

Initial Management of Children with Hypothalamic and Thalamic Tumors and the Modifying Role of Neurofibromatosis-1

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Key Words

Optic pathway glioma · Diencephalic tumor · Thalamic tumor · Neurofibromatosis

Abstract

Diencephalic gliomas may be grouped into 2 clinical categories. Optic pathway/hypothalamus gliomas (OPG) arise primarily from a slower-growing juvenile pilocytic astrocytoma, and thalamic gliomas arise primarily from a fibrillary astrocytoma which can become clinically and histologically more aggressive. Children with OPG have an excellent long-term prognosis with a 10-year survival of over 85%. The major therapeutic challenge for these patients is to maximize their quality of life by preserving visual and endocrine function while minimizing treatment-related morbidity. Treatment is often initiated at diagnosis in infants and toddlers who have a major visual impairment or the diencephalic syndrome. The judicious application of chemotherapy may serve to forestall the need for radiotherapy or surgery. Children with

neurofibromatosis-1 (NF-1) usually have a more indolent course. Tumors may grow more slowly or occasionally regress spontaneously. However, over 90% of children with OPG without NF-1 will require some form of therapy. Patients with thalamic gliomas present with a shorter history, often with hydrocephalus. Surgical intervention is often required to relieve intracranial pressure and establish the histologic identity of the tumor. Over 75% of these tumors will become locally aggressive. Current multimodality therapy is relatively ineffective. The bithalamic variant behaves similarly to a pontine glioma.

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Introduction

The management of primary CNS tumors of childhood is rapidly evolving due in large measure to the application of advances in the fields of neurosurgery, radiotherapy and oncology and to the recently appreciated value of multidisciplinary interaction. Although cooperative group activities have served to advance our knowledge and improve our clinical management for a number of the commoner CNS tumors, several less common entities are not actively advanced in a group-wide setting. We have conducted symposia every 2 years since 1993 which have focused on less common pediatric brain tumor topics such as craniopharyngioma (1993), brainstem glioma (1995) and ependymoma (1997). We are committed to the view

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that by convening experts in the pertinent clinical and scientific disciplines for several days in an intimate but open forum, we will not only stimulate lively discussion, but also gain insights which can alter our perspectives and improve the ways we manage our patients. By publishing the proceedings, we hope to make this knowledge available to a larger audience. Most importantly, by bringing attention to a rare group of childhood illnesses, we hope to eventually stimulate both clinical and basic research which may ultimately improve not only the duration but also the quality of survival for the children who suffer from these afflictions.

This symposium will focus exclusively on the intra-axial gliomas that arise in the part of the CNS called the diencephalon, which encompasses the thalamus, hypothalamus, optic chiasm and related structures. Pediatric patients present with several distinct clinical syndromes which we will attempt to characterize, each of which poses special management considerations. Both slow and more rapidly growing gliomas arise in the diencephalon, but in distinct locations and patient populations. Since most of these tumors arise in areas that prevent a radical resection, the role of surgery is often relegated to the need to establish a histologic diagnosis and to control raised intracranial pressure. Since several of these syndromes may have distinct neuroimaging characteristics, an invasive diagnostic neurosurgical procedure may be avoided if a consensus can be reached regarding typical diagnostic MRI features such as may arise in the chiasm or thalamus. A much greater therapeutic emphasis must be placed on the medical specialties that deliver cytotoxic drugs or radiation. We felt it would be timely to critically review the recent progress we have made in the disciplines of neurosurgery, neuro-oncology and radiotherapy and attempt to reach a consensus on management guidelines and promising areas of research. We have tapped several members of our staff at the Institute of Neurology and Neurosurgery as well as invited several outside speakers from the US and abroad who have provided not only leadership, but contributed extensively to the literature in their respective fields.

