criteria for the clinical diagnosis of NF-1.[28] Neuroimaging studies included computed tomography scanning or magnetic resonance imaging (MRI). Clinical and neuroimaging studies were performed at diagnosis and were repeated every 3–6 months for 3 years, and yearly thereafter. Biopsies were not performed on chiasmatic lesions with contiguous optic nerve involvement and posterior extension along visual pathways of H/OPGs in children with NF-1. Biopsy confirmation was obtained in 26 patients without NF-1 and with globular tumors extending into the hypothalamus. The pathologic diagnosis was pilocytic astrocytoma for 15 of the cases biopsied, and fibrillary astrocytoma for the remaining 11. Median follow-up time was 72 months (range, 1 month to 16 years), the and mean follow-up time was 73 months (standard error, 7 months). Only one child, who died postoperatively (see below), was followed for less than 8 months. Seventeen children (37%) were followed for at least 10 years.

Management Plan

Children without evidence of tumor growth after diagnosis were observed without therapeutic intervention. Tumor progression, determined by visual deterioration (worsening vision on two successive examinations), neurologic deterioration by history or examination, or serial radiographic criteria was required for initiation of therapy. If an enlarging tumor cyst was symptomatic, it was drained, and the patient was observed for further progression. Between 1977 and 1990, initial treatment recommendations for children younger than 5 years of age at the time of tumor progression was chemotherapy with vincristine and actinomycin-D (AMD).[3]

Radiation therapy was reserved for children who were older than 5 years at tumor progression and those who had tumor growth during or after chemotherapy. Radiation treatments were administered by a 6- or 15-MeV linear accelerator using opposed lateral fields. Patients with chiasmatic or hypothalamic lesions received involved-field radiation. For patients with NF-1, signal–intense lesions visualized on T2-weighted MRI (unidentified bright objects) were not radiated intentionally. Age-adjusted radiation doses ranged between 4500 cGy and 5580 cGy in 180-cGy single-daily fractions. Written informed consent was obtained before therapy was initiated, and treatment protocols were approved by the hospital's institutional review board.

Evaluation of Outcomes

Treatment response was determined by neuroimaging criteria and classified as follows: complete response, no

evidence of tumor; partial response, 50% or greater reduction in tumor area determined by the product of perpendicular tumor diameters; minor response, less than 50% but greater than 25% reduction in tumor area with or without reduction in enhancement; stable disease, no change in tumor area; progressive disease, increase in the tumor area, the appearance of new tumor, or worsening visual function on two successive examinations. Measures of tumor treatment outcomes included initial tumor response, as described above, and progression-free intervals, determined separately for the first (freedom from first cytotoxic therapy) and each subsequent tumor relapse (freedom from second cytotoxic therapy).

Visual function outcomes were classified as improved, unchanged, or worse based on assessments of visual acuity and visual fields. Endocrine function outcomes were evaluated as follows: growth rates were determined from serial measurements of height and weight and thyroid function was assessed before and after therapy. Complete endocrinologic evaluations were obtained in children with growth failure, electrolyte abnormalities, or premature puberty. Normal endocrine function was defined as normal thyroid function tests, fluid and electrolytes balance, and puberty status. Intellectual function was measured by serial neuropsychologic examination. The following specific measures were selected according to the age and functional levels of the child[29]: the Bayley Mental Scale of Infant Development[30]; the Stanford–Binet Intelligence Scale, Form L-M[31]; the Leiter International Performance Scale[32]; the *Maxfield–Buchholz Test of Social Maturity;*[33] the Vineland Adaptive Behavior Scales[34]; the Wechsler Preschool and Primary Scale of Intelligence[35]; and the Wechsler Intelligence Scale for Children, Revised.[36] Behavioral adjustment and psychosocial function were measured by the Child Behavior Checklist.[37]

Statistical Methods

Kaplan–Meier curves were calculated for survival, intervention-free survival, freedom from second intervention, and time-to-radiotherapy. Standard errors for the 2-, 5-, 10-year probabilities were calculated based on Greenwood's formula.[38] Fisher's exact test was used to compare response rates between patients with and without NF-1.

