

stimulus. The consequences related to the pairing of the stimuli can be predicted. An example is Pavlov's dogs salivating in response to the bell that had previously been associated with feeding. Using verbal feedback in a practice session and then withdrawing or fading the input can be a form of classical conditioning. In *operant conditioning* a consequence is predicted associated with a behavior. A change in behavior will elicit a given response. Biofeedback is a form of operant conditioning. Both classical conditioning and operant conditioning appear to be under the control of the same cellular mechanisms.

Procedural learning results from the repetition of a movement that results in its automatic performance without much mental concentration. The rules of the movement, or the efficiencies of control, are learned and can be performed repeatedly in the same manner. Procedural learning results in implicit knowledge and is considered to be noncognitive, mediated through the striatum. In a treatment environment, there is emphasis on procedural learning in a variety of environments so that the rules of the task can be demonstrated with more than one set of constraints. This concept is demonstrated when the client learns movement strategies for a transfer in one environment and then learns the movement through experience in another context and environment.⁵¹

Declarative learning requires attention and thought that can be expressed and communicated consciously. Declarative learning results in explicit knowledge and is mediated through the medial temporal lobe. It involves describing or thinking of the components of a movement before execution and then performing the task. This concept can be demonstrated by the use of mental imaging before performing an activity. In the clinic, a client may go through the actions required for a transfer before beginning the task.⁵¹

Memory for motor behaviors is developed through different forms of learning and involves different brain regions. Memory associated with fear or other emotional stimuli is thought to involve the amygdala. Memory established through operant conditioning requires the striatum and cerebellum. Memory acquired through classical conditioning and habituation involves changes in the sensory and motor systems included in the learning. Input to the brain is processed into short-term working memory before it is transformed into a more permanent long-term storage.²¹

Motor learning, or the precision of movement, takes place as the client determines the optimal strategy of movement to perform a motor task. There are defined stages of motor learning involved in skill acquisition. The *cognitive stage* is the first stage and requires a great deal of thought, experimentation, and intervention. Performance is variable, as is seen in the first attempts to walk after brain injury. In the cognitive stage, the treatment environment is highly structured to allow clients to think and focus on a task. Feedback is given more frequently and may involve more sensory

systems. Problem solving is focused on the movement strategies necessary to complete the task. The task may be broken down at this time to work on component parts of the total movement and practiced with repetition.^{47,50}

The second stage of skill acquisition is the *associative stage*, represented by refining of the skill. Fewer errors of performance are experienced, and the motor programs elicited are more consistent and efficient. Feedback can be given in a summary format, often after a few trials. The individual will use trial and error to fine tune the movement.

The final stage is the *autonomous stage*, in which the movement is efficient and the need for attention to the activity is decreased. The motor program has been integrated by the basal ganglia, and each component is initiated with little thought. This activity can now be performed in conjunction with another activity.

The need for feedback during each stage is different. The therapist can enhance treatment by providing the correct amount of feedback for the client attempting to perform a task. For a skill to be acquired, learning principles that promote associative and automatic phases need to be incorporated in the intervention. This appears to be related to the practice conditions. It is clear that repetition is required in every stage. Initially blocked or serial practice is used until the learner understands the dynamics of the task. When cognition is limited, it may be better to keep to a blocked practice schedule longer. For a skill to become learned or transferred to other activities, random practice is more effective. Part-task training can be beneficial if the task can naturally be broken down into component parts that create the whole movement when put back together.

For maximal effectiveness, CNS injury should be treated as soon as possible. As we learn more about the role of individual parts of the brain in relation to function and learning, the location of the injury should drive the intervention. The interaction between the client with neurologic dysfunction and the therapist is critical for optimal motor learning to take place. To elicit the highest level of function within the motor system and allow insight regarding the program, goal-directed activities must be included.^{67,68}

Comorbid impairments should always be considered, as well as the individual's prior health status, age, motivation, and established life practices. In every case, it is important to remember the focus of intervention should not be so much on the disease that the person has as it should be on the person that has the disease.

References

To enhance this text and add value for the reader, all references are included on the companion Evolve site that accompanies this textbook. The reader can view the reference source and access it on-line whenever possible. There are a total of 67 cited references and other general references for this chapter.

CHAPTER 29

Infectious Disorders of the Central Nervous System

KENDA S. FULLER

OVERVIEW

Infection of the central nervous system (CNS) is relatively rare in that many protective responses limit the access of harmful organisms to the nervous tissue. However, neurologic infections are a major cause of mortality and morbidity worldwide. Bacterial infections can be serious and life-threatening. Biologic adaptations of infectious agents and altered modes of transmission present new challenges. Drug-resistant strains create new threats, and travel has increased the exposure to both viruses and the bacteria that can cause infection of the nervous system.^{15,26}

Once there is access to the brain, viruses produce a large range of neuropathologic conditions. They can be oncogenic, producing astrocytomas.⁴⁰ CNS infections can affect the brain's parenchyma, directly causing abscess. Remote infectious processes, such as bacterial endocarditis, resulting in infected emboli, can cause infectious intracranial aneurysms.³² Sepsis can cause diffuse, multi-factorial involvement of the CNS, including invasion of the meninges with resulting meningitis.³⁹ The cerebral spinal fluid (CSF) can be contaminated when an object penetrates the meninges. This is often a result of trauma or a neurosurgical procedure.⁸ Trauma to the front of the face that causes damage or fracture of nasal structures or the cribriform plate can lead to infection in the CSF. Infection of the inner ear can spread to the brain via the CSF.³³

MENINGITIS

Definition

In meningitis, the meninges of the brain and spinal cord become inflamed. The three layers of the meningeal membranes (dura mater, arachnoid, and pia mater) can be involved. The relationship of the meninges to the brain tissue is shown in Fig. 29-1. The pia mater and arachnoid become congested and opaque. The inflammation extends into the first and second layers of the cortex and spinal cord and can produce thrombosis of the cortical veins. There is an increased chance of infarction, and the scar tissue can restrict the flow of CSF, especially around the base of the brain. This block of CSF can result in hydrocephalus or a subarachnoid cyst. Stretch or pres-

sure on the meninges will cause the cardinal sign of headache.¹

Incidence

The estimated incidence of meningitis is 2 to 6 per 100,000 adults per year in developed countries and is up to 10 times higher in less-developed countries.⁴⁴ There appears to be increased susceptibility in some populations, but this may also be related to living conditions and temperate climates. There is a meningitis belt in sub-Saharan Africa, where the incidence is five to ten times higher than in the developed world. There is a genetically determined deficiency that increases susceptibility and risk, but this accounts for only a small portion of those who develop infection.^{22,35}

Etiologic and Risk Factors

Bacterial meningitis once was predominantly a disease of young children and older adults. Vaccines developed in the past 15 years to protect against the development of meningitis, primarily against *Haemophilus influenzae* type B (Hib) infection, have dramatically decreased the incidence in the countries where there is access to the vaccine. There appears to be a second period of increased susceptibility during late adolescence. In adulthood, bacterial meningitis is mostly associated with conditions that affect the defense mechanisms of the host.¹⁵ Individuals with compromised immune function related to other conditions, such as human immunodeficiency virus (HIV), remain at high risk to develop meningitis.²⁶ When there is damage or removal of the spleen, a person becomes more susceptible to pneumococcal disease. Otitis, mastoiditis, and sinusitis are common predisposing conditions that may need specialized treatment. Neoplastic meningitis is a complication that occurs infrequently but is characterized by neurologic signs and symptoms and has a poor outcome.¹⁹ Meningitis associated with cutaneous anthrax became an urgent health concern with the 2001 bioterrorism threat. Although there is meningeal involvement in only 5% of persons exposed, studies of experimental inhalation anthrax in monkeys have demonstrated meningeal involvement in 40% to 50% of cases.

Pathogenesis

The process of infection is complex, but a series of events can be established. Immune responses destroy organisms

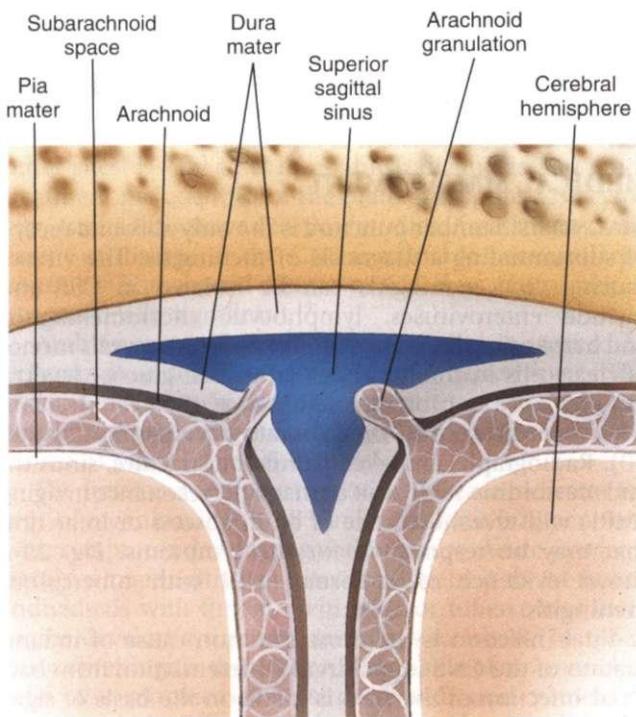


Figure 29-1

The meninges, showing the relationship of the dura, arachnoid, subarachnoid space, pia, and brain tissue. (From Lundy-Ekman L: *Neuroscience: fundamentals for rehabilitation*, ed 3, Philadelphia, 2007, Saunders.)

at the site of the infection and in the blood. Bacteria and viruses are removed from the blood by the reticuloendothelial system. Infection can be carried by blood products or other fluids and can cause changes in the cerebral capillary endothelium. The blood-brain barrier then fails to prevent entry of infectious organisms into the brain or CSF. The blood-brain barrier is a mechanism of the endothelium that selectively inhibits certain substances from entering the interstitial spaces of the brain or CSF. It is believed that the astrocytes and tight junctions with high electrical resistance between the endothelial cells of the brain capillaries create this barrier. The barrier opposes passage of most ions, small peptides, proteins, and high-molecular-weight compounds.³⁹

Once there is penetration of the blood-brain barrier and infectious agents move into the CSF and parenchyma of the brain, there is less immune protection than in the rest of the body. The CSF has about 1/200 the amount of antibody as blood, and the number of white blood cells is very low compared with the blood. The brain lacks a lymphatic system to fight infection.¹⁴

During infection and inflammation, the level of leukocytes in the brain increases. Cytokines, chemokines, macrophages, and microglia respond to viral and bacterial infections. The polymorphonuclear cells recruited to the infection cause damage to the surrounding brain tissue by the release of cytotoxic free radicals and excitatory amino acids such as glutamate. Oxidative stress may be responsible for apoptosis in the hippocampus. Responses to inflammation in the brain can block CSF,

resulting in hydrocephalus, edema, and increased intracranial pressure. Vasculitis can lead to infarction and decreases in cerebral blood flow, causing a drop in the glucose level of the CSF.^{7,35} Drugs that scavenge for free radicals and the use of N-methyl-D-aspartate (NMDA) receptor blockers can help reduce tissue injury.⁴⁰

Aseptic (Viral) Meningitis. Viral infection is the most common cause of inflammation of the CNS. Aseptic meningitis is primarily caused by contamination of the CSF by a virus or fungus. Aseptic meningitis most often is caused by enteroviruses, which are the major cause of meningitis in 40% of those 30 to 60 years old. The second most common cause of meningitis is herpes simplex virus 2, which is detected in approximately 20% of individuals with meningitis. Epstein-Barr virus (EBV) can also be responsible and is more often seen in late adolescence and early adulthood. Systemic lupus erythematosus (SLE), a disorder of connective tissue, can cause aseptic meningitis. Sarcoid tumors and other intracranial tumors or cysts can lead to aseptic meningitis through rupture.³ Often the meningitis occurs days or weeks after the exposure. Recurrent aseptic meningitis is two or more episodes with a disease-free interval between. This must be distinguished from the waxing and waning of chronic meningitis.¹⁶

Certain drugs or chemicals can cause aseptic meningitis. The drugs most commonly involved are the nonsteroidal antiinflammatory medications (NSAIDs). Chemicals can cause direct meningeal irritation and are often related to surgical procedures that expose the chemical.