The Incidence of Diencephalic Tumors in Children

The incidence of childhood CNS tumors in population-based surveys may vary from 34 cases per million children under 15 years of age in Sweden to 18 cases per million in Germany. The US has an intermediate inci-

Table 1. Distribution of low-grade gliomas by site [2]

Site	Incidence, %
Cerebellum	20
Cortical	13
Diencephalon	5
Brainstem	1
Spinal cord	1

dence of 26 cases per million. If the population of children under 22 in the US approaches 75 million, then the annual number of new cases is 2,000. There is some concern that the incidence of primary CNS tumors may be increasing related primarily to the increasing incidence of low-grade gliomas over the past 10 years. This may be more a function of advances in neurodiagnostic imaging and reporting practices, because the incidence of malignant tumors such as medulloblastomas and ependymomas appears to be relatively stable over a similar period of observation [1, 2].

A recently reported Scandinavian population-based survey identified 1,223 pediatric brain tumor cases that were accrued over a 20-year period from 1993 to 1992 [2]. Histologic documentation was available for 93% of the cases. This survey confirmed prior observations that the commonest type of childhood CNS tumor was a low-grade astrocytoma. Approximately 40% of the tumors were diagnosed as a grade 1 or 2 astrocytoma. The commonest type of malignant tumor was the PNET/medulloblastoma (19%). High-grade astrocytomas (WHO grades 3 and 4) contributed 12% of cases. Brainstem gliomas, another form of high-grade glioma for which histology is generally not obtained, should have composed 10% of cases based on other surveys [1]. Thus, the incidence of high-grade gliomas would approach 22%.

The commonest site of origin of low-grade astrocytoma is the cerebellum (20%) followed by the cerebral cortex (13%). The majority of these tumors are amenable to curative surgical resections. Only 5% of low-grade astrocytomas arise in the diencephalon (table 1). Such low-grade astrocytomas arise primarily in the ventral parts of the diencephalon in the optic nerves and chiasm, comprising 4% of CNS tumors, as well as in the contiguous hypothalamus and thalamus (1%). Although the diencephalon may be the locus of origin for only 5% of all low-grade astrocytomas, because of its relative inaccessibility,

it contributes to over 90% of the inoperable cases. Thus, much of what the field of pediatric neuro-oncology has learned regarding the activity of chemotherapy in children with low-grade astrocytomas has been derived from clinical trials in patients with diencephalic gliomas [3]. Optic pathway gliomas (OPG) refer to tumors arising in the optic nerves (anterior pathway) or chiasm which may extend locally to involve the hypothalamus or optic radiations. Children with OPG have distinctive demographic features. Their mean age at diagnosis is 4.5 years, and their overall prognosis is excellent with a 10-year survival of 85%. From 20 to 30% of patients with OPG have neurofibromatosis-1 (NF-1) [4].

High-grade astroglial tumors arise primarily in the more dorsal structures of the diencephalon such as the thalamus and may comprise 4% of the CNS brain tumors [5]. These tumors tend to arise in an older pediatric population, and their mean age at diagnosis is 10 years. Less than 1/3 of cases of thalamic astroglial tumors will behave like a low-grade glioma, and the prognosis for the majority of cases is not favorable. The overall 4-year survival for all cases with thalamic primary tumors is 37% [6]. NF-1 is distinctly uncommon in this population.

Modes of Presentation in Patients with Diencephalic Tumors

Optic Pathway Gliomas

For the purpose of simplifying the classical signs and symptoms of children with optic pathway gliomas at diagnosis, OPG can be divided into 3 anatomic/clinical sub-categories: anterior, chiasmatic and chiasmatic/hypothalamic.

Anterior Pathway Gliomas

The least common variant, they comprise approximately 0.5% of all childhood tumors. They arise within the nerve itself, usually unilaterally in patients without NF-1 and can affect both optic nerves in patients with NF-1 [7]. The majority of children are under 5 years at diagnosis. The tumors are usually relatively small (<2–3 cm), and the parents or caretakers usually recognize the initial sign of enlarging proptosis. The infant or toddler does not usually complain of visual loss. The physician may document optic atrophy, impaired acuity and abnormal visual fields in addition to the proptosis. As the tumor enlarges, the globe will become compressed and its movements limited. The initial treatment decision is proble-

matic. The tumor is typically confined to the optic nerve and does not usually extend into the chiasm. Surgical extirpation can be curative [8]. However, if useful vision exists and the growth rate cannot be adequately anticipated, then close follow-up is preferable, possibly with an attempt at chemotherapy [3]. If no useful vision exists and the cosmetic and emotional consequences are unacceptable, then surgical removal is indicated with placement of a prosthesis. The tumors are usually composed of a juvenile pilocytic astrocytoma (WHO grade 1). The management of bilateral optic nerve gliomas is more problematic. Fortunately, they tend to arise in the context of NF-1 and behave in a more indolent fashion.

