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PEDIATRIC BRAIN TUMORS

Joao Siffert, MD, Marcia Greenleaf, PhD, Rebecca Mannis, PhD, and Jeffrey Allen, MD

The first section of this article focuses on epidemiology, cause, diagnosis, and treatment of brain tumors in children and adolescents. The second section addresses the long-term consequences of tumors and their treatment, and a special emphasis is paid to cognitive and psychological outcomes.

INCIDENCE AND ETIOLOGY

Incidence

Approximately 10,000 US children under 17 years of age will develop cancer, and in 2000 the tumor will arise in the CNS for an annual incidence of 22 per million.[17, 32, 114] Amongst the many challenges in treating these disorders is the diversity in tumor histology and clinical behavior. Approximately 94% of these children will be treated at an institution affiliated with one of the two national cooperative groups (Children's Cancer Group or Pediatric Oncology Group) and will be eligible to participate in a clinical trial, if available.[18, 114] The overall incidence of pediatric CNS tumors has increased over the past 30 years, as observed in Surveillance, Epidemiology, and End Results population-based tumor registries.[32] Over two thirds of the primary brain tumors in children arise below the tentorium, in contrast to those in adults, which tend to arise above the tentorium. Although improvements in survival have been observed in specific childhood tumors over the past 25 years, such as primitive neuroectodermal tumors (PNET), an inclusive term for medulloblastoma and other histologically similar CNS tumors, most improvement occurred early in the period when craniospinal irradiation became standardized. Little change in outcome has been observed in the past 10 years. Moreover, for the majority of CNS tumors such as brainstem glioma, supratentorial high-grade glioma, ependymoma, and juvenile pilocytic astrocytoma, no significant improvement in survival was observed

From the Department of Neurology, Beth Israel Medical Center (JS, JA), Private Practice (MG, RM), New York; and the Department of Psychiatry, Albert Einstein College of Medicine (JS, MG), Bronx, New York

despite improvements in neurosurgical instrumentation, safer radiotherapy, and the greater application of chemotherapy (Table 1).[5, 6, 27, 31, 39]

A simple portrayal of the incidence and survival statistics does not adequately reflect the impact of childhood brain tumors on society as a whole or on the afflicted individuals. Oncologists tend to focus on malignancies with an exceptionally poor prognosis, such as high-grade gliomas, ependymomas, high-risk PNETs and in infants with brain tumors, in whom the 5-year survival rate averages 5% to 40%.[27, 101] These patients, however, constitute less than 45% of the patient population. The tragedy of lost lives should not minimize our concern for the disease- and treatment-related morbidity experienced by long-term survivors of the more common types of CNS tumors that have a lower growth potential. Certain brain tumor syndromes have an enormous impact on quality of life. Children with suprasellar tumors, such as craniopharyngiomas, chiasmatic or diencephalic gliomas, and germ cell tumors, have very high disease- and treatment-induced morbidity and must cope with permanent hormonal, visual, cognitive, and behavioral deficiencies. Children with intrinsic low-grade gliomas of the medulla or fourth ventricular ependymomas may acquire permanent dysphagia, respirator insufficiency, and weakness as a result of a radical surgical procedure.

Genetic Syndromes

Several hereditary syndromes can lead to the development of central or peripheral nervous system tumors, but the overwhelming majority of CNS tumors in children appear to arise sporadically, that is, without any obvious predisposing condition. Neurofibromatosis-1 is an autosomal dominant syndrome arising from a mutation on the long arm of chromosome 17.[52] The diagnosis is confirmed in younger children by the presence of at least six or more café-au-lait spots, macrocephaly, an optic nerve glioma, and a positive family history. Older children may develop peripheral nerve neurofibromas, Lisch nodules in the iris, and other intraaxial gliomas. Affected children are subject to learning disabilities. The incidence and severity of this predisposition appear related to the number of white matter lesions detectable on T2-weighted

Table 1. APPROXIMATE FREQUENCY, SURVIVAL RATE, AND PATTERNS OF RECURRENCE OF MAJOR CHILDHOOD BRAIN TUMORS

Tumor Histology	Relative Incidence (%)	5-Year Survival Rate	
		PFS	OS
PNET/medulloblastoma			
Standard risk	14	60	70
High risk	7	30	40
Astrocytoma			
Low grade	35	70	90
High grade	10	20	30
Brainstem glioma	10	5	7
Ependymoma	10	30	50

PFS = progression-free survival; OS = overall survival.

From Cohen M, Duffner P: Brain Tumors in Children, ed 2. New York, Raven Press, 1994; with permission.

MR images.[90] Neurofibromatosis-2 is also inherited as an autosomal dominant syndrome presenting with bilateral vestibular schwannomas in early adulthood, intramedullary spinal cord ependymomas, and intracranial and intraspinal meningiomas. The mutation is located on the long arm of chromosome 22.[75] Patients with the nevoid basal cell carcinoma syndrome, a dominant trait, are prone to multiple basal cell carcinomas, jaw cysts, and medulloblastomas.[30] Tuberous sclerosis is an autosomal dominant disorder comprising a wide clinical spectrum of cortical tubers, subependymal giant cell astrocytomas in the periventricular region, infantile spasms, and mental retardation. It occasionally causes intraaxial gliomas and acoustic neuromas. Patients usually develop depigmented macules, sebaceous adenomas (angiofibromas) of the face and fingers, and benign renal and rarely cardiac tumors that involute spontaneously.[64] Patients with hereditary bowel syndromes such as multiple polyposis or nonpolyposis bowel carcinomas may also develop high-grade gliomas or medulloblastomas.[51, 99]

Environmental Exposures

Several recent prospective, controlled epidemiologic surveys explore the causal role of several environmental and parental factors, including residential exposure to magnetic fields,[72] maternal diet,[21] hair-coloring products, farm life, parental occupation, and parental consumption of *N*-nitroso compounds.[20] To date, the only environmental factor that has been positively associated with the source of childhood brain tumors is prior exposure to a course of therapeutic radiation.[63, 113] Anecdotal reports of an increased risk of brain tumors in mobile telephone users have not been substantiated. A prospective trial sponsored by the World Health Organization is underway.

CLINICAL PRESENTATIONS

Clinical manifestations of brain tumors vary according to age of onset, tumor location, rate of growth, and the presence of metastatic disease.[128]

In school-age children and young adults, brain tumors produce distinct clinical syndromes that depend primarily on their anatomic location (infratentorial versus supratentorial) and whether or not they produce raised intracranial pressure.

Infratentorial Tumors

The most common CNS site of origin is the infratentorial compartment or posterior fossa, which includes the cerebellum and brainstem.[19] Tumors arising in the midline cerebellar region, that is, the vermis, frequently expand into and eventually obliterate the fourth ventricle, initially causing symptoms of raised intracranial pressure such as early morning vomiting, headache, diplopia, lethargy, and irritability, and eventually causing ataxia. A head tilt or torticollis may arise as a result of either an abducens palsy or cerebellar tonsillar herniation. Typical signs include truncal ataxia, unilateral or bilateral abducens palsies, dysarthric speech, and papilledema. Macrocrania may exist. In extreme cases, when the intracranial hypertension is severe, intermittent alterations of consciousness with or without transient decerebrate posturing may result from herniation of the cerebellum downward through the foramen magnum or up-

ward through the tentorial notch. This situation is urgent because irreversible brain injury may occur. Although the syndrome mimics an epileptic seizure or bacterial meningitis, a lumbar puncture is contraindicated.