Tuberculous Meningitis. Tuberculous meningitis is an infection by *Mycobacterium tuberculosis*, which enters the body by inhalation.^{15,42} CNS involvement includes abscess or spinal cord disease. A computed tomography (CT) image of a tuberculoma is seen in Fig. 29-2. Tuberculous brain abscesses may produce mass effect and edema. CSF may demonstrate formation of multiple cysts with lymphocytes and an elevated protein. Infected bacilli enter the subarachnoid space to cause diffuse meningitis.²⁸

Bacterial Meningitis. The organisms generally responsible for bacterial meningitis are those found in mucosal surfaces in the upper respiratory tract. Bacteria in the birth canal can be transferred from the mother to the infant during birth. Group B streptococcus, *Escherichia coli*, and *Listeria monocytogenes* are bacteria that can cause infection in the neonate, although antibodies are passed through the placenta. As these antibodies decline, the susceptibility to Hib, pneumococcus, and meningococcus increases, especially in the second half of the first year of life. On the other end of the spectrum, *Streptococcus pneumoniae* and *Neisseria meningitidis* are the most common bacteria causing infection in the adult and geriatric populations.^{31,35}

In bacterial meningitis, inflammation initially is confined to the subarachnoid space, then spreads to the adjacent brain parenchyma. Vasculitis starts in the small subarachnoid vessels. Thrombotic obstruction of vessels and decreased cerebral perfusion pressure can lead to focal ischemic lesions. Veins are more frequently affected than arteries, probably because of their thinner vessel

walls and the slower blood flow. Damage to the cell bodies causes the production of amyloid- β precursor protein (APP) that is carried through the axon and accumulates within terminal axonal swellings, or spheroids. This axonal pathology contributes to neurologic sequelae seen after bacterial meningitis.²⁹

Clinical Manifestations

Early features of meningitis include fever and headache associated with a stiff and painful neck. There is often pain in the lumbar area and the posterior aspects of the thigh. Kernig's sign, or pain with combined hip flexion and knee extension, is positive. As the inflammation progresses, flexion of the neck will produce flexion of the hips and knees. This is known as a positive Brudzinski's sign.³⁰ The positions for Kernig's and Brudzinski's tests are shown in Fig. 29-3. If the infection remains unde-

tected or untreated, the brainstem centers may be affected. The individual may then experience seizures and coma, vomiting, and papilledema. Focal neurologic signs, including cranial nerve palsies and deafness, can also be seen when the brainstem is affected.

MEDICAL MANAGEMENT

DIAGNOSIS. Lumbar puncture is the only absolute means of substantiating a diagnosis of meningitis. The viruses causing viral meningitis can be isolated in CSF and include enteroviruses, lymphocytic choriomeningitis, and herpes simplex virus. Lumbar puncture reveals mono-nuclear cells in the hundreds, a normal glucose level, a mild increase in protein, and absence of bacterial organisms (see the section on Laboratory Values in Chapter 40). Radiographs are taken to rule out fracture, sinusitis, and mastoiditis. A CT scan or magnetic resonance imaging (MRI) will reveal evidence of brain abscess or infarction that may be responsible for the symptoms. Fig. 29-2 shows evidence of abnormal MRI with tuberculous meningitis.

Viral infection is the most common cause of inflammation of the CNS in children. Differentiation from bacterial infection of the CNS is made on the basis of signs and symptoms and CSF changes. Clinical symptoms consistent with meningeal involvement are milder but overlap with those of bacterial infection.³¹

Prompt diagnosis is critical in bacterial meningitis since death can occur without antibiotic treatment. Because determining the bacterial etiology can take up to 48 hours with CSF cultures, an alternative diagnostic test should be considered. Gram stain examination of CSF is recommended when meningitis is suspected. It is fast, inexpensive, and accurate up to 90% of the time. Polymerase chain reaction (PCR) is useful for excluding a diagnosis of bacterial meningitis and may eventually, with further refinement, be used for determining etiology.¹⁴

When CSF findings suggest bacterial meningitis, but Gram stain and culture results are negative, a combination of laboratory tests is necessary to distinguish bacterial from viral meningitis. In bacterial meningitis, opening pressure generally is between 200 and 500 mm H₂O (lower in children), white blood cell count and protein concentration are elevated, glucose concentration may be

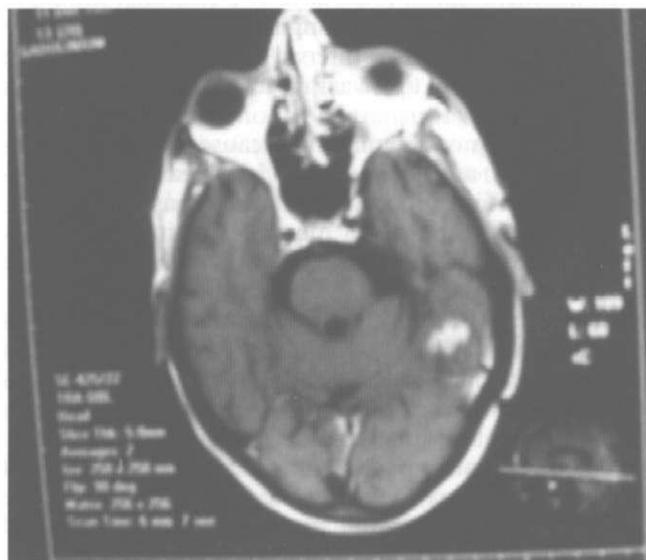


Figure 29-2

CT of the brain showing a left hemisphere tuberculoma in a diabetic patient who presented with a seizure. (From Myers JN: Miliary, central nervous system, and genitourinary tuberculosis, *Dis Mon* 53(1):22-31, 2007.)

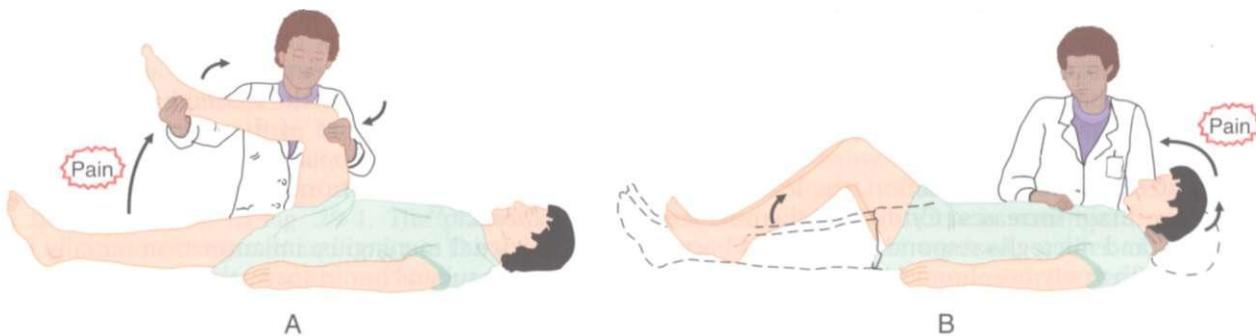


Figure 29-3

Assessing a client with meningeal irritation. **A**, Kernig's sign. **B**, Brudzinski's sign. (From Black JM: *Medical-surgical nursing: clinical management for positive outcomes*, ed 7, Philadelphia, 2004, WB Saunders.)

low, and there may be a neutrophil or lymphocyte predominance.⁴⁰

When there is a neoplasm or brain tumor, the infection may be the result of pleomorphic manifestations of neoplastic meningitis and co-occurrence of disease at other sites. Useful tests to establish diagnosis and guide treatment include MRI of the brain and spine, CSF cytology, and radioisotope CSF flow studies. Assessment of the extent of disease of the CNS is valuable because large-volume subarachnoid disease or CSF flow obstruction is prognostically significant.¹⁹

Anthrax meningitis produces CSF that is marked by polymorphonuclear pleocytosis and hemorrhage. CSF protein elevation is generally present, and CSF glucose concentrations are generally decreased, as is seen with causes of other bacterial meningitis.³⁸

The time course after onset of the disease indicates the type of organism involved. Viral meningitis is hyperacute, with symptoms developing within hours. Acute pyogenic bacterial meningitis can also develop in 4 to 24 hours. Individuals with fungal meningitis or tuberculous meningitis develop symptoms over days to weeks. In tuberculous meningitis, there is a predominance of mononuclear cells, the glucose level is decreased, and protein is increased. It is difficult to identify the tuberculosis bacterium, so clinical signs are important to follow.¹⁵

TREATMENT. Guidelines for the diagnosis and treatment of bacterial meningitis from the Infectious Diseases Society of America (IDSA) can be found at <http://www.journals.uchicago.edu/CID/journal/issues/v39n9/34796/34796.text.html>.⁴⁰

When acute bacterial meningitis is suspected, antimicrobial therapy should begin as soon as possible. Bacterial meningitis is a neurologic emergency; progression to more severe disease reduces the likelihood of a full recovery. Targeted antimicrobial therapy can begin in adults following a positive CSF Gram stain result. Antibiotic therapy should not be delayed pending the results of Gram stain or other diagnostic tests. Antimicrobial therapy should be modified as soon as the pathogen has been isolated. Duration of therapy depends on individual responses.⁴⁰

Suspected bacterial meningitis in a child or infant is considered a medical emergency. The general picture involves fever, decreased feeding, vomiting, bulging fontanel (in infants), seizures, and a high-pitched cry. In neonates with meningitis caused by gram-negative bacilli, the duration of therapy should be determined in part by repeated lumbar punctures documenting CSF sterilization. If there is no response after 48 hours of appropriate therapy, repeated CSF analysis may be necessary. Because any complications of bacterial meningitis usually occur within the first 2 or 3 days of treatment, outpatient management requires close follow-up. Criteria for outpatient therapy are inpatient antimicrobial therapy for 6 or more days; no fever for at least 24 to 48 hours; no significant neurologic dysfunction, focal findings, or seizure activity; stable or improving condition; ability to take fluids by mouth. There should be an established plan for physician and nurse visits, laboratory monitoring, and emergencies. Seizures can be controlled with antiseizure medications.

As the infection is controlled, the seizures are resolved, so a short course is all that is usually necessary.⁴⁰

The addition of dexamethasone can reduce the subarachnoid space inflammatory response that is related to morbidity and mortality and may therefore alleviate many of the pathologic consequences of bacterial meningitis related to cerebral edema or cerebral vasculitis. Change in cerebral blood flow, increase in intracranial pressure, and neuronal injury can be controlled by judicious steroid use.

Radiologic treatment is effective with neoplastic meningitis. Because neoplastic meningitis affects the entire neuraxis, chemotherapy treatment can include intra-CSF fluid. Neoplastic meningitis is often a part of a progressive systemic disease, and consequently treatment is palliative.¹⁹

Usual treatment for viral meningitis is symptomatic. Medication is given for the headache and nausea. The prognosis in viral meningitis is excellent, and most individuals recover within 1 to 2 weeks. Treatment of acute episodes of herpes meningitis with acyclovir has been shown to decrease the duration and severity of symptoms. It may work as well for prophylactic control of episodes. Tuberculous meningitis is managed with drugs given to treat the tuberculosus. In addition, adjunctive therapy with corticosteroids may reduce mortality and decrease neurologic sequelae in severe meningitis.

PROGNOSIS. Mortality ranges from 5% to 25% depending on the infecting bacteria and the health and age of the person infected. At least one neurologic complication, such as impairment of consciousness, seizures, or focal neurologic abnormalities, typically develops in 75% of individuals with bacterial meningitis. Systemic complications, cardiorespiratory failure, or sepsis are also common and found about 40% of the time. Hyponatremia occurs about 30% of the time, with an average duration of 3 days, well managed by fluid restriction.