Case 1 (Anterior Pathway Glioma). This 2.5-year-old female presented with a 3-month history of progressive unilateral proptosis involving the right eye. On examination, she had no cutaneous stigmata of NF-1, a bulging right eye, optic atrophy and light perception only in the temporal field (fig. 1). She was followed expectantly for 3 months, and the tumor grew on MRI. Because of the retention of some vision in the temporal field, we decided to give her a trial of carboplatin/vincristine chemotherapy [3]. After a 10-week period of chemotherapy, the tumor progressed clinically and radiologically, and the decision was made to remove it with the adjacent portion of the optic nerve. The histology was consistent with a juvenile pilocytic astrocytoma, and the optic nerve appeared free of tumor at its attachment to the chiasm.

Chiasmatic Gliomas

These comprise 1.5% of childhood brain tumors, and the commonest pathology is a juvenile pilocytic astrocytoma. When confined to the chiasm, the tumor is usually relatively small (<3 cm in diameter) at diagnosis. The parents or caretakers usually first notice unilateral or bilateral pendular nystagmus which may be intermittent at the beginning. The child may hold objects close to his/her face and be fearful of walking in new places. By the time the child is brought to medical attention, optic atrophy, and unilateral or bilateral impairment of visual acuity and loss of peripheral vision are apparent.

The MRI scan identifies a diffuse, heterogeneously enhancing, intra-axial expansion of the optic chiasm with displacement or invasion of the hypothalamus. There may be exophytic extensions into the suprasellar cistern or third ventricle. If the child has NF-1, the MRI findings alone may be sufficient for diagnostic purposes. A CT scan should be obtained; intratumoral calcifications suggest the diagnosis of craniopharyngioma. Endocrine features such as diabetes insipidus, short stature or precocious puberty are commoner in other disorders that may arise in the suprasellar region such as germ cell tumors and histiocytosis. In the absence of NF-1 and other clini-



Fig. 1. MRI revealing an intrinsic optic nerve mass arising behind and compressing the globe with a 1-cm distance of normal-appearing nerve between the tumor and the chiasm.

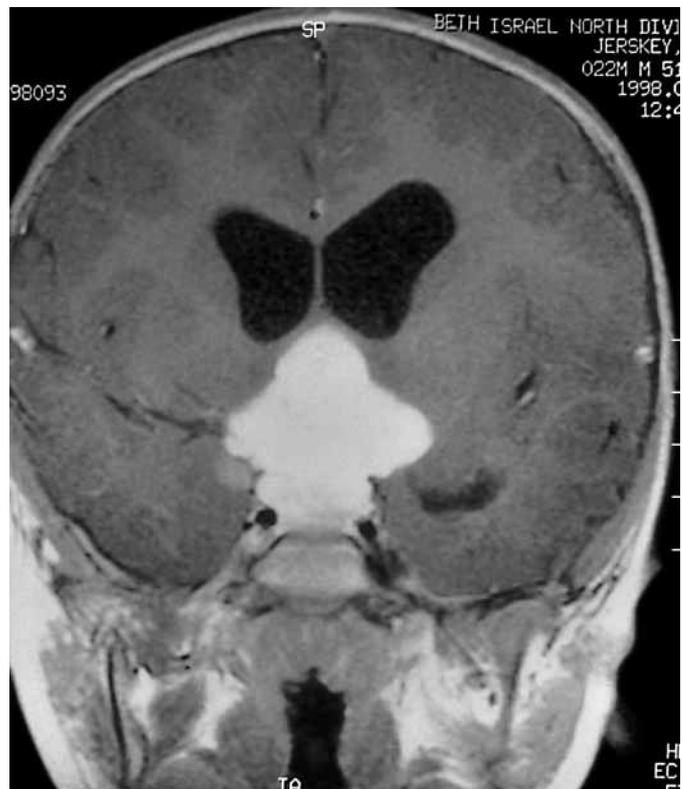


Fig. 2. MRI identifying an intrinsic, uniformly enhancing expansion of the chiasm which measured 3 × 3.5 cm with exophytic extension into the sellar and third ventricle.

cal features, a short period of observation is often used to determine the growth rate of the tumor. A biopsy may be required to confirm the histology. Children with NF-1 have a more indolent course, and treatment should be deferred as long as possible.