Results

Presentation

Table 1 summarizes the age at diagnosis, NF-1 status, and tumor location for the 46 study patients. Greater than 60% presented when they were younger than 3 years of age, and NF-1 was diagnosed in 33% of the children. Signs and symptoms found at diagnosis are listed in Figure 1. The most common presenting sign was strabismus, usually esotropia. Decreased visual acuity was the most common abnormality found on diagnostic evaluation. By contrast, no child reported decreased visual acuity or reduced visual fields. This discrepancy may reflect the ability of children to compensate for gradually diminishing visual acuity and visual fields. Relatively few children presented with signs or symptoms of systemic illness and none had classical diencephalic syndrome. In three patients, however, failure to thrive led the treating physician to request a computed tomography scan, which revealed the tumor. In six asymptomatic children with NF-1, H/OPGs were identified by routine screening neuroimaging studies.

Table 1. Demographic Characteristics of Children < 5 Years of Age With Optic Pathway/Hypothalamic Gliomas

No. of patients	46
Age at diagnosis (mo)	
Mean	34
Median	27
Range	1–60
Sex	
Male	24 (52%)
Female	22 (48%)
Neurofibromatosis type I	15 (33%)
Tumor location	
Chiasm only	7 (15%)
Chiasm + optic pathways	20 (44%)
Chiasm + hypothalamus	19 (41%)

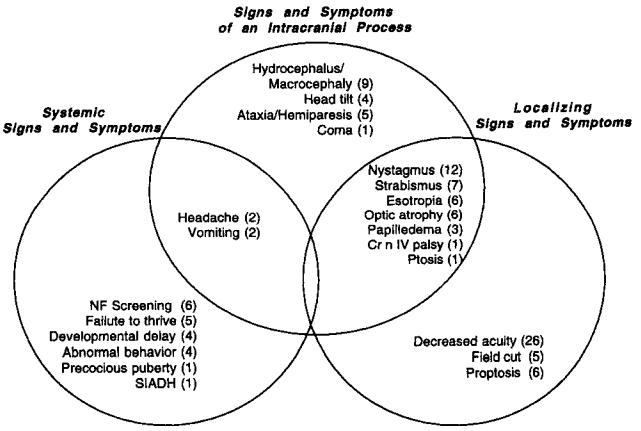

Figure 1. Presenting signs and symptoms of 46 children with optic pathway/hypothalamic gliomas. Adjacent to each symptom listed is the number of children with the feature at presentation. Children are represented more than once in this figure if they presented with multiple signs and symptoms.

Table 2. Outcome of Initial Management in 46 Children <5 Years of Age With Hypothalamic/Optic Pathway Gliomas

Initial management	Outcome				Total
	SD	*PD*	*Death*	*LTFU*	
Observation only	5	0	0	1	6
Resection only	2	0	1	0	3
Radiation therapy	4	1	0	0	5
Chemotherapy*	9	22	0	1	32

SD: stable disease; PD: progressive disease; LTFU: lost to follow-up; AMD: actinomycin D; VCR: vincristine; VP16: etoposide.

* Chemotherapy denotes treatment with AMD/VCR (n = 31) or VP16/VCR (n = 1).

Initial Management

Table 2 lists the initial management and outcome for each patient. Only 9 children in this series of 46 patients did not receive either radiation or chemotherapy as initial management. Six children had no tumor progression during their period of observation (median, 26 months; range, 10–56 months) and received no therapy. Treatment was limited to resection in three patients. One infant with massive chiasmatic tumor died of peritonitis after undergoing a biopsy and before specific therapy was initiated. Tumor ruptured through the optic nerve sheath in the two patients with NF-1. The ruptured nerve was resected in one child to reverse proptosis and was removed during enucleation in the second child; the remaining intracranial tumors in these two children did not progress in more than 3 years.