Decreased attention span and progressive cognitive impairment also are manifestations of chronic hydrocephalus, which may occur in a slowly growing pilocytic cerebellar astrocytoma. Astrocytomas arising in the cerebellar hemisphere may present with limb ataxia and head tilt rather than symptoms of raised intracranial pressure. Ependymomas that arise from ependymal tissue lining the fourth ventricle or the lateral foramina of Luschka present not only with symptoms of raised intracranial pressure, but in addition lower cranial nerve signs as they extend into the cisterns adjacent to the medulla. Malignant tumors usually present with a short-history (<3 months) and slow-growing tumor such as an astrocytoma, or an ependymoma with a longer history (>6 months). The most important diagnostic test is a head MR imaging scan or CT scan. Intravenous contrast should be administered if a tumor is suspected. All these tumors may cause hydrocephalus and will enhance with gadolinium, and some, such as the PNET, may produce metastatic lesions. MR imaging is indicated for all newly diagnosed children with PNETs and ependymomas[13] (Fig. 1).

Brainstem tumors can be divided into three main categories based on location (pons, midbrain, and medulla) and tumor grade. Diffuse, intrinsic tumors of the pons comprise 70% to 80% of brainstem tumors and carry the worst prognosis. They consist of fibrillary astrocytomas that will invariably behave aggressively over a span of 6 to 12 months. Children present with a short history (<3 months) of diplopia or facial weakness followed by dysphagia, dysarthria, ataxia, and hemiparesis. Symptoms of raised intracranial pressure are unusual at diagnosis[12, 28] (Fig. 2). Tumors arising in the tectum of the midbrain are usually composed of low-grade astrocytomas. Children present with a long history of signs and symptoms of obstructive hydrocephalus. Parinaud's syndrome (decreased upward gaze and convergence nystagmus) is occasionally present at diagnosis in patients with tectal gliomas. The tumors are indolent and require no further management beyond a cerebrospinal fluid diverting procedure, such as a third ventriculostomy or ventriculoperitoneal shunt.[104] The MR image typically reveals hydrocephalus with large lateral and third ventricles, a small fourth ventricle, and occlusion of the aqueduct due to an intrinsic tectum expansion. The tumor rarely enhances.

Tumors arising in the medulla have a variable growth potential, but the majority behave in an indolent fashion. Children present with a long history of lower cranial nerve deficits related to dysphagia and dysarthria and eventually develop a gait disorder. They are undernourished and have frequent episodes of aspiration pneumonia. The diagnosis is often delayed by evaluations for gastrointestinal, pulmonary, immunologic, or behavioral disorders. The MR image usually shows an intrinsic but asymmetric tumor, frequently with an exophytic component that may extend into the cervical cord. The tumor markedly enhances with contrast.[1, 43]

Supratentorial Tumors

Intrinsic supratentorial brain tumors arise either in the diencephalon (optic pathways, hypothalamus, and thalamus) or in the cerebral hemispheres. Extrinsic tumors may arise in the suprasellar, pineal, intraventricular, or leptomeningeal regions.

Diencephalic tumors affecting the optic apparatus are difficult to diagnose in

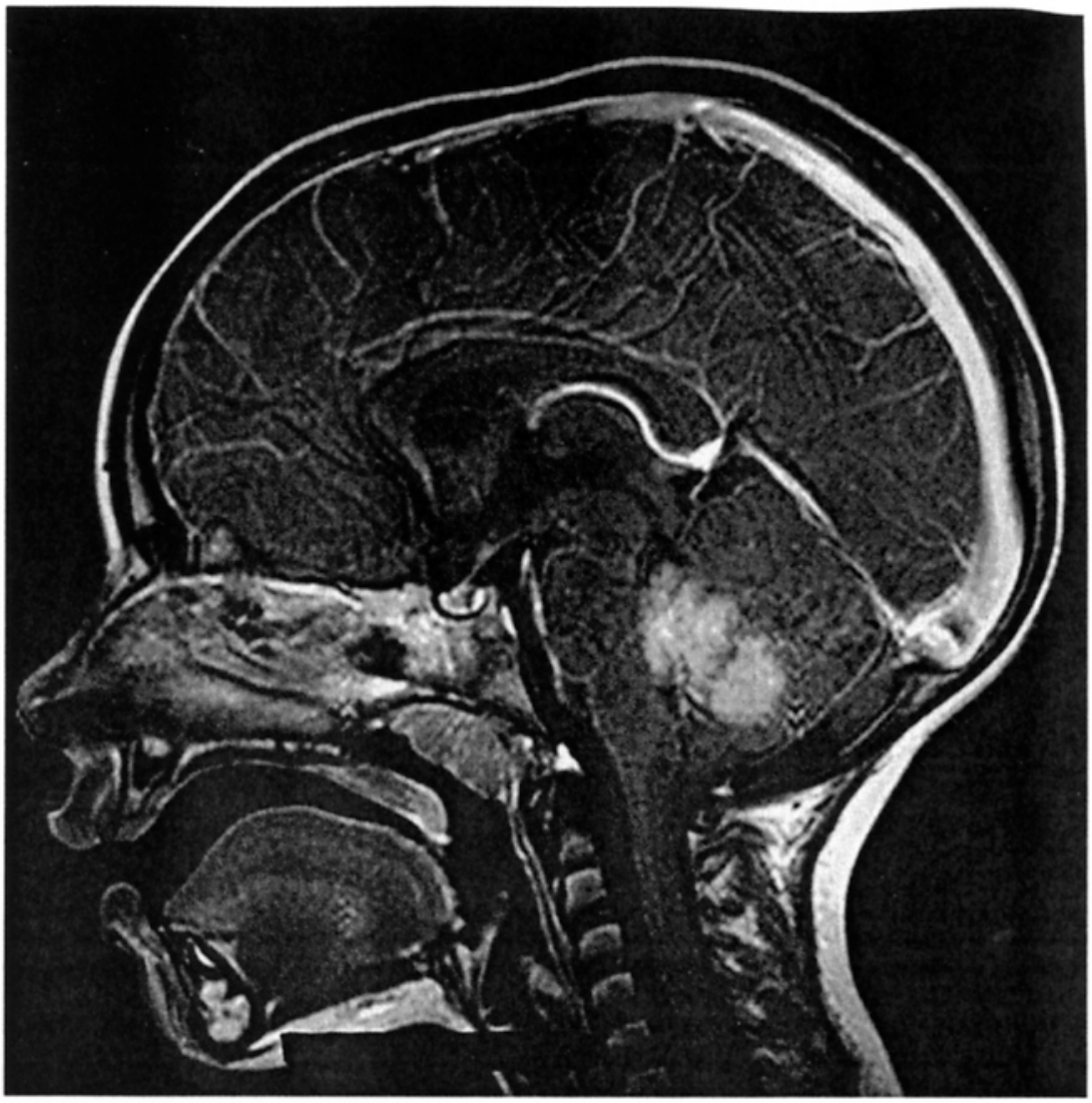

Figure 1. Gadolinium-enhanced sagittal T1 weighted MR imaging scan of a 3½-year-old child demonstrating an enhancing PNET/medulloblastoma arising from the cerebellar vermis and extending into the IV ventricle.