Management practices in patients without NF-1 are evolving. Children diagnosed at an earlier age appear to have a more aggressive clinical course [4]. Clinicians are often more willing to initiate therapy earlier in infants because of the perceived more aggressive course and because their visual function is more difficult to assess. Since the tumor is rarely fatal, and over 85% of children will be alive 10 years from diagnosis, the goals of therapy are to maximize the quality of life by preventing progression of disease and minimizing treatment-related neuro-

logic, endocrine and cognitive sequelae. Unfortunately, in non-NF patients diagnosed at less than 5 years, there is a high probability that the tumor will grow. Within 1 year of diagnosis, 50% of children will require some form of intervention and by 10 years, 90% will be treated [4].

In the past, the preferred intervention was high-dose radiotherapy through lateral opposed fields [9]. This type of treatment, although often effective in halting radiologic tumor progression, rarely improved visual function. Late treatment effects emerged in long-term survivors who were treated at a young age, such as cognitive impairment, endocrine deficiencies, a progressive vasocclusive disorder of the circle of Willis (Moyamoya) and second primary malignancies (see articles by Larry Kun, MD, and Joao Siffert, MD, to follow in this series). Newer forms of

radiotherapy delivery using 3-D conformal and fractionated stereotactic techniques may spare children some of these late consequences (see article by Nancy Tarbell, MD, to follow in this series). Chemotherapy has increasing appeal for younger symptomatic patients. Clinical trials with carboplatin and vincristine have produced stabilization and/or tumor regression in over 50% of children with progressive low-grade astrocytomas. However, the long-term clinical benefits, the late effects of therapy and the durability of remission remain to be fully ascertained, but the short-term toxicities have been manageable [10].

Case 2 (Chiasmatic Glioma). This 1.5-year-old female presented with a 3-month history of unusual eye movements and the need to hold objects close to her face. Her exam revealed a well-nourished child with bilateral pendular horizontal and vertical eye movements, optic atrophy and bilateral impairment of visual acuity. Her fields appeared full. There were no stigmata of NF-1. There was no hydrocephalus (fig. 2). Because of the profound impairment of visual acuity, both the parents and clinicians favored clinical intervention at the time of diagnosis. She was randomized on CCG protocol to receive carboplatin/vincristine chemotherapy, and 8 months after the initiation of chemotherapy, she experienced an 80% reduction in the volume of the chiasmatic tumor and improvement in her visual acuity.

Chiasmatic Hypothalamic Gliomas

These most probably arise in the chiasm and grow dorsally towards the area of least resistance, that is, the third ventricle and hypothalamus. For whatever reasons, they are diagnosed late in their evolution, often with signs and symptoms of raised intracranial pressure after they have reached considerable size. They comprise 2% of intracranial tumors and are usually composed of juvenile pilocytic astrocytomas. Hydrocephalus arises when the tumor fills the third ventricle. Large tumoral cysts and/or tumor may extend towards the adjacent temporal and frontal lobes. The tumor may also extend from the chiasm rostrally to involve the proximal portions of the optic nerves. On rare occasions, the tumor appears to arise within the hypothalamus, sparing the optic pathways. Other than the absence of visual symptoms, the presentation is similar.

The clinical signs and symptoms at diagnosis may be variable. Visual, endocrine and neurologic presentations may be staggered, but are frequently apparent on close examination. Early symptoms relate to the visual pathways, that is, nystagmus, impaired acuity and fields. As the tumor extends dorsally, macrocephaly may arise in infants and young children, and eventually symptoms of raised intracranial pressure, that is, irritability, lethargy, morning vomiting, gait disorders and diplopia. The diencephalic syndrome is unique to this tumor syndrome and

arises primarily in patients under 3 years. It will be discussed below.