Five children were treated with radiation therapy alone. Two children who were younger than 5 years at diagnosis had initial progression treated with radiation therapy at 7 and 8 years, respectively. Three children received radiation as initial management before age 5 years, either because their treatment was initiated at another institution or because chemotherapy was not otherwise feasible. Four children maintained stable disease 10–16 years after receiving radiation. One experienced progression but maintained a second response to vincristine/AMD for more than 10 years.

Thirty-two children were treated primarily with chemotherapy: 31 with vincristine/AMD and one with vincristine and etoposide. Figure 2 lists the management strategies and outcomes of the patients treated with chemotherapy. At the time of this report, 27 patients were stable, 4 had died, and 1 was lost to follow-up at 24 months after the start of chemotherapy. In one patient, vincristine/AMD was discontinued after 6 months by parental request. Nine months later, tumor regrowth was treated with surgical drainage of a tumor cyst, and the tumor remained stable for 16 months.

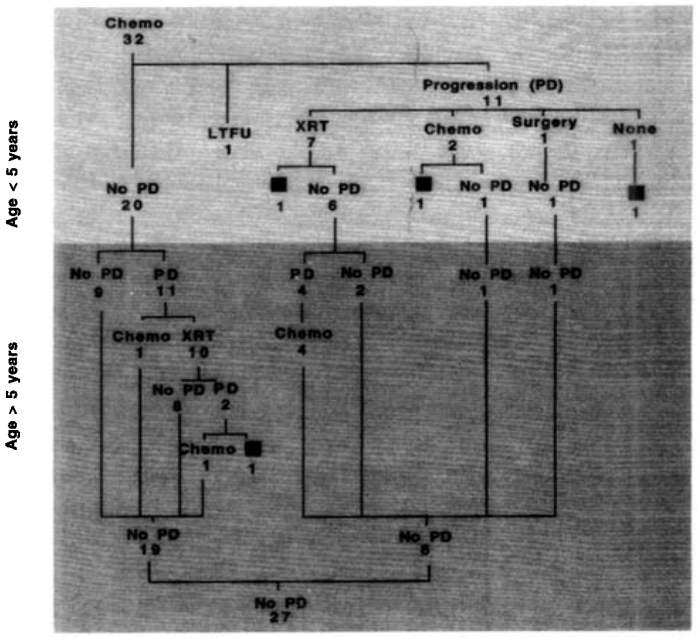

Figure 2. Overview of management and outcomes of 32 children younger than 5 years of age with optic pathway/hypothalamic gliomas treated with chemotherapy (vincristine plus actinomycin-D [n = 31] or etoposide plus vincristine [n = 1]). The number of children with progressive tumor (PD), stable tumor (No PD), or death (■) is indicated in the flow diagram. Treatment of those who had progressive tumor also is indicated as chemotherapy (Chemo) or radiation therapy (XRT). The outcome (progressive tumor, stable tumor, death, or lost to follow-up) of the children was determined before age 5 years (lightly shaded area) and after age 5 years (darkly shaded area).

Treatment Outcomes

Initial tumor response. Twenty-nine patients (94%) were evaluable for response to vincristine/AMD. No tumor had a complete radiologic response; however, 2 (7%) had greater than 50% reduction in tumor area, 17 (59%) had a minor response, 9 (31%) were stable during treatment, and 1 (3%) experienced progression on treatment.

Tumor progression. Twenty-two children experienced tumor progression after stabilization or shrinkage (Fig. 2). Median time to progression in these 22 children was 27 months (range, 1–92). Of the 32 children treated with chemotherapy, 12 were older than 5 at the time of progression. One child received no therapy at the time of tumor progression and subsequently died, and one child underwent surgical drainage of tumor cyst and the tumor was stable thereafter. Seventeen patients were irradiated. Of the 17, 10 remained stable with disease, 2 died of disease, and 5 had progression and received a variety of therapies. Three children received alternative chemotherapy: two had clinical and radiologic evidence of response, and the third died of progressive tumor.