the early stages. Younger children may develop unilateral or bilateral pendular nystagmus related to impaired visual acuity. This may be misdiagnosed as spasmus nutans, a benign, self-limited condition presenting in the first year of life with nystagmus and torticollis. Older children rarely appreciate a loss in visual acuity and may be diagnosed on a screening visual examination at school. As the tumor enlarges and extends into the hypothalamus, signs and symptoms may develop such as endocrine dysfunction (growth failure, precocious puberty, lethargy, obesity, hypothermia, and behavior changes). If the tumor extends into the third ventricle, it causes hydrocephalus and raised intracranial pressure.[62]

Infants and younger children may develop the "diencephalic syndrome," which consists of emaciation with relative preservation of appetite. As opposed to malnourished children, they are often lively. They may have macrocrania and impairment of visual acuity.[105, 117] Optic pathway and hypothalamic tumors usually are comprised of low-grade (juvenile pilocytic) astrocytomas. Thalamic tumors are usually of astrocytic origin. If they are fibrillary, they have a greater tendency to undergo malignant degeneration. If they affect the extrapyramidal

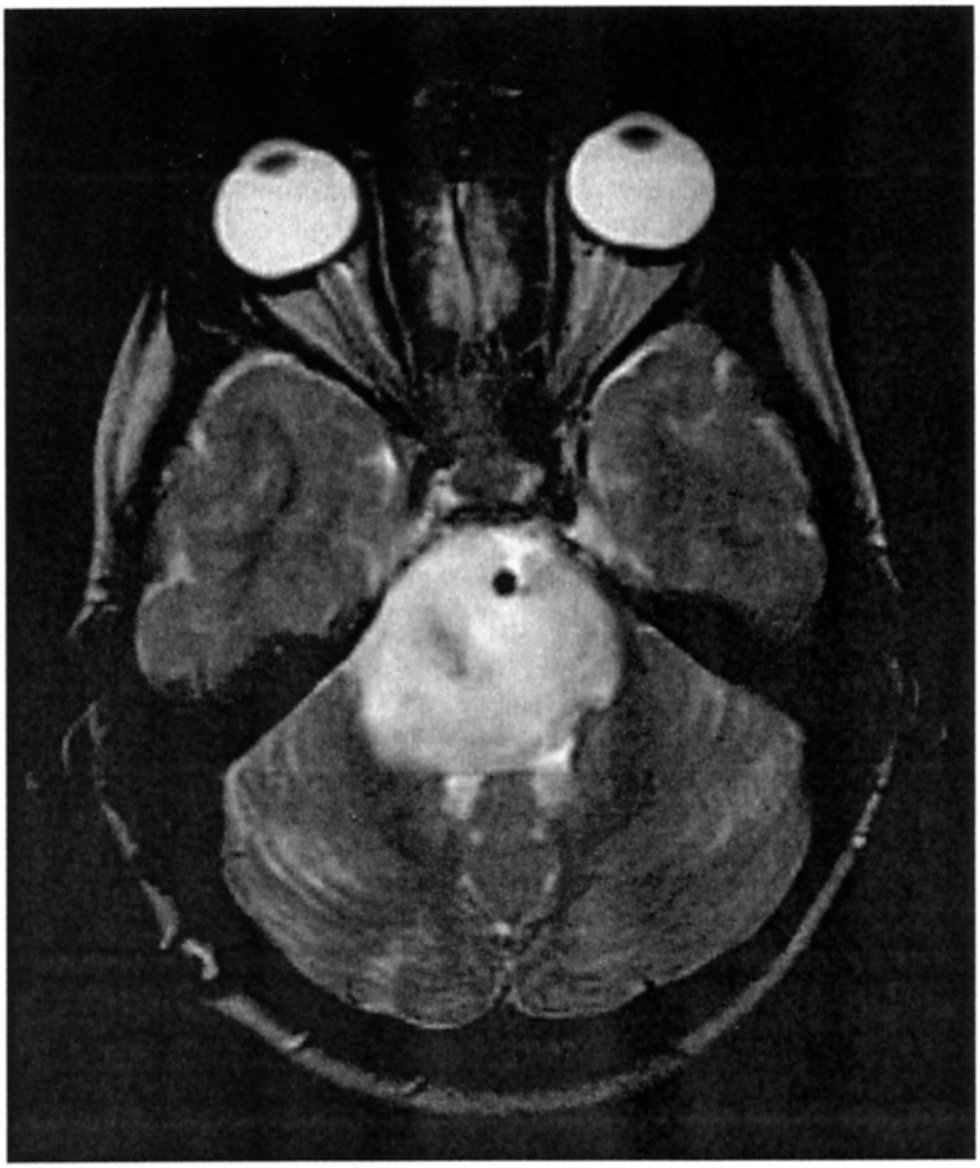

Figure 2. Axial T2-weighted MR imaging scan of an 8-year-old child with an intrinsic diffusely infiltrative brainstem glioma involving the pons and compressing the IV ventricle. Note investment of the basilar artery (dark signal in the ventral portion of the tumor) by the exophytic component of the tumor.

pathways, early symptoms may consist of tremor or alteration of muscle tone. Contiguity to the internal capsule frequently produces pyramidal upper motor weakness as well. Other less common symptoms include sensory disturbances and language abnormalities (thalamic aphasias).

Extrinsic tumors arising in the suprasellar region, such as a craniopharyngioma or germ cell tumor, may present with a long history of visual pathway deficits, endocrine abnormalities, and eventually raised intracranial pressure. Signs and symptoms of diabetes insipidus are more characteristic of germ cell tumors (Fig. 3).[56, 112]

Children who have tumors arising in the cerebral hemispheres usually present with seizures or focal neurologic deficits such as weakness, sensory changes, visual field abnormalities, and, less commonly, headaches. The frequency of seizures may relate to location with epileptogenic brain regions, such