Most children with chiasmatic/hypothalamic gliomas require urgent attention. For children with symptomatic hydrocephalus, the neurosurgeon must insert a shunt to control intracranial pressure. There is a high frequency of shunt failure in ventriculoperitoneal systems, possibly related to high CSF protein. A modest resection of the dorsal component of the tumor, using a transcallosal approach, may relieve some of the hypothalamic signs and symptoms. The next treatment option in younger patients is chemotherapy. Radiotherapy and/or radical surgical procedures are deferred unless initial chemotherapy alternatives are ineffective. Multiple hormonal supplements are often required to normalize the metabolism. The early therapeutic efforts are usually richly rewarded as the child undergoes rapid improvement, but the long-term prognosis is guarded.

Case 3 (Chiasmatic Hypothalamic Glioma). This 15-month-old female presented with a 9-month history of progressive left hemiparesis, irritability and left visual neglect. She was initially thought to have cerebral palsy and enrolled in an early intervention program. A physical therapist was concerned about progressive left-sided weakness (fig. 3). There was an initial resection of the tumor at another hospital, and the diagnosis was a juvenile pilocytic astrocytoma. The left middle cerebral artery was injured and the child suffered an infarct with an altered sensorium, hemiplegia and a seizure disorder. After 5 months of rehabilitation, carboplatin and vincristine chemotherapy was administered at our institution to control residual tumor. A 95% response was observed after 10 months of chemotherapy. The child has been followed for 16 months off chemotherapy and a small local recurrence emerged which was removed surgically.

Thalamic Gliomas

Thalamic gliomas are comprised of a mixed group of histologies. Over 90% of cases are of astroglial origin [6]. Approximately one third of cases will present with a long history of focal neurologic signs and symptoms such as a tremor, movement disorder, hemiparesis or pain syndrome. For these children, the MRI scan usually reveals a fairly localized, heterogeneously enhancing mass with associated cysts and calcifications, but with minimal surrounding edema on the T₂ image. If the symptoms are progressive, a stereotactic biopsy may be required to confirm the diagnosis of a juvenile pilocytic astrocytoma or low-grade fibrillary astrocytoma. The tumor usually cannot be safely resected. When treatment is considered necessary, radiotherapy or chemotherapy would be the preferred choices.

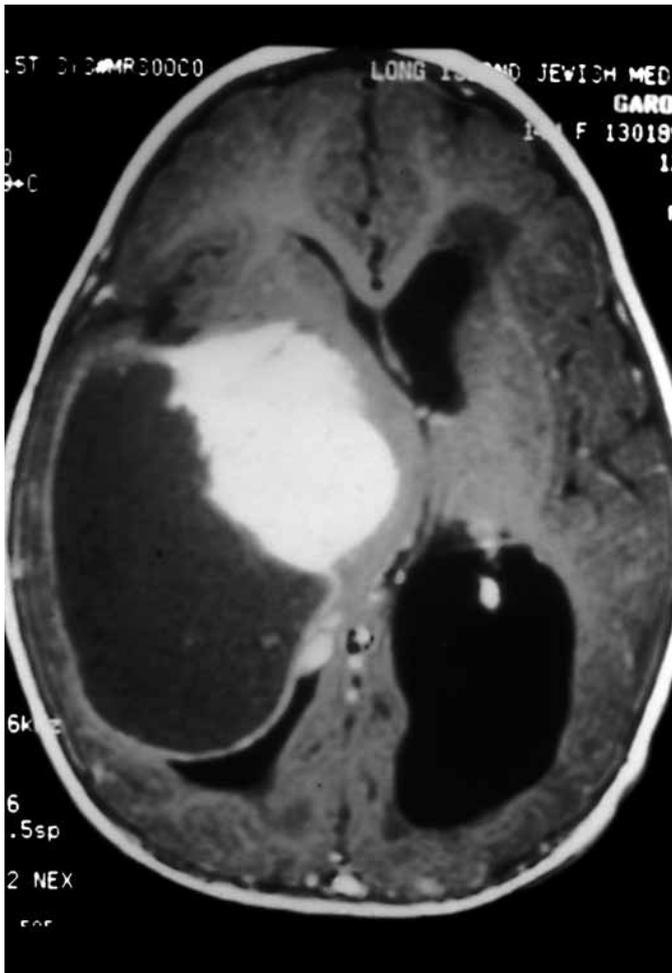


Fig. 3. The initial MRI revealed hydrocephalus, a large, enhancing midline tumor extending from the chiasm dorsally within the hypothalamus with an adjacent cyst occluding the right lateral ventricle.