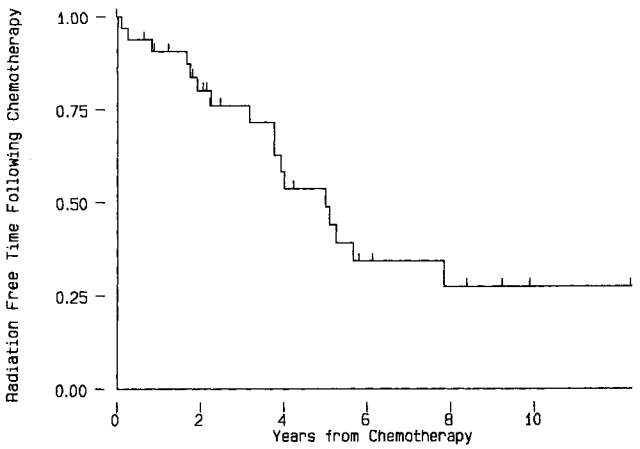

Figure 3. Delay in radiation therapy after chemotherapy among 32 children younger than age 5 years who presented with optic pathway/hypothalamic gliomas and who were treated with chemotherapy (vincristine plus actinomycin-D [AMD] [n = 31] or etoposide plus AMD [n = 1]). Time after the initiation of chemotherapy is plotted along the abscissa, and the proportion of these 32 children not irradiated is presented along the ordinate.

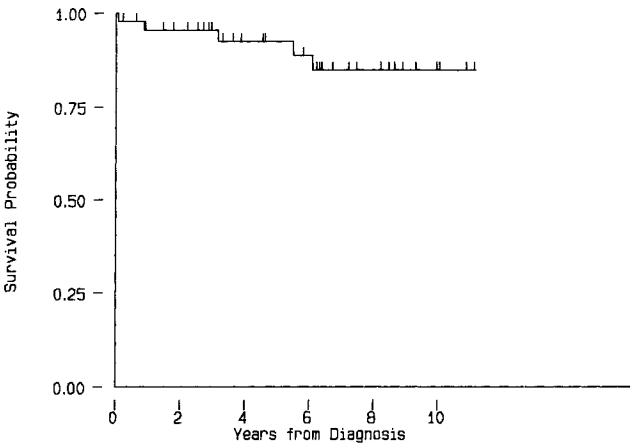

Figure 4. Survival. Time after presentation is plotted along the abscissa, and the proportion of the 46 children alive along the ordinate. Median follow-up time was 6 years (range, 1–172 months). Tic marks indicate censored individuals. The probability of survival at 2, 5, and 10 years, with corresponding standard error, was 0.95 ± 0.03, 0.93 ± 0.04, and, 0.85 ± 0.06, respectively (n = 46).

Therefore, of 29 fully evaluable patients initially treated with vincristine and AMD, 8 had no progression, 12 remained free of second recurrence, 5 who had a second recurrence were alive with disease controlled by tertiary therapy, and 4 died of disease.

Delay in radiation therapy. Although 72% of patients treated with chemotherapy had eventual tumor progression, chemotherapy delayed the use of radiation beyond 5 years of age in greater than 70% of the patients. Figure 3 lists the delay in radiation therapy for the 32 children treated with chemotherapy as their first medical intervention. Radiation therapy was delayed a median of 4 years and 3 months (range, 1 month to longer than 10 years).

Survival. Survival, first progression-free survival, and second progression-free survival are listed in Figures 4, 5, and 6. Despite survival of 93% of the patients, freedom from progression was only 19% at 5 years, and only 46% of the 37 children who had a first progression were free of a second progression 5 years after their first progression.