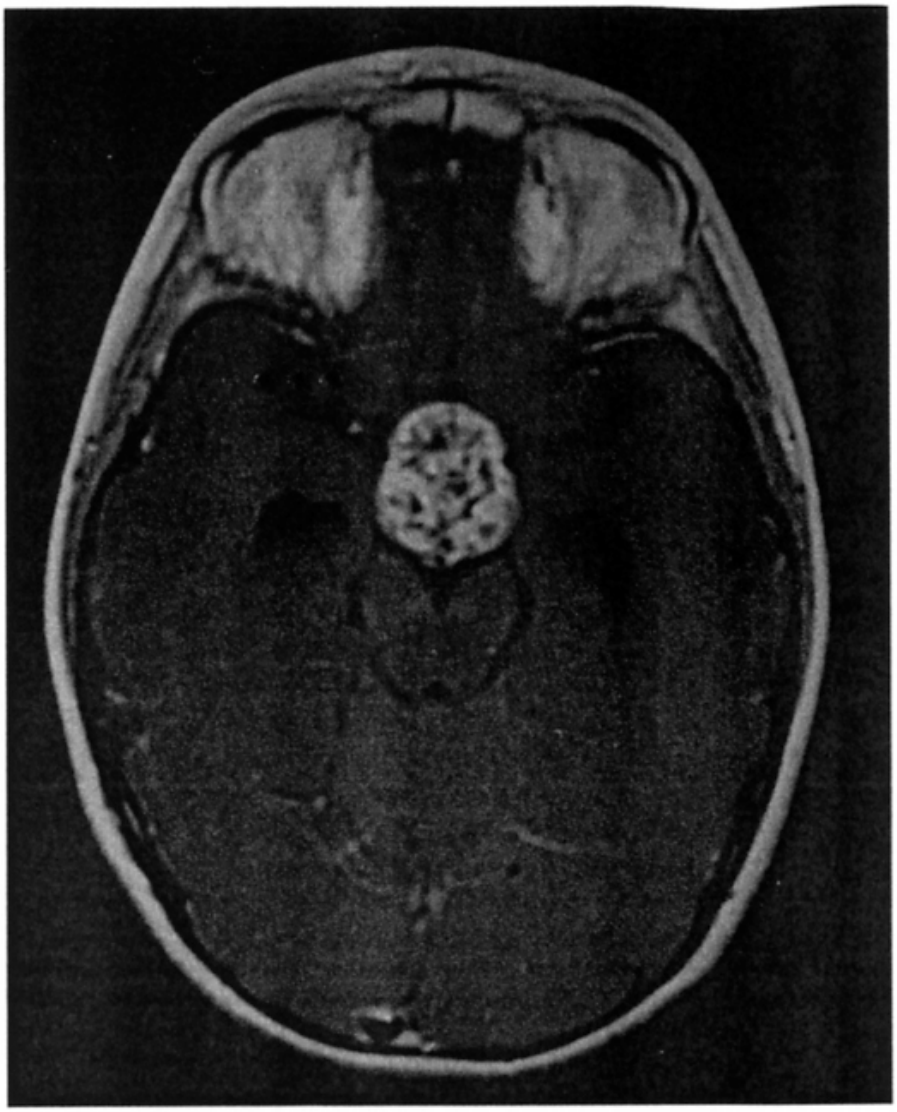

Figure 3. Gadolinium-enhanced axial T1-weighted image of an 8-year-old boy with a suprasellar enhancing mass presenting with diabetes insipidus and lethargy. Differential diagnosis includes craniopharyngioma, germ cell tumor, and glioma.

as the temporal lobes. The majority of cerebral tumors in children are of low-grade astroglial histology, such as astrocytomas and mixed glial tumors.[102] Occasionally a PNET or ependymoma may arise in the brain. Tumors affecting the frontal lobes and right parietal lobe, especially those that are slow growing, may generate few clinical signs. Frontal lobe dysfunction such as abulia, poor planning and language disorders, and neglect syndromes from parietal lobe dysfunction can be late findings in pediatric patients.

Tumors of the pineal region present with Parinaud's syndrome and signs and symptoms of raised intracranial pressure due to compression of the tectal plate and occlusion of the aqueduct. The histology relates to age and sex. Younger patients may have a pineoblastoma, a variant of PNET, or ependymoma. Older boys usually have a germ cell tumor such as a germinoma. Biopsy or the presence of germ cell tumor markers is required for a definitive diagnosis.[44]

Psychiatric Symptoms

Depression may accompany any chronic illness, especially when there is a feeling of malaise and loss of neurologic function. Tumors causing endocrine abnormalities may be accompanied by depression as well. Frontal lobe tumors may present primarily with behavioral symptoms, such as a change in personality and cognitive deficiencies. Apraxias or difficulty in performing simple, repetitive procedures may be apparent. A formal neurologic examination will usually reveal abnormalities in reflexes, tone, strength, and higher cortical function. Frontal release signs such as increased grasp and palmomental reflex and persistence of glabellar reflex are occasionally present as well. Behavioral changes commonly observed in younger children often are related to raised intracranial pressure, which causes intermittent pain and discomfort. These manifestations often are mistaken for abdominal discomfort or developmental disturbances. Occasionally, patients with intrinsic diffuse pontine glioma are noted to have behavioral changes that precede the diagnosis by weeks or months. The parents often describe decreased attention, irritability, and even personality changes. It remains unclear why a lesion in the brainstem leads to behavioral changes.

In the child or adolescent patient with chronic weight loss, recurrent vomiting without associated gastroenterologic dysfunction, and signs of depression or anorexia nervosa, a complete neurologic examination and in some cases, an MR imaging scan, should be performed to exclude a diagnosis of a primary brain tumor.

PRINCIPLES OF THERAPY

Clinical Challenges of Primary CNS Tumors

Medulloblastoma or PNETs are the most common form of childhood CNS cancer, with the highest predisposition to spread to the leptomeninges either at diagnosis (30%) or recurrence (40% to 60%).[3, 36] This feature is the most important prognostic variable at diagnosis. Standard-risk patients with localized, radically resected primary tumors and no metastases (< 1.5 cm^2 postoperative residual, M-0) have a 5-year survival rate greater than 70% when they receive radiotherapy (craniospinal, 36 or 24 Gy; boost, 54 Gy) with or without adjuvant chemotherapy.[6, 36] Improvements in the quality of life for standard-risk patients will require alternative methods of preventing leptomeningeal metastases.

High-risk patients (>1.5 cm^2 postoperative residual, M1–4 or age < 3 years at diagnosis, or all noncerebellar primaries) have a 5-year survival rate of less than 40% and are treated with more intensive chemotherapy and radiotherapy, age permitting.[5, 77] Because medulloblastomas are moderately sensitive to radiotherapy and chemotherapy, improvement in outcome for high-risk patients may come from the discovery of safer methods of intensifying radiotherapy and chemotherapy or the discovery of less toxic new modalities. Intensification of chemotherapy has been explored in several types of clinical contexts in children. High-dose chemotherapy with cytokine or stem cell support is being used for children with high-risk PNETs, with varying success and increased morbidity.

Children develop a diverse spectrum of glial tumors, with a predominance of low-grade gliomas that have a low transformative potential. The 10-year survival rate for children with low-grade gliomas, the most common form (35% to 40%) of childhood brain and spinal cord tumors, is greater than 80% (see

Table 1).[29, 102] Radical resection is the most effective measure to ensure long-term control, and the degree to which these tumors are amenable to a gross-total resection is primarily a function of their location. Variables such as their growth pattern (cystic versus infiltrative) and histology also may influence their resectability. Local control also may be afforded with radiotherapy but the late effects of treating midline cerebral tumors are consequential.[63] Chemotherapy is emerging as an effective alternative with both deferral and curative potential, even for infants.[98] Malignant transformation rarely occurs in the absence of radiotherapy, and leptomeningeal dissemination occurs in less than 2% of newly diagnosed pediatric cases.[76]

Childhood high-grade gliomas have a biology and lethality similar to that in adults and comprise approximately 20% of primary childhood brain tumors (see Table 1). Their evolution in any given child is often variable; that is, some appear to arise de novo with a rapidly evolving clinical course and others appear to evolve more slowly. Sites with the worst prognosis are the brainstem and thalamus. The fully malignant potential of high-grade gliomas is exemplified by their relative resistance to radiotherapy and chemotherapy and their ability to infiltrate or metastasize.[4, 37] Radical resection, when possible, remains the most effective therapy, and improvements in prognosis await the discovery of more effective medical alternatives. The 5-year survival rate for children with more superficial cortical tumors that are radically resected is greater than 30%.[45, 103] The 3-year survival rate for children with diffuse pontine gliomas and unresectable thalamic tumors is less than 5%, and greater than 30% will die with leptomeningeal metastases.[37, 96]