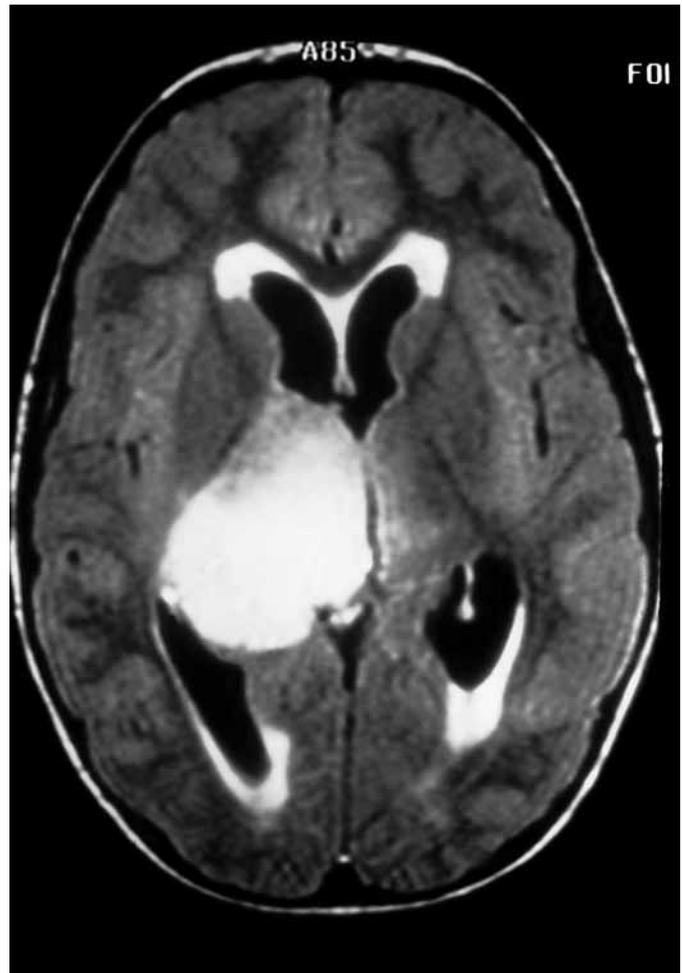


Fig. 4. MRI scan revealing hydrocephalus with a large diffuse nonenhancing mass filling the anatomic confines of the right thalamus with compression of the third ventricle.

Patients with more aggressive tumors usually present with a shorter prodrome of 1–2 months with symptoms of raised intracranial pressure such as headache, lethargy, diplopia, morning vomiting and change in behavior. Subtle neurologic signs may be present such as a reflex asymmetry or a mild hemiparesis in addition to papilledema and bilateral abducens palsies. The MRI scan may reveal 1 of 2 variants of the malignant glioma syndrome. Hydrocephalus may be due to a large enhancing unilateral mass within the thalamus with areas of necrosis and extensive surrounding edema on the T₂ study. Another malignant variant is the diffuse bithalamic or unithalamic glioma. Again, the child usually presents with signs and symptoms of raised intracranial pressure over a short period. The

MRI scan shows a large bilateral or unilateral diffuse, nonenhancing mass that remains within the anatomic confines of the thalamus and hydrocephalus. This MRI appearance is similar to that of an intrinsic pontine glioma. In either presentation of the high-grade thalamic glioma, the appropriate surgical management includes a procedure to control raised intracranial pressure such as a shunt or third ventriculostomy and a stereotactic or endoscopic biopsy. The histology reveals either a grade 3–4 astrocytoma, or in the diffuse glioma syndrome an infiltrative grade 2 or 3 astrocytoma. Occasionally, other histologies may be encountered such as a PNET.