Table 3 compares tumor progression in children with and without NF-1. One of the 15 children with NF-1 was lost to follow-up after 27 months. Three patients had no tumor progression and did not require any therapy. Two children were stable after enucleation and resection of the optic nerve (see above). None of the patients with NF-1 whose primary therapy was irradiation had progression of tumor. Six patients with NF-1 received chemotherapy; two had progressive disease. Therefore, 2 of 14 evaluable patients with NF-1 developed tumor progression after observation or initial therapy as compared with 21 of 29 children without NF-1 (P = 0.0028; Fisher's exact test). Figure 7 compares survival in children with and without NF-1 who were diagnosed with H/OPGs before the age of 5.

Vision. Records of serial assessments of visual function were available for 27 patients. Eight children had bilateral acuity of 20/30 or better with or without field cuts. Five experienced improvement in acuity, 14 remained stable, and 8 experienced deteriorating vision.

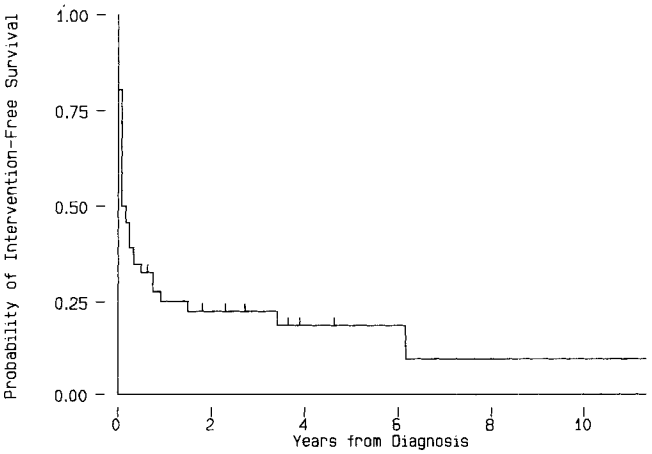

Figure 5. Survival free of surgical or cytotoxic therapy. Time after presentation is plotted along the abscissa, and the proportion of the 46 children who had not had any medical intervention (chemotherapy or radiation therapy) to treat tumor progression is plotted along the ordinate. This graph is analogous to a Kaplan–Meier plot of progression-free survival (see text). The probability of progression-free survival at 2, 5, and 10 years, with corresponding standard error, was 0.23 ± 0.06, 0.19 ± 0.06, and 0.09 ± 0.07 (n = 46), respectively.

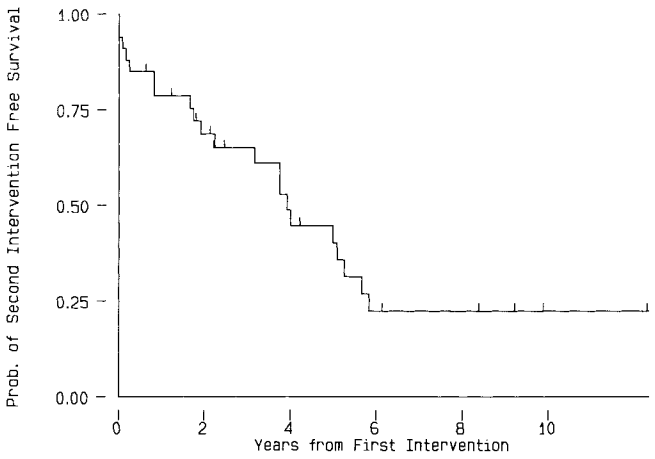

Figure 6. Survival free of second cytotoxic therapy. Time after first medical intervention is plotted along the abscissa, and the proportion of the 37 children who received a first medical intervention (chemotherapy or radiation) and did not require a second medical intervention to treat a second tumor progression is plotted along the ordinate. This graph is analogous to a Kaplan–Meier plot at survival free of a second progression (see text). The probability of survival free of second progression, after a first progression, at 2, 5, and 10 years was 0.72 ± 0.08, 0.46 ± 0.09, and 0.29 ± 0.09, respectively (n = 37).