Cranial nerve palsies occur about 30% of the time, with hearing impairment during hospitalization a common complaint, but more than half have full return of hearing. The severity of hearing loss was graded as mild one-third of the time, moderate one-third, and profound in another third. When there is hearing loss, it is more likely to be bilateral than unilateral.⁴⁴

In children, long-term neurologic consequences of bacterial meningitis include developmental impairment, hearing loss, blindness, hydrocephalus, hypothalamic dysfunction, hemiparesis, and tetraparesis. There is a 30% mortality rate, with increasing death with individuals over 60 years. Most death occurs within 2 weeks, as a result of both systemic and neurologic complications. Aseptic or viral meningitis is usually self-limiting, and there is not the same degree of neurologic sequelae involved. Mortality rates for tuberculous meningitis range from 20% to 50%, and survivors may be left with neurologic sequelae similar to those seen in acute bacterial meningitis.^{22,23} With better understanding of the role of cytokines, therapies targeting these processes are under study and show promise. These therapies may help to further control damage to the nervous system during the infectious or inflammatory process.⁷

ENCEPHALITIS

Definition

Encephalitis is an acute inflammatory disease of the parenchyma, or tissue of the brain, caused by direct viral invasion or hypersensitivity initiated by a virus. Encephalitis is characterized by inflammation primarily in the gray matter of the CNS. Neuronal death can result in cerebral edema. There can also be damage to the vascular system and inflammation of the arachnoid and pia mater.² Viruses carried by mosquitoes or ticks are responsible for most of the worldwide known cases of primary CNS infection. In many cases, such as West Nile virus and herpes simplex virus, the individual can develop either encephalitis or meningitis. This is reflected in the different levels of impairment that may be experienced after exposure.

Incidence

Before 1994, outbreaks of West Nile virus were sporadic and occurred primarily in the Mediterranean region, Africa, and eastern Europe. Since 1994, outbreaks have occurred with a higher incidence of severe human disease, particularly affecting the nervous system. By 2002, incidence was 4 to 14 per 100,000 population in the Midwest. Fig. 29-4 illustrates the spread of the virus through the United States. The virus has caused meningitis, encephalitis, and poliomyelitis, resulting in significant morbidity and mortality.²⁷ Norwegian scientists have reported that an unexpectedly large number of dogs in the Arendal area of southern Norway have antibodies to tick-borne

encephalitis virus caused by flavivirus passed on by forest-living, blood-sucking ticks. Human beings, dogs, sheep, cows, and other mammals become infected when fed on by a tick, although the virus also spreads through the consumption of raw milk from infected animals, and it can cross the placenta from mother to fetus. Human symptoms include meningitis and encephalitis. Up to 20% of infected people suffer permanent neurologic damage, and 2% die.⁶

Etiologic and Risk Factors

The cause cannot be identified in almost two-thirds of cases of viral encephalitis. Viral infection may cause encephalitis as a primary manifestation or as a secondary complication. Risk of neuroinvasive disease in an organ recipient infected with West Nile virus is estimated as 40% compared with less than 1% in the general population.¹¹

Acute viral encephalitides, such as eastern and western equine encephalitis, St Louis encephalitis, and California virus encephalitis, and the most recent outbreak of West Nile virus depend on mosquitos for transmission and tend to occur in the mid to late summer. The eastern variety is the least common but most deadly. It occurs in outbreaks along the entire east coast of the United States. It is rapidly progressive with lesions in the basal ganglia. It carries high mortality and morbidity rates. The western version has a much lower mortality but appears to be particularly severe in infants and children.¹¹

West Nile virus is a flavivirus that was originally isolated in 1937 from the blood of a febrile woman in the West Nile province of Uganda. The virus is widely distrib-

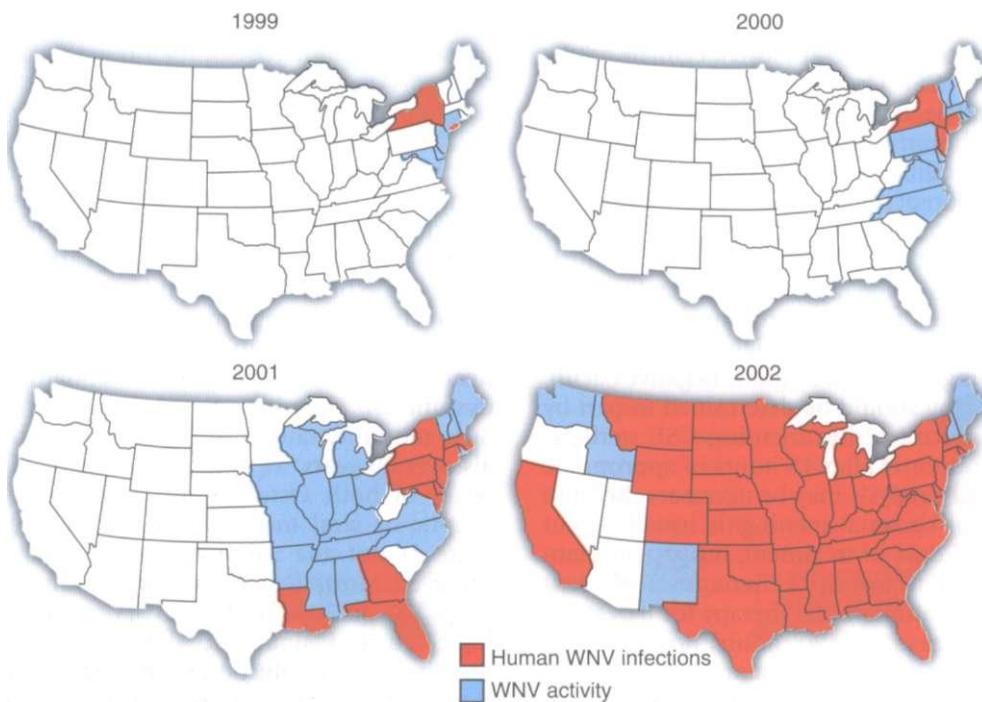


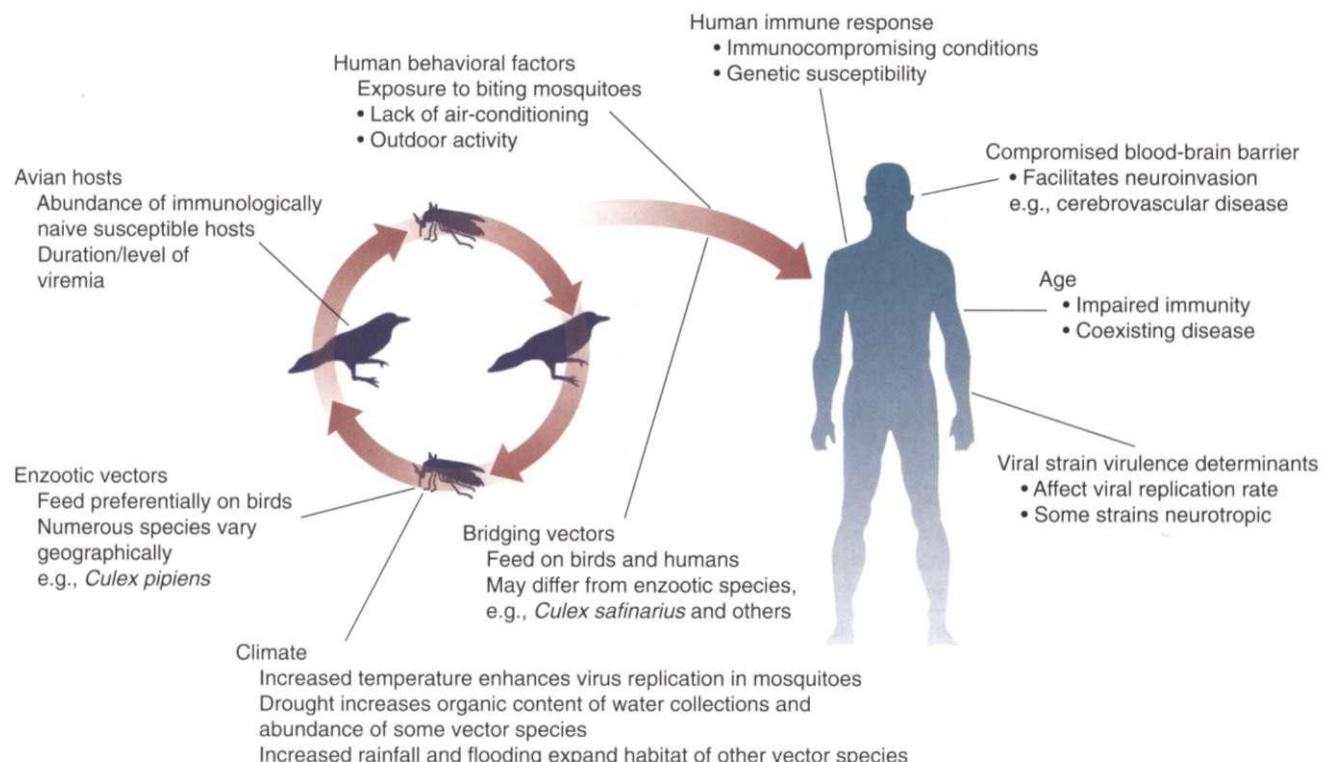
Figure 29-4

West Nile virus activity, United States, 1999-2002. (From Simon RP: Parameningeal infections. In Mandell GL, Bennett JE, Dolin R, eds: *Principles and practice of infectious diseases*, ed 6, New York, 2005, Churchill Livingstone.)

Table 29-1 Human Illness From West Nile Virus Infections Reported in the United States, 1999-2005

	1999	2000	2001	2002	2003	2004	2005
Cases	62	21	66	4156	9862	2539	3000
Neuroinvasive disease (%)	95.2	90.5	97	70.9	29.1	45	43.1
Deaths	7	2	9	284	264	100	119

Data from the US Centers for Disease Control and Prevention as of January 10, 2006; Kramer LD: West Nile virus, *Lancet Neurol* 6(2):171-181, 2007.

**Figure 29-5**

West Nile virus transmission cycle and examples of modifying climatologic, vertebrate, mosquito, and human factors on infection and illness. [From Tsai TF, Vaughn DW, Solomon T: Flaviviruses. In Mandell GL, Bennett JE, Dolin R, eds: *Principles and practice of infectious diseases*, ed 6, New York, 2005, Churchill Livingstone.]

uted in Africa, Europe, Australia, and Asia, and since 1999, it has spread rapidly throughout the western hemisphere, including the United States, Canada, Mexico, and the Caribbean and into parts of Central and South America. Table 29-1 shows the human illness associated with West Nile infections since 1999.

West Nile virus is transmitted primarily between avian hosts and mosquitos. Fig. 29-5 shows the cycle of transmission. Mosquitoes of the genus *Culex* carry the virus, and it is maintained during the dormant period of the adult mosquito and reintroduction of the virus by migratory birds from their winter breeding grounds or from locations where the virus may be transmitted all year round.¹³

Pathogenesis

Encephalitis produces an inflammatory response and pathologic changes in the brain. Ballooning of infected cells and degeneration of the cellular nuclei can lead to cell death. Plasma membranes are destroyed, and cells

form multinucleated giant cells. There is perivascular cuffing causing damage to the lining of a vessel and hemorrhagic necrosis. The oligodendrocytes are affected, creating gliosis, or scarring. Widespread destruction of white matter can occur through inflammation and thrombosis of perforating vessels. Focal damage can hit discrete areas such as the optic nerve.²⁰

West Nile virus is thought to initially replicate in dendritic cells after the host has been bitten by an infected mosquito. The infection then spreads to regional lymph nodes and into the bloodstream. The way in which the virus invades the nervous system is still unknown; retrograde transport along peripheral nerve axons has been proposed. Histologic CNS findings of West Nile virus infection are usually characterized by perivascular lymphoplasmacytic infiltration, microglia, astrocytes, necrosis, and neuronal loss with predilection to structures like the thalamus, brainstem, and cerebellar Purkinje cells. These variable anatomic involvements explain different clinical presentations.²¹

Box 29-1**CLINICAL CHARACTERISTICS OF NONFATAL AND FATAL HOSPITALIZED WEST NILE VIRUS-INFECTED PATIENTS****Signs and Symptoms Most Likely Related to Death**

Fever >38° C (>100.4° F)

Headache

Mental status changes

Nausea

Vomiting

Chills

Muscle weakness

Confusion

Fatigue

Lethargy

Abdominal pain

Underlying Conditions that Have Potential to Increase Risk of Complications

Diabetes

Hypertension

Chronic obstructive pulmonary disease

Dementia

Coronary artery disease

Alcoholism

Asthma

Cancer

Immunosuppression

Other Common Signs and Symptoms

Decreased appetite

Diarrhea

Myalgia

Malaise

Neck stiffness

Skin rash

Shortness of breath

Cough

Dizziness

Increased sleepiness

Balance problems

Photophobia

Back pain

Joint pain (arthralgia)

Tremor

Weight loss

Slurred speech

Neck pain

Sore throat

Seizures

Blurred vision

Coma

Numbness

Flaccid paralysis

Lymphadenopathy

Paresthesias

From Mazurek JM: The epidemiology and early clinical features of West Nile virus infection, *Am J Emerg Med* 23(4):536-543, 2005.