Radical surgical resection is the most effective therapy for ependymomas. The 5-year survival rate for children with gross-total resections is greater than 60% and for those with postoperative residual disease is less than 30%.[54, 103] Totally resected ependymomas that arise above the tentorium may be curable with surgery alone.[11] Histologic grading of childhood ependymomas is not prognostic.[86] Less than 10% of children present with leptomeningeal metastases (LM) but 20% may develop it in the latter stages of their illness.[6, 109] Medical therapies to date have had little impact on the quality or length of survival for these children, especially infants.[50, 87, 120]

Causes of Treatment Failure

The primary cause of treatment failure for both low-grade and high-grade tumors is the inability to achieve local control either because of surgical inaccessibility or lack of therapeutic intent at the initial surgical resection. Radical surgical procedures afford the greatest assurance of remission for most CNS neoplasms, save those like germinomas that are exquisitely sensitive to medical therapy, but often at the cost of neurologic morbidity. For low-grade tumors such as astrocytomas, mixed gliomas, craniopharyngiomas, and certain ependymomas, a gross-total resection may be the only therapy needed to promote long-term, progression-free survival.[14, 33, 41, 48, 56, 102] For high-grade tumors such as PNETs and glioblastoma, radical removal promotes prolongation of survival by minimizing the amount of tumor that may develop resistance to marginally effective therapies.[2, 130] Thus any technology that increases the ability of neurosurgeons to more safely resect brain and spinal tumors will improve the efficacy of marginally effective medical therapy. Conversely, as medical therapies become more effective, the surgeon will have less need to perform such radical resections, thereby lowering the potential for injury.

The molecular mechanisms that account for the wide spectrum of sensitivity to cytotoxic therapies, for example, germinoma compared with glioblastoma, are poorly understood. Radiotherapy resistance may be related to factors such as intratumoral hypoxia, free-radical scavengers, and alternative intracellular methods of repairing sublethal DNA injury. Cancer cells develop novel resistance pathways to chemotherapy related not only to DNA repair mechanisms, but also to pharmacokinetic issues such as altered drug permeability, increased drug efflux, or enhanced drug metabolism.[65] Resistance to specific chemotherapy agents is relative to and is limited by specific organ tolerance.

Promising Directions for Clinical Research

Neuroimaging

Modern neuroimaging techniques utilizing MR and nuclear medicine devices, such as positron emission tomography (PET) and single photon emission computed tomography (SPECT), constitute new prospects in the clinical management of brain tumors. Functional MR imaging is now utilized for localization of specific neurologic functions such as language and primary motor cortex, allowing a more accurate surgical approach while sparing eloquent areas of the CNS.[116] A comparison with the Wada test has confirmed the validity of this instrument in the preoperative evaluation of patients undergoing epilepsy surgery and tumor resections.[16] New techniques such as perfusion MR (measure of blood flow) and MR spectroscopy (analysis of the chemical composition of brain or tumor) are currently under clinical investigation and may become part of the routine diagnostic procedures for brain tumors. Perfusion MR, SPECT, and PET scans are also utilized for distinguishing recurrent tumor from necrosis after radiation and chemotherapy.

Neurosurgery

In addition to the improvements in supportive care and neuroanesthesia, several recent technologic improvements have facilitated the performance of radical neurosurgical procedures with greater safety. The neuronavigation guidance systems are based on CT- or MR imaging–guided frameless stereotaxy.[15, 122] They are most useful for planning operative trajectories, minimizing the size of the craniotomy, and locating deep-seated structures. The surgeon can annotate an image set used for navigation during surgery by delineating regions of residual tumor.[59] The radiation oncologist can fuse these data with those obtained from the postoperative MR imaging scans to get a more accurate postoperative treatment volume. Improvements in intraoperative neurophysiologic monitoring will permit identification of brainstem nuclei, motor and sensory white matter tracts, and eloquent cortical functional locations. Neuroendoscopy facilitates minimally invasive surgical procedures such as biopsy and resection of lesions close to the ventricles.[108, 110, 127, 131] In addition, a third ventriculostomy is a welcomed alternative to a shunt catheter in selected patients.

Radiotherapy

The major goals in radiotherapy are to improve local control while minimizing injury to adjacent tissues. Recent software innovations combined with modified linear accelerators permit sharply defined treatment fields using either

three-dimensional conformal or fractionated stereotactic radiotherapy.[79, 118, 119, 125] Brachytherapy and radiosurgery (gamma knife or modified linear accelerator) can control small, localized tumors (<3 cm) at the expense of producing focal tissue necrosis.[47, 123] None of these techniques has been applied extensively in a pediatric population. Hyperfractionation has been used as a rationale to escalate the dose of radiotherapy, thereby improving local control in children with diffuse brainstem gliomas. Unfortunately, cumulative doses as high as 72 Gy have not had a significant impact on survival.[97] Hyperfractionation has also been used in larger volumes to treat children with high-risk PNETs to improve not only local control (72 Gy), but also reduce the late effects of craniospinal radiotherapy with 36 Gy.[5] The hyperfractionated treatment plan to the craniospinal axis appears to produce fewer endocrine deficits and one could postulate that cognitive side effects could also be lessened by this delivery schedule.[25]

Chemotherapy

Strategies to improve the efficacy of chemotherapy will be directed toward continuing the search for chemicals with novel mechanisms of action, achieving a better understanding of the mechanisms of drug resistance, and developing methods to provide a greater bioavailability and distribution of effective cytotoxic drugs. Other areas of research in medical therapy of brain tumors include blood-brain barrier disruption prior to chemotherapy, angiogenesis inhibition, and gene therapy.

LONG-TERM CONSEQUENCES

Biologic Principles

Each treatment modality has both transient and long-term side effects, several of which may have a major impact on the quality and duration of survival. Neurosurgery-induced deficits, except for those related to occlusion of a major cerebral artery, almost invariably improve with appropriate rehabilitation. The prevention or recovery on a cellular basis from surgical-induced injury is poorly understood, but "neuroprotective drugs" are being used for other forms of acquired neurologic injuries.[8, 24, 38] Poorly understood concepts such as neuronal plasticity and recruitment of normal neurons often are invoked as the pediatric patient undergoes rehabilitation and learns to adapt to disability.[26, 72]

The acute effects of radiation therapy are short-lived but the late effects on the CNS are progressive and potentially devastating. The degree of radiation-induced injury is directly related to dose and volume and is progressive over time. Volume loss is detectable over time. Histologically, there are neuronal dropout, gliosis, and a proliferative and sclerosing angiopathy.[40, 106]

Irradiation of the brain causes cognitive and hormonal deficits and hearing loss.[10, 33] Irradiation of the spine may cause primary hypothyroidism, cardiac damage, restrictive pulmonary disease, and impaired vertebral growth.[60, 74, 91] There also is an inverse relationship between age at treatment and the severity of injury.[89, 94] Rare and more serious consequences include radiation necrosis and the development of a second primary neoplasm.[63] Reduction in the incidence and severity of radiation-induced late effects may occur with the application of new software paradigms and hyperfractionated dose schedules.

Cognitive Outcome

There are both short-term and long-term effects associated with tumor location, surgery, and radiotherapy that leave survivors of brain tumors at higher risk for cognitive, behavioral, and emotional difficulties than children with other types of neoplasms.[22] Less is known about long-term effects of chemotherapy on the developing nervous system, but drugs such as interferon (utilized in certain treatment regimens) have recently been identified as causing CNS dysfunction.