In a retrospective review of 36 patients with thalamic gliomas at St. Jude's Research Hospital from 1985 to

1996, the median age at diagnosis was 10 years [6]. Twenty-four patients had low-grade histologies, and 12 had high-grade histologies. The 4-year progression-free and overall survival for the entire cohort was 28 and 37 months, respectively. Twelve (33%) of these patients had bithalamic presentation. Initial biopsy revealed a grade 2 fibrillary astrocytoma in 9 and grade 3–4 astrocytoma in 3 of these patients. None of these 12 patients survived beyond 2 years. Thus, the appearance on MRI of a diffuse, nonenhancing bithalamic glioma is a signature of an aggressive neoplasm with a prognosis similar to that of a pontine glioma. A diagnostic biopsy is probably not necessary. Adjuvant therapy was deferred in 7 of the 36 patients who had radical resection of a low-grade glioma. The remaining 29 patients received a course of radiotherapy with or without chemotherapy. The 4-year survival for the patients with low-grade histologies was 52% compared to 0% for those with high-grade histologies.

Case 4 (Diffuse Unithalamic Glioma). This 4-year-old boy presented with progressive headaches, morning vomiting, diplopia and lethargy over a 2-month period (fig. 4). His exam revealed a somnolent child with papilledema, a mild left central VII nerve paresis and a left hemiparesis. A subtotal resection was achieved with improvement in his hydrocephalus and hemiparesis, and the histology was consistent with a grade 2 fibrillary astrocytoma with an MIB-1 of 4%. The child was placed on carboplatin and vincristine chemotherapy. The child developed clinical and radiologic progression within 2 months, and was offered a course of radiotherapy and adjuvant chemotherapy.

Specific Clinical Syndromes in Patients with Diencephalic Gliomas

Spasmus nutans

Spasmus nutans consists of unilateral or bilateral nystagmus, head tilt and titubation of the head. It is usually a benign, self-limited syndrome that arises in infants, and its etiology is poorly understood. On occasions, symptoms similar to spasmus nutans may be a prelude to the diagnosis of an OPG. In a retrospective review of 67 consecutive cases of spasmus nutans diagnosed at the St. Louis Children's Hospital, the prevalence of an OPG was determined to be less than 1.4%. However, the mean period of follow-up was 3.3 years, and only 43% had some form of imaging study. These authors concluded that infants with spasmus nutans should be followed expectantly and not initially subjected to a neuroimaging study. If the syndrome does not disappear in 1–2 years, an MRI should be obtained [11].

Diencephalic Syndrome

The diencephalic syndrome was first described by Russell in 1951 [12]. A typical case includes a vigilant, emaciated infant or young child with macrocephaly, nystagmus and visual deficits. Linear growth may be preserved, but the infant's weight is below the third percentile [13]. The cause of the syndrome is usually a large chiasmatic/hypothalamic low-grade glioma such as a juvenile pilocytic astrocytoma which produces hydrocephalus, an optic neuropathy and endocrine deficits. The median age of onset is 6 months, and less than 4% of cases are diagnosed after 3 years of age [14]. Prior to a definitive diagnosis, the infants are frequently evaluated for failure to thrive with extensive metabolic and gastrointestinal testing, but the macrocephaly, recurrent vomiting and visual symptoms eventually lead to a neuroimaging procedure. Although tumors of similar size and histology may be diagnosed in older children, only infants and young children appeared to be at risk for the development of the diencephalic syndrome.

Clinical improvement occurs following most forms of treatment whether it includes a surgical resection and control of the hydrocephalus, radiotherapy or chemotherapy [12, 15, 16]. The long-term prognosis, however, is guarded. In a series of 7 children who received carboplatin and vincristine chemotherapy at a median age of 11 months, 4 experienced >50% reduction in the size of their diencephalic low-grade glioma with, on average, an 80% weight gain. Disease progression occurred at a median of 24 months after initiation of chemotherapy. The goal of delaying radiotherapy was achieved in 6 of 7 patients, and 5 children are alive 59 months from diagnosis [16].