Herpes simplex virus is found in neonatal infants and appears to arise from maternal genital infection with the virus. It is acquired as the baby passes through the birth canal. Fifty percent of those who contract herpes simplex virus will develop CNS disease, whereas others may only develop skin, eye, and mouth disease. Herpes simplex encephalitis is found after the age of 3 months and is often a latent infection found in the gray matter of the temporal lobe and surrounding structures of the limbic system and the frontal lobe. It is the most common cause of sporadic nonepidemic encephalitis in the United States. Possible genetic factors are undergoing study, and in animal studies, there appears to be a connection to the 7, 34.5 gene.¹

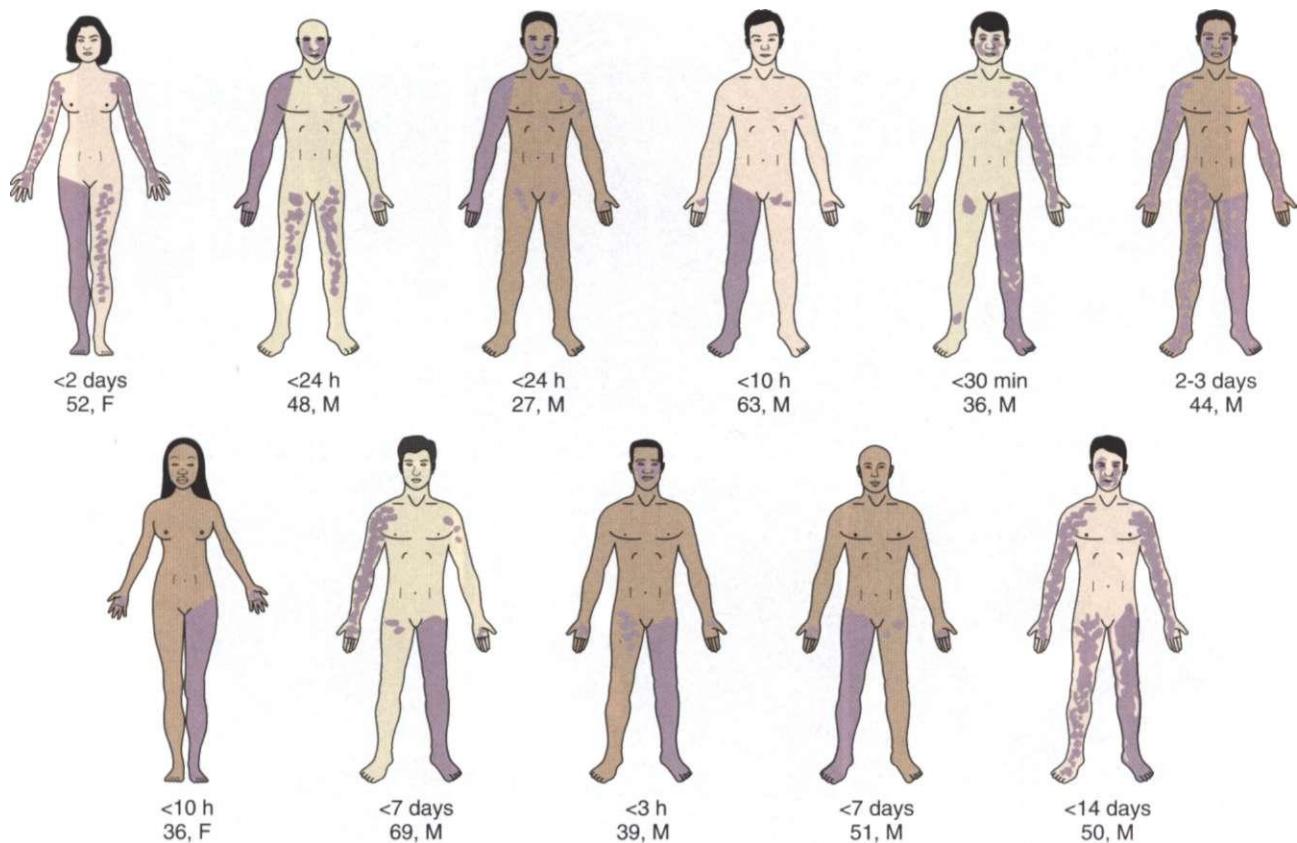
Encephalomyelitis can result from viral infections such as measles, mumps, rubella, or varicella. Mumps is usually benign and self-limited, but it can trigger encephalitis and other CNS complications such as acute, hydrocephalus, ataxia, transverse myelitis, and deafness.⁴¹ Vaccines that contain neuronal antigens have been known to precede these infections, particularly for rabies or smallpox. When there is an illness at the time of vaccination, the risk of developing infection increases. Neurologic problems typically occur within 3 weeks of the illness or vaccination.³

EBV and hepatitis A have been associated with CNS disorders of an infectious nature. Acute toxic encephalitis occurs during the course of a system infection with a common virus. Parasites, bacteria, and toxic drug reactions can lead to infection of the brain and cause encephalitis or encephalopathy.

Clinical Manifestations

Signs and symptoms of encephalitis depend on the etiologic agent, but in general, headache, nausea, and vomiting are followed by altered consciousness. If the person becomes comatose, the coma may persist for days or weeks. Agitation can be associated with the degree of infection and may be associated with abnormal sensory processing. Depending on the area of the brain involved, there may be focal neurologic signs, with hemiparesis, aphasia, ataxia, or disorders of limb movement. There can be symptoms of meningeal irritation with stiffness of the back and neck. With herpes simplex encephalitis, there can be repeated seizure activity, hallucinations, and disturbance of memory, reflecting involvement of the temporal lobe.³³

Although many individuals infected with West Nile virus are asymptomatic, symptoms develop in 20% to 40% of people with West Nile virus infection. The incubation period is 2 to 14 days before symptom onset. Most complaints are of flulike symptoms. West Nile virus is characterized by fever, headache, malaise, myalgia, fatigue, skin rash, lymphadenopathy, vomiting, and diarrhea. Kernig's and Brudzinski's signs may be found on physical examination. Less than 1% of infected individuals develop severe neuroinvasive diseases. West Nile meningitis usually presents with fever and signs of meningeal irritation such as headache, stiff neck, nuchal rigidity, and photophobia. Box 29-1 lists the findings that are most critical to watch for to determine potential for high level of disability or death. In addition, West Nile virus can

**Figure 29-6**

Clinical features induced by West Nile virus paralysis in 11 representative individuals. Weak limbs at the peak of paralysis are darkened. Degree of darkness corresponds to the severity of weakness. Duration of weakness, age and sex are noted. (From Kramer LD: West Nile virus, *Lancet Neurol* 6[2]:171-181, 2007.)

present as acute flaccid paralysis. Fig. 29-6 shows the pattern of weakness found in some individuals with this form of West Nile virus infection. The lesion of spinal anterior horns results in a paralysis similar to polio and reaches a plateau within hours. Deep tendon reflex can be diminished in severely paralysed limbs. Reports of substantial muscle ache in the lower back; bowel and bladder functions are common. There is minimal or no sensory disturbance.^{21,43}

Encephalitic lesions appear to alter sleep patterns as sequelae of brain-immune interactions. Responses of the immune system to invading pathogens are detected by the CNS, which responds by orchestrating complex changes in behavior and physiology. Sleep is one of the behaviors altered in response to immune challenge. Cytokines may play an active role in infectious challenge by regulating sleep.³⁰

MEDICAL MANAGEMENT

DIAGNOSIS. Differential diagnosis of the types of infections of the brain has improved with the use of MRI and PCR to diagnosis herpes simplex encephalitis. The electroencephalogram (EEG) will show seizure activity in the temporal lobe in herpes simplex. In general, lumbar puncture is abnormal with increased proteins. The glucose level, however, may be normal or moderately increased. CT scans do not show much until the damage is exten-

sive. MRI shows cerebral edema and vascular damage earlier in the process and leads to earlier detection.¹ In West Nile virus, lesions can sometimes be seen in the white matter, pons, substantia nigra, and thalamus. An important MRI finding is the focal abnormal signal intensity within the anterior horns; the level of abnormal spinal MRI findings corresponds to the paralysis. Change can be seen in the spinal roots, possibly a result of axonal degeneration secondary to spinal motor neuron loss or Wallerian degeneration in the spinal roots. Fig. 29-7 shows the imaging studies of individuals with West Nile virus.

West Nile virus infection begins with nonspecific symptoms, making early clinical diagnosis challenging. Immunoglobulin M (IgM) antibodies against the virus (usually by enzyme-linked immunoassay [ELISA]) are usually indicative of a recent West Nile virus infection. Blood samples that are collected between the eighth and twenty-first day after onset are likely to give the best yield. IgM antibodies are only detectable 8 days after symptom onset. There may be a negative result from a blood sample obtained before the eighth day after symptom onset. After the twenty-first day, the titre of IgM could decline. The lymphocyte count, particularly the degree of relative lymphopenia, is a readily available test; the degree of relative lymphopenia (>10%) appears to have prognostic importance in West Nile encephalitis. Clinicians should