Studies of children with medulloblastoma[35, 42, 46, 78] have shown that long-term effects of deficits in memory, language acquisition and comprehension, attention, and academic skills vary with chronologic age at tumor diagnosis, type and duration of presenting symptoms, tumor extent, radiotherapy, and duration of survival. A prospective study of cognitive function after cranial irradiation (CRT) of malignant primary brain tumors[95] demonstrated the effects of radiotherapy, independent of tumor type or location. Neuropsychological outcome in 18 consecutive children treated with CRT was compared with that of 14 children with brain tumors in similar sites who did not receive CRT. Children who received CRT demonstrated a decline on scores of baseline full-scale IQ tests and verbal IQ tests at 2-year follow-up, which correlated with age. The children treated with CRT become cognitively impaired, with effects worsening over time as assessed by deficits in fine motor, visual-motor, visual-spatial, and memory functions, along with increasing needs for special help in school. The most significant factors associated with moderate to severe neurologic abnormalities and physical disabilities were cranial radiation and supratentorial tumors, with young age an important predictor of disability in relation to CRT.[61, 111]

An analysis of 22 studies representing 544 patients[61] confirmed the effects of radiation therapy volume and age at treatment, with younger children showing a 14-point deficit in IQ as compared with older children. Another analysis of neuropsychological status of children treated for brain tumors did not find significant differences between older children receiving evolved field irradiation versus CRT, but both groups had IQ scores 12 to 14 points lower than children who were not irradiated.[85] One study of children diagnosed with acute lymphocytic leukemia who received CRT showed that final IQ score can be predicted by baseline IQ score, dose of whole-brain irradiation, and age at time of treatment.[121] Another study of cognitive sequelae of childhood acute lymphoblastic leukemia did not find differences between those treated with CRT versus no CRT, but found differences on IQ scores for girls based on treatment with high-dose methotrexate when it was followed by CRT and impairment of verbal memory and encoding for all patients independent of CRT. It was concluded that some component of chemotherapy, possibly prednisone, has a detrimental effect on the CNS.[129] Tumor site, surgery, and disease progression are additional factors that contribute to serious disturbances in cognitive function and affective status.[124, 126]

Psychological Issues and Behavioral Effects

Major psychological stresses confront the patient and the family at each stage of illness.[69] There is the initial shock of diagnosis, the uncertainty of a child's prognosis, the stress of decision making and hospitalization, multiple painful medical procedures, unexpected and novel demands on family members,

the disruption of roles and lifestyle, alteration of physical appearance, side effects of treatment, the stress of ongoing diagnostic procedures, and the fallout on each member of the family as socially appropriate activities are disrupted.[49, 84, 93] The nature and degree of psychological distress will vary with type of diagnosis, premorbid bio-psycho-social status, spiritual orientation, child age, tumor location and severity, and complexity (type, degree, and length) of medical treatment.

The duration, type, and severity of medical difficulties and isolation from peers will determine the lag in social and developmental skills.[55] Facial disfigurement, ataxia, short-term memory loss, and hair loss cause particular problems in school-age children.[55] Parents, health care professionals, and adult friends frequently substitute for the lack of peer interaction due to the myriad issues that lead to social isolation. Adult caretakers may provide a temporary solution to loneliness but this pattern usually prevents a child from developing age-appropriate social behaviors. Depending on how the effects of illness and treatment improve over time, the child can begin reintegration with peers.

Individual families will demonstrate a range of strengths and weaknesses at different phases of diagnosis and treatment, but most struggle with their expectations for a return to normalcy and to life as it existed prior to the diagnosis. During the recovery process, a child's diminished alertness, mood swings, and fatigue can appear to represent a severe emotional disorder. Behavioral changes, however, may also result from withdrawal from pain medications, hormone imbalances, or the side effects of medication used to control postoperative inflammation and seizures. Both in and out of the hospital, there is a tendency to interpret emotional, cognitive, and behavioral problems as inadequate effort or a lack of motivation on the part of the child, without regard for impairment related to the disease or treatment. The children struggle to return to normal as parents press to mainstream the child and expect age-appropriate developmental improvements, while subtle deficits go unassessed or unacknowledged.[78] Under the pressure of a medical crisis, some families pull together and become extremely close, whereas others find that the pressure of dealing with a catastrophic illness and the numerous sequelae exacerbates pre-existing family tensions or pathology.

The range of possible deficits (senses, mobility, emotional, cognitive, management of self-care, pain, participation with peers, and cosmetic) leads to moderate to severe degrees of social alienation and isolation. Siblings and parents struggle with the excessive demands of taking care of a child who may exhibit loss of impulse control or regression in developmental milestones. The stress of these problems will escalate unless a well-organized expanded family or community support system is available. Severity of stress within the family and family dynamics are predictors of behavioral problems in survivors of pediatric brain tumors.[23]

Childhood brain tumor survivors have been shown to have significantly more problems in social competency, participation in activities, and school performance than children with other types of cancer.[84] Subgroups of children with brain tumors who are at especially high risk for maladjustment have a demographic pattern of low socioeconomic standards, a young mother, single-parent family, younger patients, cosmetic disfigurement, functional impairment, and low IQ.[84] Severe late medical effects correlate with poorer self-concept, depressive symptoms, and increased perception of loss of control.[49, 84]

Lannering et al[67] studied long-term sequelae of pediatric brain tumors between 5 and 16 years after diagnosis. Craniopharyngiomas and pituitary tumors were excluded.[66] In their sample of 56 patients, areas of dysfunction

included cognitive (38%), motor (25%), visual (20%), hormonal (20%), and psychological-emotional (14%). Memory impairment was found in 22% of those with normal intelligence; moderate or severe disability was found in 34%, whereas 66% had no or mild disability interfering with an active life style and employment, yet they were less likely to be married or have children as compared with a group of healthy subjects. Differences were found between supra- and infratentorial tumors: moderate to severe disability was found in 48% with supratentorial tumors and 21% with infratentorial tumors. The major finding of this study was that intellectual and psychological-emotional sequelae, that is, mental retardation as assessed by IQ tests, memory and learning difficulties, and impairments in concentration, may or may not lead to affective states characterized by anxiety, depression, and suicidal ideation, but clearly had the most serious impact on patients' lives.[66]

Long-term medical therapy, such as that involving the use of antiepileptic drugs and steroids, may also affect psychological and cognitive function of patients with brain tumors. Antiepileptics can cause mood changes and, when in toxic range, alter the level of consciousness and attention. Steroids (such as dexamethasone), often utilized to abate symptoms related to tumor or swelling, can cause mood abnormalities such as irritability, excitation, and also insomnia. Steroid psychosis is a well-recognized clinical entity seen in the immediate postoperative period, but can also be seen later on if the doses utilized are high.

Quality of Life

Quality of life is a broad concept that includes medical issues, health status, education, standard of living, work activities, community and peer participation, and family life. One assessment of child health is defined as "the ability to participate fully in developmentally appropriate activities and requires physical, psychological, and social energy."[107] Long-term psycho-social functioning of survivors of childhood acute lymphoblastic leukemia treated by intrathecal methotrexate with cranial radiation demonstrated significantly poorer academic achievement and self-images and greater psychological distress than in those who did not receive CRT.[55] The psychological vulnerabilities of the samples studied and reviewed are low self-esteem, preoccupation with physical conditions and body image, depression, stress of ongoing treatment, disease recurrence, and a lack of family support. Hill et al[56] report increased adjustment problems associated with disease onset at later ages and length of time spent in a medical setting, which reduces school attendance and performance, with an increase in special education interventions and decreased enrollment in college.