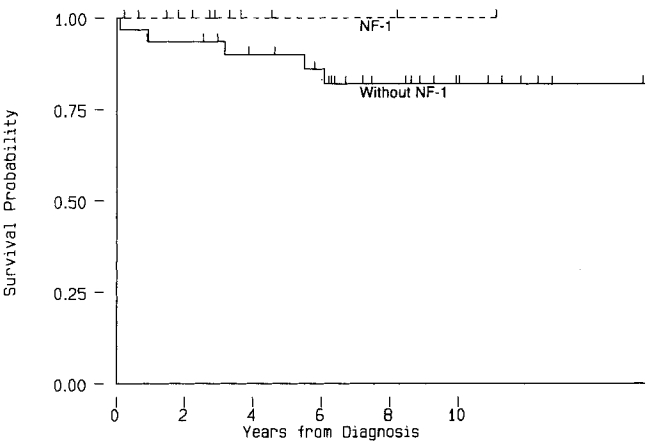

Figure 7. Comparison of survival in children with and without NF-1. Time after presentation is plotted along the abscissa, and the proportion of children with (- - -) and without NF-1 (—) who survived, along the ordinate.

Four children now are blind, and one other is legally classified as blind.

Endocrine function. Endocrinologic evaluations of 34 children with H/OPGs were available for review (Fig. 8). Records of the remaining 12 children were limited to growth charts. Four children had hypothyroidism requiring thyroid replacement, but only two were irradiated. Growth hormone deficiency was found in two children not treated with radiation and six patients after radiation. Three children had diabetes insipidus, which required replacement therapy with vasopressin. Seven girls and four boys developed precocious puberty, three before and four after completion of diencephalic radiation. The remaining four patients never received radiation. Three boys, all of whom previously had been irradiated, were testosterone deficient and had not entered puberty by age 15. Panhypopituitarism, defined as requirement of at least thyroid hormone, corticotropins and antidiuretic hormone, was seen in three children. Fourteen children had normal endocrine function, seven received radiation therapy, and seven did not. Endocrinologic dysfunction in these children did not correlate with diencephalic radiation (P = 1.0; Fisher's exact test).

Table 3. Optic Pathway/Hypothalamic Gliomas in Children < 5 Years of Age With and Without NF-1: Progression Following Observation or Initial Management With Radiation Therapy or Chemotherapy

Outcome after initial management	With NF-1	Without NF-1
No. of patients	15	31
SD	12	8
PD	2	21*
Postoperative death	0	1
LTFU	1	1

SD: stable disease; PD: progressive disease; LTFU: lost to follow-up; NF-1: neurofibromatosis type 1.
* P = 0.0028.

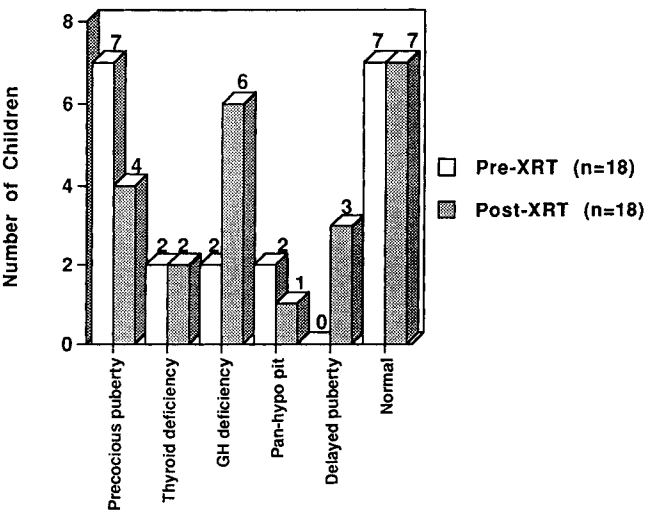

Figure 8. Endocrine status in children with optic pathway/hypothalamic gliomas. This bar graph illustrates the number of children with documented endocrinopathy or documented normal endocrinologic state and indicates whether the condition was noted after irradiation (post XRT) or before any irradiation (w/o XRT). GH: growth hormone; pan-hypo pit: pan-hypopituitarism.