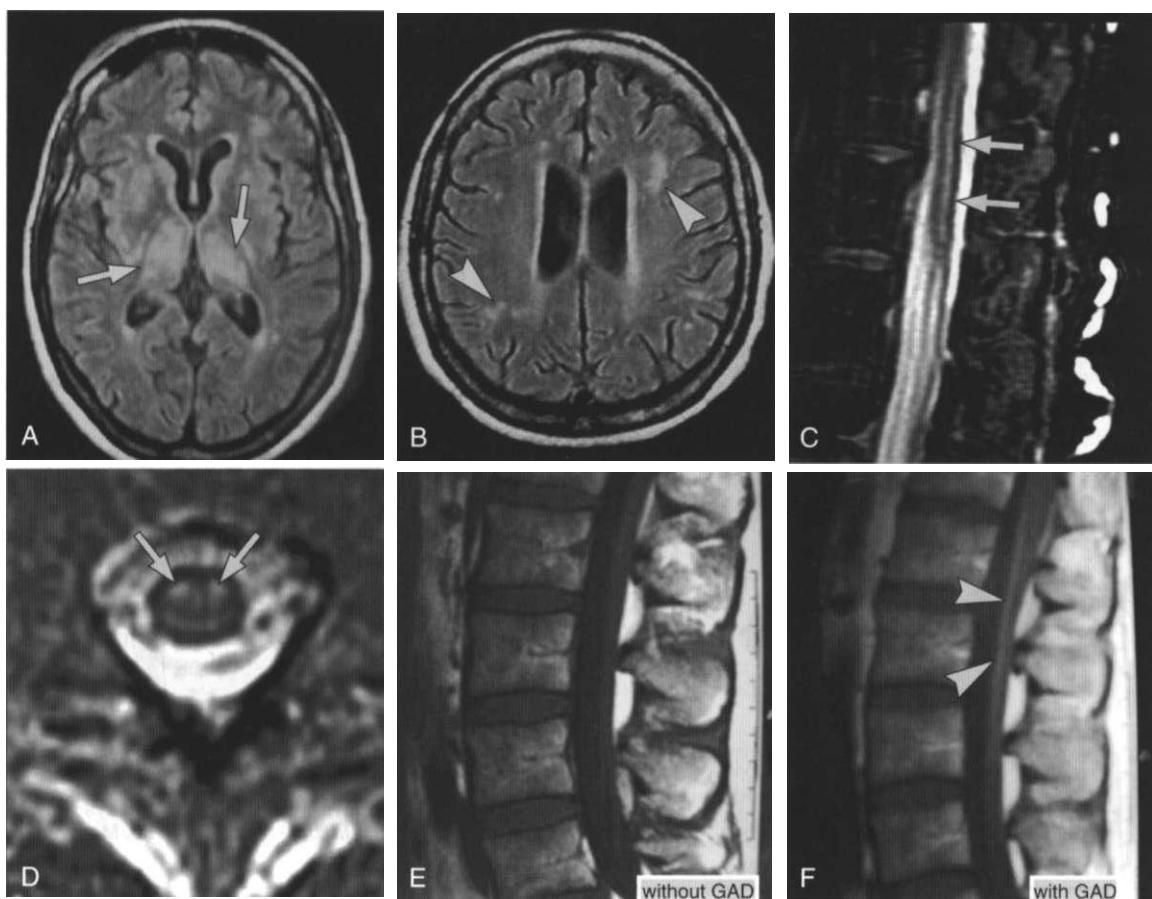


Figure 29-7

Abnormal MRI findings in patients with West Nile virus. **A**, Image of the brain from a 57-year-old woman with encephalitis shows abnormal signals in bilateral thalamus and weighted MRI in other areas of basal ganglion. **B**, Focal white matter lesions are also seen. **C**, Sagittal T2-weighted MRI of the lumbar spinal cord shows abnormal signal intensity (arrows) conspicuous within the cord. **D**, Transverse view of the cord at the midlumbar level; abnormal signal intensity (arrows) is confined to the anterior horns. **E**, T1-weighted lumbar spine MRI from a patient with both meningitis and acute flaccid paralysis shows no discernible abnormality; however, after giving gadolinium contrast, spinal roots are significantly enhanced (**F**). (From Kramer LD: West Nile virus, *Lancet Neurol* 6(2):171-181, 2007; C and D from Li J, Loeb JA, Shy ME, et al: Asymmetric flaccid paralysis: a neuromuscular presentation of West Nile virus infection, *Ann Neurol* 53:703-710, 2003.)

maintain a high index of suspicion for West Nile virus infection during the epidemic season, particularly when evaluating the elderly with neurologic or gastrointestinal symptoms.^{12,27}

West Nile meningitis and encephalitis have similar degrees of pleocytosis, or multiple cystic lesions. However, West Nile encephalitis tends to create higher concentrations of total protein in the CSF and leads to a more severe outcome. Electrophysiologic studies are helpful for the diagnosis of paralysis induced by West Nile virus. Motor-nerve conduction studies may reveal severely reduced amplitudes of compound muscle action potentials in symptomatic limbs. However, if the nerve conduction study is done in the early phase of the illness, compound muscle action potentials can be normal because Wallerian degeneration can take 7 to 10 days to complete. Nerve conduction velocities are usually preserved, and sensory nerve conduction is typically normal. Needle electromyography shows severe denervation in muscles of weak limbs and its corresponding paraspinal muscles. Taken together, these abnormalities in the paralyzed limbs localize the lesions to the anterior horn motor

neurons or their ventral nerve roots. The localization is typically consistent with the MRI findings. Individuals presenting with an otherwise unexplained facial palsy during the summer should be tested not only for neuroborreliosis but also for West Nile virus. West Nile encephalitis may present with cranial nerve abnormalities involving the cranial nerves VI or VII.^{13,21}

TREATMENT. Treatment varies with the infectious agent. No antiviral treatment is available for encephalitis except for that caused by the herpes simplex virus. Acyclovir appears to improve the outcome in herpes simplex encephalitis.

There is no specific regime currently available for treatment of flavivirus infections. Close monitoring of the symptoms is critical, especially with the complication of cerebral edema, which may require surgical decompression, hyperventilation, or administration of mannitol. The use of corticosteroids is controversial because of the potential suppression of antibody protection within the CNS. Because no effective therapy is known, only supportive care is now available. However, there may be

advantages to immunosuppression in postinfectious disorders with possible repair of a damaged blood-brain barrier. Human vaccines for flavivirus infections are currently available only for yellow fever, Japanese encephalitis, and tick-borne encephalitis.¹¹

PROGNOSIS. The prognosis depends on the infectious agent. The rate of recovery can range from 10% to 50% even in individuals who may have been very ill at the onset. Individuals with mumps meningoencephalitis and Venezuelan equine encephalitis have an excellent prognosis. Other encephalitides, such as western equine, St Louis, and California encephalitis and West Nile virus, have a moderate-to-good rate of survival. Although, with the use of medication, herpes simplex encephalitis has a moderately good outcome (20% mortality), neurologic sequelae are common in 50% of persons.^{2,11} Recovery for paralysis is remarkably variable. The variation may be caused by different degrees of motor neuron or motor unit loss.²¹

Some recovery is complete within weeks, but outcome is highly variable. The severity of the original illness does not always predict the final outcome. Prediction of post-West Nile virus poliomyelitis syndrome similar to post-polio syndrome is not yet possible. Permanent cerebral problems are more likely to occur in infants. Young children will take longer to recover than adults with similar infections. Anti-West Nile virus IgM can persist for 1 year or longer.

Development of West Nile virus vaccines have been explored, including immunization of animals with recombinant viral proteins, inactivated West Nile virus, deoxyribonucleic acid (DNA) that expresses viral antigens, or attenuated West Nile virus isolates.²¹

BRAIN ABSCESS

Definition

Brain abscess is an uncommon disorder accounting for only 2% of intracranial mass lesions. CNS abscesses are circumscribed, enlarging, focal infections that produce symptoms and findings similar to those of other space-occupying lesions such as brain tumors. Brain abscesses, however, often progress more rapidly than tumors and more frequently affect meningeal structures. Brain abscesses occur when microorganisms reach the brain and cause a local infection. There may be only one area of abscess, or many areas may be infected because of spread by blood-borne pathogens. Although the site and size of the abscess influence the initial symptoms, evidence of increased intracranial pressure is common.

Risk Factors and Pathogenesis

Persons with a compromised immune system receiving steroids, immunosuppressants, or cytotoxic chemotherapy or persons with a systemic illness, such as HIV infection, have an increased risk of developing a brain abscess. Whereas viruses tend to cause diffuse brain infections as described previously, most bacteria, fungi, and other parasites cause localized brain disease. Brain abscesses

Table 29-2 Potential Causes of Brain Abscess and Related Organisms Based on 123 Patients Treated Between 1986 and 2000

	Patients (No.)
Causes	
Hematogenous spread	32
Neurosurgical procedures	19
Contiguous otogenic	17
Contiguous paranasal sinuses	11
Unknown	44
Organisms	
Gram-negative bacilli	27
<i>Streptococcus</i> sp	21
<i>Staphylococcus</i> sp	9
<i>Corynebacterium</i> sp	4
Anaerobes	17
Mixed bacterial	16
Culture negative	29
Deaths	21

Data modified from Lu CH, Chang WN, Lin YC, et al: Bacterial brain abscess: microbiological features, epidemiological trends and therapeutic outcomes, *JM* 95:501-509, 2002; Goldman L, ed: *Cecil textbook of medicine*, ed 22, Philadelphia, 2004, WB Saunders.

may develop from other infections in the cranium such as sinusitis or mastoiditis.

Infections leading to brain abscess can come from extracerebral locations; blood-borne metastases; infection from lung or heart; or infections within the cranium such as otitis, cranial osteomyelitis, and sinusitis. Recent or remote head trauma or neurosurgical procedures may be the cause. Blood-borne infections seed the brain and spread and produce abscesses in brain regions in proportion to the blood flow; accordingly, parietal lobe abscesses predominate. Extension of infection from otitis and mastoiditis involves contiguous brain regions of the temporal lobe and cerebellum, whereas abscesses resulting from sinusitis affect the frontal and temporal lobes. Table 29-2 presents typical sources of brain abscesses.

Most brain abscesses evolve over a number of stages, with involvement of the cerebrum occurring during the first 1 to 3 days. Inflammatory infiltrates of polymorphonuclear cells, lymphocytes, and plasma cells follow within 24 hours. By 3 days, the surrounding area shows an increase in perivascular inflammation. The late cerebritis phase develops approximately 4 to 9 days after infection, during which time the center becomes necrotic, containing a mixture of debris and inflammatory cells. Early reactive astrocytes surround the zone of infection and proceed to early capsule formation between approximately 10 and 13 days. At this time, the necrotic center shrinks slightly, and a well-developed peripheral fibroblast layer evolves. The late capsule stage continues to evolve between 14 days and 5 weeks, with continual shrinking of the necrotic center and a relative decrease in the inflammatory cells. The capsule thickens with astrocyte scarring.³⁹

If the infection is carried in the blood from another site in the body, the abscess will usually develop at the

Table 29-3 Manifestations of Brain Abscess

Symptom	Incidence (%)
Headache	55
Disturbed consciousness	48
Fever	58
Nuchal rigidity	29
Nausea, vomiting	32
Seizures	19
Visual disturbance	15
Dysarthria	20
Hemiparesis	48
Sepsis	17

Data from Lu CH, Chang WN, Lin YC, et al: Bacterial brain abscess: microbiological features, epidemiological trends and therapeutic outcomes, QJM 95:501-509, 2002; Goldman L, ed: *Cecil textbook of medicine*, ed 22, Philadelphia, 2004, WB Saunders.

junction of the gray and white matter. Anaerobic bacteria are found in over one-half of brain abscesses. The infection usually begins as local encephalitis with necrosis and inflammation of the neurons and glial cells. As the process continues, a capsule wall is formed by the proliferation of fibroblasts. There is usually an area of cerebral edema around the abscess. Bacterial and fungal abscesses will continue to grow until they become lethal. Abscesses caused by other parasites are usually self-limiting.³³

Clinical Manifestations

Normal body temperature is common, and white cell counts are not always high. Neck stiffness is rare in the absence of increased intracranial pressure. Otherwise, the presenting features resemble those of any expanding intracranial mass, like a slow-growing neoplasm, or it may be rapid and progress to possible herniation and brainstem compression, causing death. A headache of recent onset is the most common symptom, representing distortion or irritation of pain-sensitive structures within the cranial vault, especially those of the great venous sinuses and the dura mater about the base of the brain. If the process continues untreated, isolated headache increases in severity and becomes accompanied by focal signs, such as hemiparesis or aphasia, followed by obtundation and coma. The period of evolution may be as brief as hours or as long as many days to weeks with more indolent organisms. Seizures may occur with abscesses that involve the cortical gray matter.³⁹ Lethargy and confusion progress with the increased intracranial pressure present with the growing mass. Focal signs reflect the area of the brain that is affected, with paresis resulting from frontal and parietal lesions and visual disturbances noted with occipital lobe dysfunction.³³ Table 29-3 lists typical manifestations of brain abscess.

MEDICAL MANAGEMENT

DIAGNOSIS. A history of infection or immunosuppression will lead to suspicion of abscess rather than neoplasm. CT and MRI will support the diagnosis based on the different configurations of tumor and abscess. Although the early signs are similar to meningitis, the focal signs of compression in one area of the brain dis-

tinguish the abscess over time. The EEG is often abnormal.²⁰

TREATMENT. Appropriate and timely antibiotic protocol and surgical drainage is required to reduce the mass effect. Careful clinical observation is necessary with multiple abscesses, and CT scans should be repeated often to determine if the abscess continues to expand. Initially, corticosteroids may be used to control the cerebral edema caused by the abscess, but these are used for a short time only because of their interference with capsule formation and immunosuppressive action in the brain.