A case-control study of 219 long-term survivors of pediatric cancer with a mean age of 30 years concentrated on educational and economic issues.[53] There was such a discrepancy between outcome for those who had CNS tumors versus those with other forms of cancer that the data had to be analyzed separately. As a group, these survivors had significantly more limited educational experiences and lower rates of marriage and children. Only half were employed, the divorce rate was higher, and there were more difficulties with interpersonal relationships in the workplace. Lack of achievement stood out; only 10% were college graduates or had advanced degrees and less than 10% were in the highest income bracket.

In a study of neuropsychological sequelae of treatment of children with medulloblastoma, Dennis et al[34, 35] confirm not only deficits that affect academic achievement, but emotional and behavioral disorders that negatively influence

psychological function and quality of life. McCabe et al[78] in their study of survivors of medulloblastoma confirm cognitive deficits, with 54% of their sample displaying severe impairment as measured by maladaptive behaviors. Idiosyncratic communication, affect, and interpersonal skills increase the difficulties associated with neuropsychological deficits and impede social adjustment.[78] This leads to increased isolation with a concomitant lack of social support, a risk factor for depression and maladjustment.

Assessment Needs

Early assessment of a child's deficits and strengths is necessary to help parents and teachers provide proper care, support, and recovery after hospitalization.[69] Lannering et al[67] suggest that one third of those who survive pediatric brain tumors are so severely impaired as to necessitate long-term multidisciplinary team follow-up and treatment, and the remaining two thirds may require support for psychological-emotional difficulties.[66]

Neuropsychological testing provides a survey of several cognitive functions and is an important tool in pediatric rehabilitation planning and educational advocacy. Published data suggest that long-term survivors who received cranial irradiation are at high risk for developing difficulties in assimilating new verbally based knowledge in an age-appropriate manner. They can acquire a range of problems such as intellectual function at below-average levels, formal learning disabilities, performance below learning potential, and impairments in perceptual-motor coordination, fine motor dexterity, attention, concentration, sequencing, and memory, particularly visual memory.[35, 78] These deficits are progressive over time and have a negative impact on psycho-social adjustment.[57, 83] The range and importance of these sequelae make it critical to assess cognitive function at regular intervals after therapy so that the appropriate interventions may be instituted in a timely fashion.[61, 80]

Sequential IQ testing is still used as a global assessment of CNS injury as a consequence of cranial irradiation but appropriate cognitive rehabilitation requires more specific testing.[61, 80, 115] A neuropsychological model is particularly useful in considering changes in both global intelligence and specific functions. Decrements in Full Scale IQ (FSIQ), Verbal IQ (VIQ) and Performance IQ (PIQ) may not be statistically significant for a particular individual, but weaknesses in a range of cognitive functions can only be evidenced on a more thorough neuropsychological evaluation.[9] A complete battery includes testing of intellectual functions, receptive and expressive language, gross and fine motor function, visual and verbal memory recall and recognition, attention and executive functions, visual perception and reasoning, academic achievement, and personality functions. A thorough evaluation significantly enhances the amount of information gleaned from IQ testing, which is not sensitive to the range and complexity of deficits with which the patient may present (Table 2). Specific instruments need to take many independent variables into account; for example, younger children may be at greater risk for physical deficits whereas older children and adolescents may be at greater risk for psychosocial problems.

To determine quality-of-life issues, the health status of the child should be assessed in different phases of treatment and recovery for the ability to participate in age-appropriate learning activities and attain developmental milestones, and the capacity for normal patterns of social and educational behaviors.[107] Specific domains for assessment would include the following: activity and mobility; psychological well-being; social integration; comfort or pain; achievement of

Table 2. NEUROPSYCHOLOGICAL MEASURES

Function	Measure
Intellectual functions (IQ)	WPPSI III
	WISC III
Receptive and expressive language skills	Peabody Picture Vocabulary Test
	Token Test for Children
	Boston Naming Test
	NEPSY
	Roswell-Chall Auditory Blending Test
	Clinical Evaluation of Language Functions
	Benton F-A-S
	Rapid Automatized Naming
	Test of Auditory Comprehension of Language–Revised
	Test of Adolescent Language
Visual, motor, and visual-motor functions	Beery Visual Motor Integration
	PANESS
	Ravens Matrices
	Quick Neurologic Screening Test
	Purdue Pegboard or Grooved Pegboard
	Kaufman Assessment Battery for Children, Hand Movements
	Jordan Right-Left Reversals Test
	Lateral Preference Evaluation
Memory	Wide Range Assessment of Memory and Learning
	Rey Complex Figure
	Detroit Tests of Learning Aptitude (II and III). Oral Directions, Word Sequences, and Visual Sequences subtests
	Stanford-Binet Bead Memory
Attention and executive functions	Wisconsin Card Sorting Test
	Continuous Performance Test
	Target Detection Test
	Trail Making Test
	NEPSY Tower
Academic functions	Roswell-Chall Reading Test
	Woodcock Reading Mastery Test–III: Word ID, Word Attack, Visual-Auditory Learning
	Wechsler Individual Achievement Test
	Gray Oral Reading Test–III
	Gates-MacGinitie Reading Test
	Key Math Test
	Test of Written Language III

cognitive developmental expectation; fertility and sexual maturation and sensory function; and satisfaction. It is also important to assess the level of function within the family unit.[69, 93] Individual family members are each at risk for social alienation from the community while simultaneously dealing with abnormal amounts of stress.

Because of the broad spectrum of early and late effects that may arise in long-term survivors, such as hormonal deficiencies and second primary malignancies as well as cognitive and behavioral dysfunction, children and family members require an extensive clinical team that includes experts in neurosurgery, anesthesia, neurooncology, neuropsychology, psychiatry, nursing, psychol-

ogy, social work, child life specialties, chaplaincy, rehabilitation, and social and cognitive remediation. Parents and children need extensive professional guidance to get the necessary neuropsychological testing, physical and occupational rehabilitation, and cognitive and social skill remediation as well as legal entitlements to learning and support services.[69]

Education

Most children who survive surgery will return to school on a full-time basis, or will require home study instruction. They will develop special educational needs. Unless the performance of a battery of neuropsychological tests is part of a research protocol or standard of care routine offered by the treating institution, parents should request neuropsychological and educational testing from the school because often it will be administered by the school only when the school district deems it necessary. Furthermore, school districts often have different agendas than do parents in seeking evaluation. The school district tests children to classify their disabilities and determine whether the district is legally required to provide a "less restrictive environment" in which to educate the child. This contrasts with the purpose of a neuropsychological evaluation, which is typically more comprehensive. Although the neuropsychological assessment can be used to assist in the classification process, its function is to better understand level of function and cognitive style. This is a key element in ensuring provision of appropriate services and methodologies. If not evaluated, undetected learning difficulties may interfere with cognitive and emotional functioning before help is offered. Many deficits are pervasive in the educational setting and additional examinations will be required. The cognitive deficiencies that this group of children develop often are atypical and may not be easily comprehended nor remediated by the routine educational specialist.