Intellect. Formal cognitive assessments before and after therapy were obtained from nine patients; seven of these had more than two consecutive tests. Two of the four children who were followed for 2 years after the establishment of baseline evaluations, which preceded radiation therapy, had intelligence quotients (IQs) lower than 80; both were irradiated before age 5 years. Serial IQ scores recorded before irradiation showed no decline. Among those receiving radiation, IQ changes fell a median of 12 points from baseline (range, 10–30 IQ points).

Behavior. Parents of 17 children returned the Child Behavior Checklist. Seven of 17 children showed a clinical degree of behavioral impairment: 5 showed internalizing disorders such as anxiety or depression; 2 showed externalizing disorders such as aggression or noncompliance. Of the seven with abnormal behavior, four received radiation before age 5 years, one at age 5 and one-half years, one at age 11 years, and one was never irradiated. Of the 10 who showed normal behavior, 6 were never irradiated, one was irradiated at age 3.9 years, and the other 3 were irradiated at ages 6 and one-half years, 6 and three-quarters years, and 9 and one-half years. Ten of these 17 children are receiving special education; 5 of the 10 were irradiated before age 5 years, one at age 6 and one-half years, and one at age 6 and three-quarters years, and 3 were not irradiated. All of the seven children who received "normal" education were irradiated after age 5 years or not at all. The association between radiation before age 5 years and the need for special education was statistically significant ($P = 0.044$; Fisher's exact Test). Because only 17 of 37 (50%) children responded to the Child Behavior Checklist, this result may not be generalizable to the population of children with H/OPGs diagnosed before age 5 years.

Social competence scores were also obtained from the Child Behavior Checklist for the 14 children aged 6 and older. Eight of 14 children scored in the clinically low range on activities such as hobbies and participation in sports and clubs, and 9 of 17 children scored within the clinically low range on social skills such as number of friends and frequency of contacts with friends.

Discussion

This analysis of 46 children younger than age 5 years with H/OPGs supports a number of conclusions. First, despite high survival, the majority of patients experience tumor progression, suggesting that this tumor behaves more aggressively in the young. Second, chemotherapy can delay the use of radiation therapy by years in most children. Third, these tumors in children with NF-1 are less aggressive than the same tumors in children without NF-1. Finally, endocrinopathies in these children did not correlate with prior radiation.

The low mortality of children with H/OPGs has been emphasized in previous reports.[1–12,15–25] This current series, however, demonstrates the relentless progression of most of these tumors. Although 5-year survival was 93%, greater than 80% of the 46 children in this series required surgery, chemotherapy, or radiation within 2 years after diagnosis, and all but 9% eventually required radiation or chemotherapy. Approximately 80% of the children who experienced tumor progression needed a second cytotoxic therapy because of further tumor growth, and in a third of these children, the second intervention was required within 2 years of the first therapy. Five children have died, four despite aggressive attempts to control the tumors with surgery, radiation, and/or chemotherapy. These results make it clear that in children diagnosed before 5 years of age, H/OPGs are not "non-neoplastic, self-limiting tumors", as proposed by Hoyt and Baghdassarian.[39]

The effect of age on the clinical behavior of H/OPGs is controversial. A retrospective review by Alvord and Lofton[11] concludes that the prognosis for death and tumor progression is worse with increasing age (older than 20 years). Reviews limited to pediatric populations, however, suggest that H/OPGs may behave more aggressively in infants.[12] Two recent studies support the idea that age is a significant factor in tumor biology. Nishio et al.[13] demonstrated significantly greater mortality among patients younger than 2 years of age with H/OPGs. Symptomatic presentation of optic gliomas and H/OPGs in children with NF-1 was limited to children younger than 6 years of age.[14] The rate of tumor progression and need for medical intervention in this study is greater than that previously reported (22–48%).[2,10,40] This may be due to the fact H/OPGs are more biologically aggressive in younger children and previous studies were not limited to children younger than 5 years of age. Other factors that may account for differences in reports on H/OPGs include shorter periods of follow-up and different management strategies.