PROGNOSIS. Mortality from brain abscess can be lowered from 65% to 30% with control of the infection with antibiotics and surgery. Nearly one-half of the clients are left with some neurologic sequelae, which may include focal signs and seizure activity.³⁹

PRION DISEASE

Definition

Rare forms of encephalopathies include the prion diseases of Creutzfeldt-Jakob disease, kuru, and bovine spongiform encephalopathy, also known as mad cow disease. The incubation period is slow and can be up to 5 to 8 years. Most often the disease has been found in young adults ranging from 16 to 30 years.¹⁰

Classic Creutzfeldt-Jakob disease (CJD) is a rare, fatal, and degenerative neurologic disease with a long asymptomatic latent period that was first described in 1920. The causative agent of CJD is thought by most experts to be a prion protein (PrP^{Sc}), an abnormal conformation of a normal cellular protein (PrP^c) that can recruit additional PrP^c to PrP^{Sc}, resulting in deposition of insoluble precipitates in neural tissue. CJD is one of a variety of prion diseases of humans that occur spontaneously at a rate of approximately 1 per million throughout the world and can be transmitted vertically in familial conditions, such as Gerstmann-Straussler-Scheinker syndrome, or through ritualistic cannibalism (kuru).

Like classic CJD, variant CJD (vCJD) is a fatal, degenerative neurologic disease, although it occurs in younger persons and has distinctive clinical, histopathologic, and biochemical features, including the presence of readily detectable prion protein in non-CNS lymphoreticular tissues such as appendix, spleen, tonsil, and lymph nodes. In contrast to classical CJD, vCJD disease is new, first reported in the United Kingdom in 1996. The causative agent of vCJD, a prion, is the same agent that causes bovine spongiform encephalopathy (BSE). A massive epidemic of BSE occurred in Great Britain in the 1980s and early 1990s as a result of the recycling and processing of material from dead sheep and cattle into food meal for cattle. Although this practice was stopped in the mid-1990s after appreciation of the BSE epidemic, an estimated 250,000 cattle had already been infected with BSE. Transmission of the BSE prions to humans occurred by oral consumption of beef and other cattle products containing reticular endothelial or neural tissue, resulting in a delayed outbreak of vCJD in the United Kingdom.¹⁸

Etiologic and Risk Factors

In Italy the incidence of genetic transmissible spongiform encephalopathy diseases is the second highest among European countries.²⁴ Infection with BSE-derived or vCJD-derived prions depends on the host's genetic makeup, which means that there could be a substantial number of symptom-free human carriers of these infectious agents. There is now evidence that vCJD prions can be transmitted through blood transfusion and other iatrogenic routes.^{4,5}

Iatrogenic transmission has occurred via corneal and dural transplants and depth cerebral electrodes. Hormone therapy using human pituitary products can be a cause. Transmission of prion disease is also possible through ingesting nervous system products that contain infected material. Eating nervous system products of beef that had been fed rendered protein led to the increased incidence in the United Kingdom in the 1990s.³⁷ Skeletal muscle tissue from CWD-infected deer has shown prion infectivity; however, the implications of these findings for human beings are unclear. It is very difficult, if not impossible, to predict how prions from one species will behave when they transit species barriers.³⁴

Pathogenesis

Like oncogenes, mutations of the normal cellular prion protein gene cause disease. Abnormal prion protein differs from oncogene products in that the prion protein programs its own creation from normal cellular proteins and then instructs the normal protein to change so that it is functionally similar to the abnormal protein. The microscopic alterations consist of spongy change in neuropil, neuronal loss, and gliosis. The spongiform change is similar to that seen after anoxia and in some cases of Alzheimer's disorders. The prion is a substance that contains no nucleic acid but can replicate within the nervous system. There appears to be accelerated death of Purkinje's cells, resulting in the ataxia that is commonly seen.¹⁷

Clinical Manifestations

Movement becomes abnormal, with dementia that also worsens over time. Sleep-wake symptoms develop with severe sleep EEG abnormalities with loss of sleep spindles, very low sleep efficiency, and virtual absence of rapid eye movement (REM) sleep.²⁵ Akinetic mutism will eventually develop with overriding myoclonic jerks.

MEDICAL MANAGEMENT

DIAGNOSIS. Detection of spongy change alone is not sufficient for the neuropathologic diagnosis of prion disease but must be corroborated with Western blot testing. If familial prion proteinopathy is suspected, molecular genetic analysis of DNA from lymphocytes can be performed.¹⁷

TREATMENT AND PROGNOSIS. At this time there is no known treatment for prion diseases, although clinical trials of methods to disrupt replication are being considered. Once diagnosed, these disorders are rapidly progressive and eventually fatal. Control of the use of potentially

infected animal feed has increased in the early 2000s, and it is believed that this will help to eliminate the current concerns.¹⁷

SPECIAL IMPLICATIONS FOR THE THERAPIST

29-1

EFMH

Infectious Disorders of the Central Nervous System

PREFERRED PRACTICE PATTERNS

5D: Impaired Motor Function and Sensory Integrity Associated with Nonprogressive Disorders of the Central Nervous System—Acquired in Adolescence or Adulthood

5I: Impaired Arousal, Range of Motion, and Motor Control Associated with Coma, Near Coma, or Vegetative State

The therapist must understand and observe all isolation procedures. Often the treatment of these clients begins in the intensive care unit. Monitoring vital signs throughout the treatment session may be necessary when the client is in the acute stage. The client may demonstrate symptoms that are similar to many non-infectious brain disorders. The clinical picture may represent the diffuse disorders typical of brain trauma, or there may be only focal neurologic symptoms that may appear similar to stroke or neoplasm.³⁶

Initially, when the inflammatory response is greatest, there may be a profound alteration of consciousness. The therapist should be familiar with the scales used to monitor levels of consciousness such as the Glasgow Coma Scale. The client may be agitated, with difficulty in processing sensory input resulting in increased sensitivity to sound and light. Cognitive and perceptual disorders with memory deficits probably represent the involvement of the brain in the area of the ventricles.³³ It is essential that the therapist understand the behavioral changes that accompany diffuse brain disorders. See Chapter 33 for further details.

Sensory dysfunction should be thoroughly evaluated. If the client has a history of instability of heart rate, blood pressure, or respiration, these should be monitored during the evaluation of sensation, since sensory input may aggravate responses in some individuals. Cutaneous sensation may be affected in different distributions, depending on whether the damage is diffuse or deep in one area of the brain. Distorted or absent sensory input can affect mobility and functional status in a dramatic way. For further description of sensory and motor deficits related to specific areas of damage, see Chapter 32.

Movement disorders also reflect the nature and depth of the insult to the brain. Abnormal posturing of the client in the acute phase may be noted, and abnormal postural reflexes may be present. Decorticate posturing and decerebrate posturing are often seen in the early stages of these brain disorders.⁹ Positioning and range of motion exercises are critical in the early phases because the stiffness of the back and neck can exacerbate the pain. Often, maintaining a darkened environment during treatment will decrease the complaints of headache. Understanding motor learning

Continued.

strategies is important, since movement often must be relearned in the context of residual damage or agitated behaviors (see Special Implications for the Therapist: Motor Learning Strategies in Chapter 28).

When interacting with the client and family, it is important to be familiar with the acute, subacute, and chronic prognosis related to the type of infection causing the brain injury. Knowing there may be a good outcome will be encouraging during the acute and devastating onset of the infections. Neurologic recovery will continue for many years if the brain remains stimulated as a course of appropriate physical rehabilitation.³³

During the late summer season, the therapist should be aware of the manifestations of mosquito or tick-

borne illnesses. Changes in clients that are consistent with infections should be monitored and a referral made to the appropriate health care provider when necessary.

References

To enhance this text and add value for the reader, all references are included on the companion Evolve site that accompanies this textbook. The reader can view the reference source and access it on-line whenever possible. There are a total of 44 cited references and other general references for this chapter.

CHAPTER 30

Central Nervous System Neoplasms

SHARON M. KONECNE

INTRODUCTION

Several categories of neoplasia affect the central nervous system (CNS). Primary tumors, which may be either benign or malignant, may develop in the brain, spinal cord, or surrounding structures. Secondary, or *metastatic*, tumors may spread to the CNS from another site, such as the lung or breast. *Paraneoplastic syndromes* may occur due to remote or indirect effects on the CNS from cancer elsewhere in the body. Additionally and less commonly, *leptomeningeal carcinomatosis* may occur, in which carcinoma metastasizes throughout the CNS with multiple lesions to the meninges and CSF pathways of the brain and/or spinal cord.

The presence of any CNS tumor or paraneoplastic syndrome is cause for concern due to the vital functions of the brain and spinal cord. The critical areas and confined spaces in the CNS make it vulnerable to a space-occupying lesion. Most primary malignant CNS tumors are locally invasive and cause significant morbidity and mortality.⁷⁷

The early effects of a CNS tumor are related to mechanical displacement of brain or spinal cord tissue, or a mild block in cerebrospinal fluid (CSF) circulation, causing increased intracranial pressure (ICP). As a tumor grows, compression or destruction of local brain or nerve tissue may occur, resulting in specific neurologic deficits. Symptoms of brain tumors may range from minimal, such as mild lethargy, to marked, such as seizures, blindness, and paralysis, as the tumor progresses. Likewise, symptoms of spinal cord tumors may range from mild to severe and include pain, sensory impairments, weakness, and paralysis. Although primary CNS tumors typically do not metastasize outside the CNS because of the lack of a CNS lymphatic system to transport cancer cells, these cells may infrequently travel through the CSF to the spinal cord as "drop metastasis" and cause spinal cord complications.

The diagnosis of a CNS tumor with its threat of significant loss of neurologic and cognitive function is devastating to the client and family. A CNS tumor robs a person of independence and dignity, and is viewed as a humiliating and inextricably fatal process.⁶⁹ Difficult decisions about treatment options and quality-of-life issues add

stress for the client and family. In children with brain tumors, the diagnosis creates parental fear and emotional upheaval, and requires adjusting and decision making for the different needs at varying stages of the illness.⁴⁰ Caregiving and financial struggles frequently are encountered with both brain and spinal cord tumors.

Despite the inescapable realities of these difficult issues, the situation is improving, with dramatic new advances in radiologic imaging, neurosurgery, and adjuvant therapy. At present, including those with both benign and malignant tumors, approximately 50% of patients with CNS tumors can be successfully treated and have an excellent long-term prognosis.¹²⁶ A knowledge and awareness of current treatment advances provide the health professional with the information and skills to care for the client and family in a sensitive, compassionate, and hopeful but realistic manner.

Classification

The major purpose of tumor classification is to facilitate communication about tumor behavior and treatment, and to design studies to learn more about the tumors.¹⁴³ Primary brain tumors are classified by light microscopy according to their predominant cell type.¹³⁵ The World Health Organization (WHO) classification system, which incorporates the Ringerz system for astrocytomas, is becoming the most commonly accepted system, making it easier for clinicians to accurately compare the effects of treatment.^{15,30,87,135} It is a three-tiered system, based on neuroembryonal origin, that is, naming a tumor by the most likely cell of origin, and adding qualifying phrases to describe its behavior.¹⁴³

See Table 30-1 for the WHO classification of primary tumors. The grading, from I to IV, indicates the aggressiveness of the tumor, with grade IV being the most aggressive. The St. Anne-Mayo (Daumas-Duport)¹⁰⁰ system is another classification system in use. It is four tiered, based on the presence or absence of four major criteria (nuclear atypia, mitoses [cells in a state of division], endothelial proliferation, and necrosis), with grade I having none of these features, grade II having one, and so on. Various other systems exist, based on a number of distinguishing criteria: neuroembryonal origin, primary

Table 30-1 World Health Organization (WHO) Classification of Primary Brain Tumors According to Histology

Most Common Tumors	Grade† (WHO)
Astrocytic tumors	
Pilocytic	1
Astrocytoma (diffuse, infiltrative, fibrillary)	2
Anaplastic	3
Glioblastoma multiforme	4
Oligodendroglial tumors and mixed gliomas	
Oligodendrogloma, well differentiated	2
Anaplastic oligodendrogloma	3
Mixed oligodendrogloma/astrocytoma*	2
Mixed anaplastic oligodendrogloma/anaplastic astrocytoma*	3
Ependymal tumors	
Myxopapillary ependymoma	1
Ependymoma	2
Anaplastic	3
Choroid plexus tumors	
Choroid plexus papilloma	1
Choroid plexus carcinoma	3
Neuronal and mixed neuronal-glia tumors	
Ganglioglioma	1-2
Central neurocytoma	2
Filum terminale paraganglioma	1
Dysembryoplastic neuroepithelial tumor (DNET)	1
Pineal parenchymal tumors	
Pineocytoma	2
Pineoblastoma	4
Embryonal tumors	
Medulloblastoma	4
Supratentorial primitive neuroectodermal tumor (PNET)	4
Atypical teratoid/rhabdoid tumor	4
Meningeal tumors	
Meningioma	1
Atypical, clear cell, chordoid	2
Rhabdoid, papillary, or anaplastic (malignant)	3
Pituitary tumors	
Adenomas	1
Carcinomas	2
Tumors of cranial and spinal nerves	
Neurinomas (schwannoma; acoustic neuroma)	1-2

Adapted from Schiff D, Batchelor T: Classification of brain tumors. UpToDate website. Available on-line at <http://uptodateonline.com>. Accessed September 25, 2006; and data from Kleihues P, Cavenee WK, eds: *Pathology and genetics—tumors of the nervous system*, Lyon, 2000, International Agency for Research on Cancer.