Leptomeningeal Gliomatosis

Leptomeningeal gliomatosis is a rare complication of childhood intra-axial tumors, especially those that arise in the diencephalon [17]. The availability of advanced MRI imaging of the entire neuraxis with gadolinium in the early 1990's has increased the awareness of this syndrome. The diagnosis is usually suspected by its typical MRI characteristics, that is, diffuse nodular enhancement of the intracranial subarachnoid space in the context of a primary intra-axial enhancing tumor, often in the presence of hydrocephalus. The diagnosis is confirmed by biopsy of the primary and/or leptomeningeal tumors, and finding of a similar pattern of enhancement in the spinal subarachnoid space. Symptoms of leptomeningeal gliomatosis from the spinal metastases include back pain, meningismus and a gait disorder. The intracranial lesions may cause seizures and a diffuse encephalopathy. The ini-

tial treatment is often a procedure to control raised intracranial pressure followed by chemotherapy in the younger patient. The long-term prognosis is remarkably favorable [18].

In a retrospective review of 150 cases of histologically confirmed low-grade astrocytomas at St. Jude's Research Hospital from 1985 to 1994, leptomeningeal metastases were diagnosed in 8 (5%) patients. Symptoms related specifically to leptomeningeal gliomatosis were either minimal or absent. The primary tumor site in 4 of these cases was the hypothalamus. Seven of the 8 patients are alive with stable or progressive disease at a median of 15 months from diagnosis, and several forms of therapy, including chemotherapy and radiotherapy, produced durable remissions [18].

Modifying Influence of NF-1 on OPG

Special management considerations are required for patients with OPG and NF-1. Young children with NF-1 have a relatively high predisposition to develop OPG. In a prospective head CT survey of all patients followed in an NF clinic, OPG were detected in 10 (15%) of 65 children, none of whom had visual complaints or ocular abnormalities [7]. In another study, only 3 of 26 NF-1 patients with OPG developed tumor growth or progression of visual deficits after a median follow-up of 4.2 years [19]. OPG in NF-1 patients may on occasions spontaneously regress.

The incidence of NF-1 in clinical series of patients with OPG ranges from 20–30% [4, 20, 21]. The median time to tumor progression was 8.4 years in 16 patients with NF-1 compared to 2.4 years in 28 patients without NF-1. However, the overall survival at 10 years in the 2 groups was comparable (81% with NF-1, 76% without NF-1) [21]. In another series from the Children's Hospital of Philadelphia which included 46 children with OPG diagnosed at under 5 years, 15 (33%) had NF-1. Only 2 of 14 (14%) evaluable patients with NF-1 had tumor progression following initial treatment compared to 21 of 29 (72%) children without NF-1 [4]. The histology in the majority of NF-1 patients with OPG is the same as in those without NF-1, that is, a juvenile pilocytic astrocytoma. However, the NF-1 condition must exert an attenuating effect on the proliferation of this form of low-grade astrocytoma. Thus, it is prudent to defer chemotherapy and radiotherapy in the majority of NF-1 patients with OPG until symptomatic tumor progression occurs.

In summary, different management strategies should be applied to children with low-grade OPG and high-grade thalamic gliomas. Patients with optic pathway gliomas are diagnosed at an earlier age and have an excellent

long-term prognosis. They are composed primarily of juvenile pilocytic astrocytomas which grow slowly and are largely inoperable by virtue of their location and infiltration behavior. The therapeutic goal for these children is to maximize the quality of their survival by deferring therapy altogether in those patients with NF-1 and by postponing those therapies in younger patients such as radiotherapy that have serious long-term consequences. The majority of patients (90%) without NF will develop tumor progression by 10 years, but chemotherapy may forestall the need for radiotherapy for several years. The role of chemotherapy for patients with low-grade gliomas has only recently been explored, and new agents should be identified which can further prolong progression-free survival. Radiotherapy is becoming safer with computer-assisted treatment planning, and some of the serious consequences of this treatment may be lessened.

Patients with high-grade gliomas have a dismal outlook with a nil 3-year survival, comparable to that observed in patient with intrinsic pontine gliomas. At present, we are using intensive radiotherapy and chemotherapy since most of these patients have surgically unresectable tumors. Curative therapy awaits advances in our understanding of glial tumor biology and perhaps the role that angiogenesis plays in tumor growth and invasion.

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