Because the data that suggest irradiation before age 5 years is particularly damaging to neuropsychologic function, the majority of children received vincristine and AMD as their primary therapy.[3,20–27] Treatment with vincristine and AMD effectively delayed radiation, and in greater than 70% of the children, the delay allowed them to reach an age older than 5. This result confirms the findings of Packer et al.,[16] who first suggested that this combination therapy could delay the need for radiation in young children diagnosed with H/OPGs.

Seven of 17 children who required radiation after chemotherapy have incurred a third progression. This rate raises the possibility that the chemotherapy may render the tumors radioresistant. However, this number is currently no different from the recurrence rate observed in two of four children treated with radiation first and no different from rate quoted in the literature.[7,11]

The results of the Child Behavior Checklist indicate a possible association between radiation before the age of 5 and the need for special education. The same checklist suggested a tendency for children irradiated before age 5 years to incur behavioral impairment. The limited number of children in this study who had serial IQ tests does not permit firm conclusions about the effects of radiation or chemotherapy on intellect. The data available are consistent with previous reports documenting declines in cognitive and behavioral function in children radiated at a young age.[26,27,29,41] These results support the policy of postponing radiation. They also underscore the need for further studies in, and serial neuropsychologic and psychosocial assessment of, children with a tumor in the central nervous system who subsequently may be subjected to radiation and/or chemotherapy.

de Los A. Pons et al.[42] investigated the combination vincristine and etoposide for low grade gliomas. This combined therapy does not appear more or less effective than vincristine and AMD, but it does introduce a risk of secondary acute myeloid leukemia.[43] Packer et al.[44] have used vincristine and carboplatinum, a combination that is well tolerated and is at least as effective as vincristine and AMD. Exploration of combinations of drugs, particularly those not associated with serious late effects is continuing. Wisoff et al.[12] have advocated surgery as an alternative to chemotherapy or radiation therapy in young children. Experience at this institution suggests that radiologic stabilization of tumor as well as clinical improvement may follow surgical drainage of tumor cysts or partial resection of solid tumor (see above).

Of the 46 children in this study, only 6 have never received chemotherapy or radiation, and 5 of these 6 have NF-1. Our finding that H/OPGs in children without NF-1 were more likely to progress than those in children with NF-1 indicates that the latter group may have more indolent tumors and confirms previous reports.[14,42,45–47]

Although endocrinopathy is a well known late effect of irradiation of the central nervous system,[48,49] this study shows that endocrinopathies, including growth hormone deficiency, diabetes insipidus, precocious puberty, and testosterone deficiency, may be the effect of tumor and cannot be attributed solely to the effects of radiation in children diagnosed with H/OPGs before the age of 5. Studies that evaluate the effects of radiation on endocrine function should be careful to exclude this population from the discussion.

Based on this study and our results in older children, a conservative age-based strategy for treating H/OPGs appears to be justified: initiation of therapy should be delayed until at least two successive ophthalmologic examinations document visual deterioration or two successive imaging studies show tumor growth, and the child has neurologic deterioration or is in imminent danger of blindness. This is suggested by our experience with surveillance scanning in children with NF-1 and accumulated experience in older children in whom progression may be followed by months or years of stabilization.

Even with deliberate attempts at early intervention and reduction of treatment-related sequelae, young children with H/OPGs suffer significant morbidity and mortality.

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