*Mixed tumors that consist of oligodendrogloma/anaplastic astrocytoma or anaplastic oligodendrogloma/astrocytoma are usually graded according to the highest-grade component, although there is no consensus from the WHO on this issue.

†Arabic numbers correspond with roman numerals in text.

versus secondary, benign versus malignant, histologic grade, anatomic location, and childhood versus adult tumors. The multiplicity of grading systems has been confusing, making it difficult for clinicians to accurately compare the effects of treatment,¹⁰⁰ so the acceptance of one system will be beneficial.

Primary brain tumors originate from the various cells and structures normally found within the brain. Second-

ary or metastatic brain tumors originate from structures outside the brain, most often from primary tumors of the lungs, breast, gastrointestinal tract, or genitourinary tract,⁵² or from melanoma.¹³⁶

Primary CNS tumors also may be subdivided into *malignant* tumors, such as astrocytomas, and so-called *benign tumors*, such as meningiomas, neurinomas, and hemangioblastomas. A histologically benign tumor has a slow growth rate and is relatively noninvasive. However, because of space-occupying properties in vital tissue with a resultant high threat of functional limitation, the use of the term *benign* is somewhat misleading. Some authors insist that because of location even a very slow-growing CNS tumor should be considered basically malignant.^{39,135} The histologically benign tumor may be surgically inaccessible or located in a vital area, such as the pons or medulla, and will continue to grow, thereby causing an increase in ICP, neurologic deficits, herniation syndromes, and, finally, death.

Malignant CNS tumors typically have a high growth rate and are invasive and infiltrative. They are capable of modulating the surrounding extracellular matrix by secretion of substances that allow for invasion of surrounding tissue by the tumor cells.¹⁰⁰ Tumors also have the ability to create new blood vessels to sustain the tumor, a process called *angiogenesis*.

Anatomic brain tumor location refers to the location of the lesion in reference to the tentorium or cerebral tissue. Knowing the anatomic location helps to predict probable deficits based on the function of that particular area in the brain. Box 30-1 lists the anatomic location of the most common CNS tumors.

There are other typically recognized subdivisions. In the brain are two main groups of primary tumors: *gliomas*, the most common type, which includes astrocytomas and glioblastomas; and tumors arising from supporting structures, such as meningiomas, neurinomas, and pituitary adenomas. A third group arising from embryonal undifferentiated nerve cells has been termed *primitive neuroectodermal tumors* or *PNETs*⁴⁷ and arise more frequently in children. Examples of primary tumors in the spinal cord include the more common neurinomas (schwannomas or neurilemomas) and the less frequent gliomas and meningiomas.

Further subgroups of gliomas have been established based on cellular atypism, the presence of mitotic figures, the incidence of endothelial hyperplasia, and the presence of necrotic areas. It is hoped that newer techniques of molecular biology, such as the ability to identify growth factors and inhibitors necessary for cell growth and differentiation, may lead to a more sophisticated subclassification. Molecular and genetic signatures may predict brain tumor behavior and may soon guide not only tumor classification and diagnosis but also tumor-specific treatment strategies.³⁷

Because the clinical presentation, treatment, and prognosis are heavily dependent on the location of involvement and whether the tumor is primary or metastatic, this discussion is divided into four parts: (1) primary brain tumors, (2) primary intraspinal tumors, (3) metastatic tumors, and (4) childhood brain tumors.

Box 30-1**ANATOMICAL SITES OF THE MOST COMMON CENTRAL NERVOUS SYSTEM TUMORS****Supratentorial Tumors**

- Cerebral hemispheres
 - Metastases
 - Meningiomas
 - Gliomas (malignant gliomas: anaplastic astrocytoma and glioblastoma multiforme, astrocytoma, oligodendrogioma)

Midline Tumors

- Pituitary adenomas
- Pineal tumors
- Craniopharyngiomas

Infratentorial Tumors

- Adults
 - Acoustic schwannomas (neurinomas, neurilemmomas)
 - Metastases
 - Meningiomas
 - Hemangioblastomas
- Children
 - Cerebellar astrocytomas
 - Medulloblastomas
 - Ependymomas
 - Brainstem gliomas

Spinal Cord Tumors

- Extradural
 - Metastases
- Intradural
 - Extramedullary
 - Meningiomas
 - Schwannomas, neurofibromas
 - Intramedullary
 - Ependymomas
 - Astrocytomas

Adapted from Weiss HD: Neoplasms. In Samuels MA, ed: *Manual of neurologic therapeutics*, ed 5, Boston, 1995, Little, Brown, p 225.

bined estimate of 40,900 new primary malignant and benign brain tumors in 2004, the most recent estimate available,^{3,4} or 14 per 100,000 U.S. population. The number of people living with either a benign or malignant brain tumor (prevalence) in the United States in 2003 was estimated to be approximately 350,000 to 360,000.^{3,10,4} Of brain tumor survivors, about 75% have a diagnosis of benign tumors, about 23% have malignant tumors, and 2% have tumors of uncertain behavior.

Although malignant brain tumors accounted for a small percentage of the approximately 1.3 million new cases of all types of cancer projected to occur in 2006,⁴ brain tumors kill more Americans each year than multiple sclerosis and Hodgkin's disease.¹¹⁷ For all the intracranial diseases, death from intracranial neoplasms is second only to stroke.⁴⁷ Approximately 12,820 deaths each year in the United States are due to primary brain and nervous system tumors, and many more are caused by metastasis.⁴

The incidence of primary brain and nervous system tumors peaks in the pediatric population, then increases by about 1.2% per year until it plateaus in the population over 70 years of age.¹⁰⁰ Primary brain tumors are the second most common form of cancer in children,^{9,101} and primary CNS tumors are the second leading cause of death from cancer in children. Gliomas account for approximately 50% of CNS tumors. The average age of onset for all primary brain tumors is 53 years.¹⁰¹ Table 30-2 summarizes the frequency of primary CNS tumors.

More than 60% of tumors in adults are supratentorial, or located in the cerebral hemispheres, above the tentorium. The tentorium is a flap of meninges separating the cerebral hemispheres from the posterior fossa structures. The majority of pediatric tumors are infratentorial, involving primarily the cerebellum and brainstem.²⁶ Certain tumor types have a predilection for specific areas of the brain, although they may arise elsewhere in the brain. Topologic distribution and preferred sites of primary CNS tumors are illustrated in Fig. 30-1.

Pathogenesis

Brain tumors affect the brain through compression of cerebral tissue, including brain substance and cranial nerves; invasion or infiltration of cerebral tissue; and sometimes erosion of bone.⁵² These mechanisms precipitate pathophysiologic changes such as cerebral edema and increased ICP.

In most brain tumors, vasogenic edema develops in the surrounding tissue of the tumor because of compression and obstruction of CSF pathways, moving CSF across ventricular walls.⁴⁷ Substances released from tumor cells altering the blood-brain barrier also may cause rapid cerebral edema. Seepage of plasma into the extracellular space and between the layers of the myelin sheath results from the increased permeability of the capillary endothelial cells of the white matter. This impairs cellular activity and causes electrochemical instability, resulting in seizures. As the edema continues to develop, signs and symptoms of increased ICP become more apparent.

Initially the brain may have a surprising tolerance to the compressive and infiltrative effects of brain tumors,

PRIMARY BRAIN TUMORS**Incidence and Prevalence**

Tumors of the CNS are not uncommon. The National Cancer Institute projected that 18,820 new malignant primary tumors of the brain and nervous system would be diagnosed in 2006 in the United States: 10,730 in men and 8090 in women.^{3,124,25} This corresponds to 7.6 and 5.4 per 100,000 men and women, respectively, in the U.S. population. The National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) data indicate that in 2003 there were approximately 111,212 people alive who had had a history of CNS cancer. The mean age at diagnosis of brain and nervous system cancer is 55 years of age. The overall 5-year relative survival rate for 1996 to 2002 was reported to be 33.5%. Estimates were that 12,820 men and women would die of brain and other nervous system cancers in 2006.^{21,32}

Benign primary brain tumors add to the total incidence. The American Brain Tumor Association reported a com-

Table 30-2 Frequency of Primary Central Nervous System Tumors

CHILDREN (0-14 YR)		ADULTS (≥15 YR)	
Type	Percentage	Type	Percentage
Glioblastoma	20	Glioblastoma	50
Astrocytoma	21	Astrocytoma	10
Ependymoma	7	Ependymoma	2
Oligodendrogioma	1	Oligodendrogioma	3
Medulloblastoma	24	Medulloblastoma	2
Neuroblastoma	3	Pituitary adenoma	4
Neurinoma	1	Neurinoma	2
Craniopharyngioma	5	Craniopharyngioma	1
Meningioma	5	Meningioma	17
Teratoma	2		
Pinealoma	2	Pinealoma	1
Hemangioma	3	Hemangioma	2
Sarcoma	1	Sarcoma	1
Others	5	Others	5
Total	100	Total	100

Adapted from Janus TJ, Yung WKA: Primary neurological tumors. In Goetz CG, ed: *Textbook of clinical neurology*, ed 2, Philadelphia, 2003, Saunders.

particularly with slow growing tumors, and early symptoms may be few. Compensatory mechanisms to accommodate the edema and maintain normal ICP are limited but include decreasing (1) the volume of brain tissue, (2) CSF, and (3) cerebral blood volume. When the brain can no longer compensate, the resultant increase in ICP leads to more evident signs and symptoms. Intracranial herniation and herniation through the foramen magnum are potential results of serious ICP elevation. Fig. 30-2 illustrates intracranial herniation syndromes evoked by supratentorial masses.

Clinical Manifestations

The particular clinical presentation of a brain tumor depends on the compression or infiltration of specific cerebral tissue, the related cerebral edema, and the development of increased ICP.⁵² Cerebral edema surrounding the tumor results from the inflammatory response of tissues to the tumor and contributes to the increase in ICP. Box 30-2 lists common signs and symptoms of brain tumors.