Table 2 presents a list of neuropsychological measures that often are used to evaluate cognitive functions. Ideally, the evaluation is done shortly after surgery to provide a baseline level of function, and is repeated every other year for a minimum of 5 years of follow-up.

Data from a neuropsychological evaluation can be used to formulate specific methodologies in a remediation plan that optimizes cognitive strengths while also accommodating areas of impairment.[58, 71] Cognitive functions affect development of academic skills. Attention and executive functions are necessary to focus on course content and to complete tasks with efficiency. Impairments of receptive language can affect how a child processes instructions. Language expression deficits can inhibit rate and accuracy of word retrieval and limit the sophistication with which ideas can be expressed. Visual perceptual weaknesses impede scanning of text which, in turn, influences reading rate, accuracy, and comprehension, and can complicate written expression. Similarly, spatial weaknesses complicate learning of mathematics and spelling, and interfere with children's abilities to conceptualize information in visual form. This pattern, described as a nonverbal learning disability, is particularly pervasive in patients receiving cranial irradiation. Deficits in memory limit a student's ability to process and integrate new information.[92, 100]

On their return to school, many children experience a decreased rate of processing or output. The child has the capacity to comprehend or produce the information, but the speed with which he or she works is much slower than that of classmates. As a result, he or she is unable to master the range of information with the speed that the academic setting requires. Attention and

executive limitations, frequently attributed to frontal lobe injury, appear to underlie production deficits. Production deficits include disabilities related to difficulty in word retrieval, language sequencing, oral and written expression, and speeded output in a variety of cognitive functions, including motor skills, writing, language, and retrieval of familiar concepts.

Motor weaknesses also affect learning. Fine motor and graphomotor deficits contribute to difficulties in speed and accuracy. Motor sequencing can also interfere with classroom learning. Gross motor limitations ranging from clumsiness to actual weakness can interfere with mobility in the classroom or school. A range of rehabilitative services can be offered, which could include speech and language therapy, occupational therapy, physical therapy, psychotherapy, and educational remediation. A rehabilitation team leader must coordinate these efforts and determine the optimum rehabilitation setting (school, inpatient or outpatient rehabilitation institute) to minimize the inconvenience to the patients and their families and to maximize efficiency of the remediation.

Children returning to school are entitled to education in the "least restrictive environment," as dictated by the Individuals with Disabilities Education Act, as summarized by Latham and Latham.[68] Appropriate services are typically available to them from birth until 21 years of age by virtue of their being "other health impaired" or diagnosed as learning disabled. A team consisting of a learning specialist, advocate, and education attorney can assist parents in requesting specific services as part of the child's Individualized Education Plan, which is reviewed every 3 years. Home tutoring may be appropriate as a transitional maneuver following the initial neurosurgical procedure, especially if the child has acquired a significant neurologic handicap. This decision should be temporary, however, because prolonged absence from school deepens the feeling of isolation and alienation.

A patient's profile may necessitate a specialized, self-contained setting, such as a modified instructional service classroom, whereas others only require supplemental instructional service, such as a resource room or speech and language assistance in conjunction with a mainstreamed environment. In advocating for a patient, the physician or advocate can emphasize specific educational needs related to neurologic rather than psychiatric impairments.

The hospital-based team plays a critical role in communicating with the school about the child's capabilities and deficits. Because schools typically provide services to children with learning disabilities of a different source, it is crucial that the team explain the complexities of the treatment, the anticipated frequency of absences required for treatment, and the anticipated time to recovery. The child's educational needs may change in contrast to those with developmental disabilities.

The school-based team can also integrate the treatment team's recommendations regarding accommodations (modifications) versus remediation into the curriculum. Mooney[82] and Lenz and Scanlon[70] highlight the need to provide instructional services to develop compensatory strategies (such as specific educational techniques) in addition to accommodations such as untimed test administration or reduced course loads. As adaptive educational technology develops, schools are responding to requests for providing a range of computers and adaptive software that children can use to compensate for learning deficits and in some cases, impairments in hearing or vision.

A child's return to school after diagnosis and treatment is just the beginning of a long period of adjustments and accommodations. Planned absences will set the educational goals back, but even when the child attends school, side effects of treatment such as fatigue secondary to chemotherapy-induced anemia or

lethargy and nausea due to radiation will impair the child's concentration and learning capabilities. The child may be kept at home if there is a dangerous contagion at school, such as an outbreak of chicken pox. The treatment team must educate the school officials about the importance of vigilance and prevention.

The psychiatrist and psychologist can also highlight the continuum of recovery for the teachers. A school visit may be necessary for on-site observation and discussions with teachers and staff. Specific attention can be offered to short-term and ongoing deficits. A treatment team should prioritize which deficits are most amenable to remediation at school and which ones will require special help outside the school setting.

ROLE OF THE PSYCHIATRIST IN MANAGEMENT

The psychiatrist brings special expertise in psychopharmacology and in the ability to help the team make differential diagnoses among pain syndromes, mood disorders, behavioral problems, and drug side effects. There is a potential need for psychiatric assessment and intervention in the first 48 hours following operation (pain, mood disturbance, suicidal ideation, avoidance, withdrawal); during an extended stay on the hospital unit (development of phobias, pain, mood disturbance, suicidal ideation, withdrawal, anger); and after discharge, if any of these conditions persist or appear for a first time.

During hospitalization and outpatient treatment, expertise in hypnosis, imagery, family systems interventions, and other behavioral techniques can be applied to prepare the child for surgery and in the management of the stress of hospitalization, pain, anxiety, needle phobias, and insomnia as well as nausea and vomiting associated with chemotherapy.[49, 93] These brief interventions can have a significant positive impact on the recovery process and quality of life. If there is comorbidity, the psychiatrist will play an important role in the diagnosis and treatment of psychopathology that existed premorbidly or developed postdiagnosis in the patient or a family member.

Individual therapy includes crisis intervention, brief psychotherapy, behavioral interventions, or long-term supportive care for the patient and family members; group process can help resolve feelings of isolation for patients, siblings, and parents as well as establish an important milieu for reality testing and problem solving. A comprehensive range of therapies and support services is described elsewhere.[69]

The psychiatrist plays a critical role in guiding and directing the patient and family by providing psychotherapy, by dealing with medication issues related to the patient's emotional state (with particular focus on depression, temper outbursts, fatigue, and attention), and by referring to various members of the rehabilitation and supportive care team. A common challenge is the need to discern differences among affective reactions to the trauma of illness, emotional problems related to neuropsychological difficulties, and cognitive disruptions related to the tumor or treatment. The psychiatrist also guides patients, families, and school officials to determine appropriate academic expectations after neuropsychological testing has illuminated the effects of the brain tumor, its treatment, and ongoing medical management.

The use of psychotropic medications may become necessary and is best determined by a child psychiatrist. Stimulants such as methylphenidate and others have also been increasingly utilized in the management of postradiation syndrome, which can last for as long as 6 months after radiotherapy. This

syndrome is characterized by increased somnolence and fatigue as well as decreased attention. Preliminary results with use of methylphenidate have been encouraging, but controlled trials have not been conducted.[81] Antidepressants and mood stabilizers, such as carbamazepine and valproate, are sometimes indicated and should be utilized according to standard indications.

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Address reprint requests to

Joao Siffert, MD
Beth Israel Hospital
170 East End Avenue
New York, NY 10128