The initial clinical signs of an intracranial tumor are related to the generalized effect of an increase in ICP. Headache is commonly present (in one third to one half of cases), is typically generalized or retro-orbital, and is typically worse in the morning and better later in the day. The headache is intensified or precipitated by any activity that tends to raise the ICP, such as stooping, straining, coughing, or exercising. Irritation, compression, or traction of pain-sensitive structures such as the dura mater and blood vessels causes the headache.¹⁰⁵ Although tension-type headache is more common, migraine-type and other types may be exhibited.¹³⁷ The sixth cranial nerve (abducens) is highly susceptible to elevated ICP because of its local anatomic relationships as the basis pontis slips caudally during transtentorial herniation, not, as previously believed, because of its long intracranial path.⁴⁹ This causes weakness in the lateral rectus

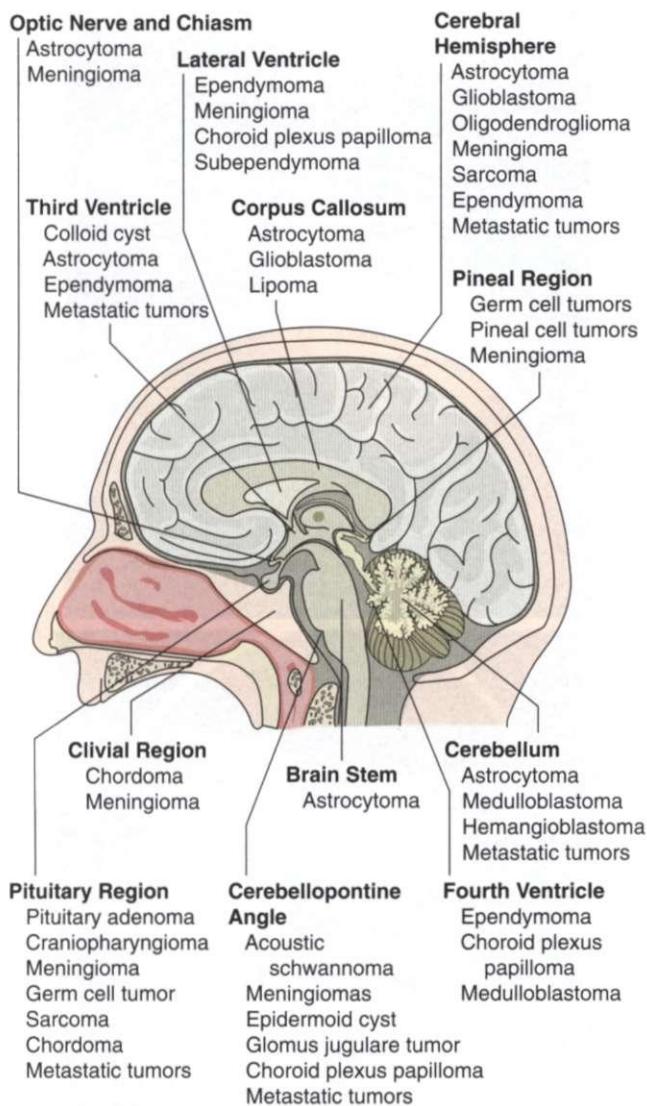
Box 30-2

SIGNS AND SYMPTOMS OF BRAIN TUMORS

- Headache
- Visual changes (double vision, blurred vision)
- Nausea
- Vomiting
- Cognitive changes—impairment of memory, judgment, personality
- Lethargy
- Behavioral changes
- Seizures
- Syncope
- Weakness
- Hemiparesis, hemiplegia
- Apraxia
- Cortical sensory deficits (graphesthesia, stereognosis difficulties)
- Sensory impairments (tingling, spatial orientation changes)
- Cranial nerve palsies
- Aphasia
- Facial numbness
- Hearing disturbances
- Anosmia
- Swallowing difficulties
- Paralysis of outward gaze (sixth cranial nerve)
- Papilledema
- Incoordination
- Ataxia
- In children, diastases of cranial sutures and enlarging head size

muscle and diplopia. Nausea and vomiting are common, often due to increased ICP. In glioblastoma multiforme (GBM), about one third of patients suffer nausea and vomiting. Box 30-3 lists signs and symptoms of intracranial hypertension.

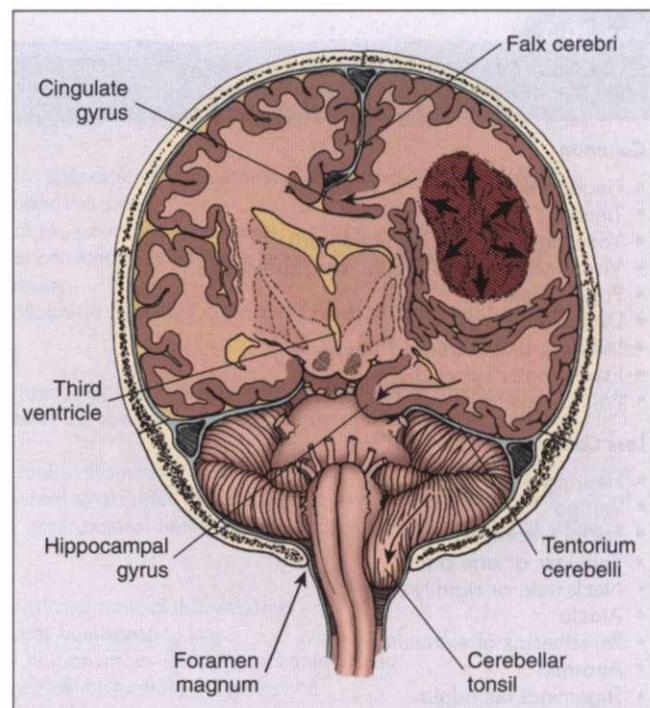
Other common initial signs are mental clouding, lethargy, alterations in consciousness and cognition, syncope (fainting), and easy fatigability. Behavioral changes may

**Figure 30-1**

Topologic distribution and preferred sites of primary central nervous system tumors. (Adapted from Burger PC, Schneithauer BW, Vogel FS: *Surgical pathology of the nervous system and its coverings*, ed 3, New York, 1991, Churchill Livingstone.)

include irritability, flat affect, emotional lability, and lack of initiative and spontaneity. Increasing intracranial CSF pressure may precipitate an increase in perioptic pressure, which in turn impedes venous drainage from the optic head area and retina, causing papilledema, or edema of the optic disc. Papilledema, present in about 70% to 75% of patients with brain tumors, is associated with visual changes, such as decreased visual acuity, an enlarged blind spot, diplopia, and deficits in the visual fields. Often deterioration in vision may be the precipitating factor in the patient's seeking an appointment with an optometrist or ophthalmologist. A dilated ophthalmologic examination showing papilledema is fairly crucial to the diagnosis when it is not straightforward.

About 20% to 50% of adults with brain tumors develop seizure activity. The cerebral edema causes hyperactive cells, which produce abnormal, paroxysmal discharges or

**Figure 30-2**

Intracranial herniation syndromes evoked by supratentorial masses. The tumor and its edema (arrows) have produced the following (curved arrows): cingulated gyrus herniation under the falx cerebri; diencephalic herniation across the midline compressing the ipsilateral ventricle and producing hydrocephalus in the contralateral ventricle; hippocampal gyrus herniation through the tentorial notch compressing the posterior cerebral artery and brainstem; and herniation of the cerebellar tonsils through the foramen magnum. (From Abeloff MD, Armitage JO, Niederhuber JE, et al: *Clinical oncology*, ed 3, Philadelphia, 2004, Churchill Livingstone. Adapted from Plum F, Posner JB: *The diagnosis of stupor and coma*, ed 2, Philadelphia, 1980, FA Davis.)

seizure activity.¹⁰⁶ Seizures may be the first presenting sign of a tumor. In patients presenting with seizures, detection of low-grade gliomas is becoming increasingly frequent with magnetic resonance imaging (MRI). See Fig. 30-3 for an MRI scan of a low-grade glioma presenting with a seizure. In the later stages of illness, seizure activity is present in 70% of patients.⁹³ A common feature of a tumor-related seizure is its repetitive nature, with seizures being very stereotypical in a given patient.¹³⁷

As the tumor grows, causing progressive destruction or dysfunction of tissue, locally referable signs may occur (hemiparesis, specific cranial nerve dysfunction, aphasia, visual symptoms, ataxia), which may help to localize the tumor site. Table 30-3 provides a list of signs associated with localized brain lesions.

SPECIFIC PRIMARY BRAIN TUMORS

A wide variety of specific types of primary brain tumor exist, with similarities in medical management and implications for physical therapy. Therefore, the specific tumors are first presented individually, followed by a discussion of diagnosis, medical management, and therapy implications for all primary brain tumors.

Box 30-3**SIGN AND SYMPTOMS OF INTRACRANIAL HYPERTENSION****Common**

- Headache
- Tinnitus
- Vomiting (with or without nausea)
- Visual obscurations, visual loss, photopsias
- Papilledema
- Diplopia
- Lethargy and increased sleep
- Psychomotor retardation
- Pain on eye movement

Less Common

- Hearing distortion or loss
- Vertigo
- Facial weakness
- Shoulder or arm pain
- Neck pain or rigidity
- Ataxia
- Paresthesias of extremities
- Anosmia
- Trigeminal neuralgia

Adapted from DeAngelis LM: Tumors of the central nervous system. In Goldman LM, Ausiello D, eds: *Cecil textbook of medicine*, ed 22, Philadelphia, 2004, Saunders.

Gliomas

Overview and Incidence. Gliomas are the most common of the primary brain tumors, accounting for 40% to 45% of all brain tumors, with men more frequently affected than women in a 3:2 ratio. Gliomas are divided into *benign or low-grade gliomas*, such as the low-grade astrocytomas, and *malignant gliomas*, such as anaplastic astrocytomas and GBMs. Other gliomas are oligodendrogiomas, ependymomas, and medulloblastomas. Terms such as *brainstem glioma* and *optic nerve glioma* refer to the location of these tumors, not the type of glial cell that gave rise to them. Only a tissue sample gives the specific diagnosis.

Low-grade astrocytomas account for 10% to 12% of primary brain tumors^{11,39} and are the most common type of intracranial tumor in children. Malignant astrocytomas (anaplastic astrocytoma and GBM) are much more common in adults than low-grade astrocytomas, making up 20% to 30% of primary brain tumors. Oligodendroglomas and ependymomas make up another 5% to 7%. Medulloblastomas, sometimes termed *embryonal tumors* or *PNETs*, make up about 2% of primary brain tumors. Brainstem gliomas often affect children between 5 and 10 years of age but can also be found in adults between 30 and 40 years of age. Most optic gliomas occur in children under the age of 10. Table 30-4 lists the types of primary brain tumors, the cell of origin, and the distribution of primary CNS tumors by histologic type. The age of peak incidence is 45 to 55 years in adults. In children, the tumor occurs mainly between the ages of 2 and 10 years.¹³⁹

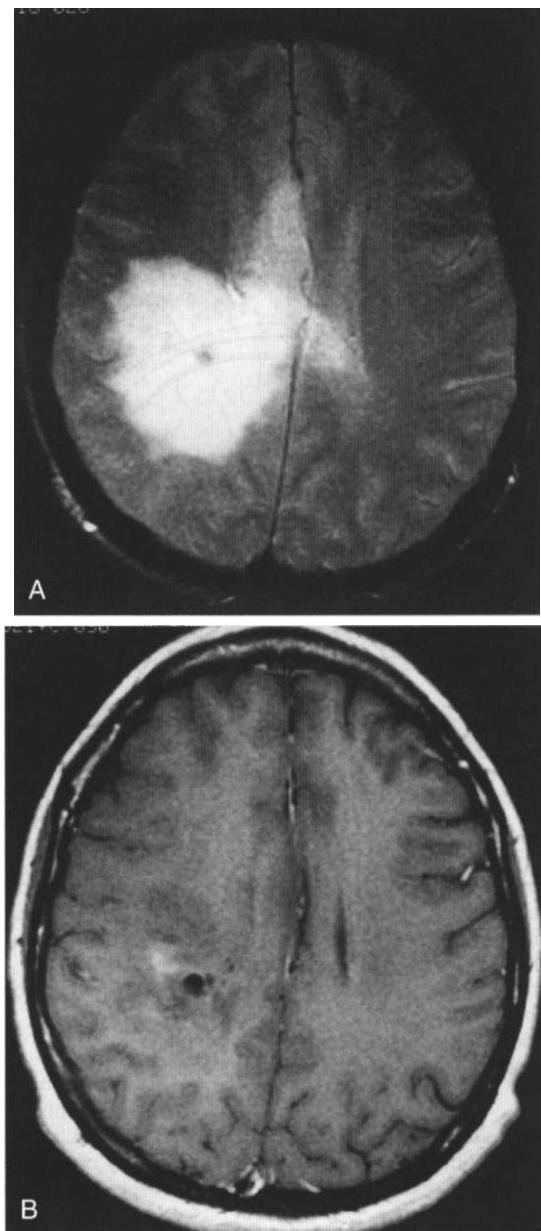


Figure 30-3

Magnetic resonance imaging (MRI) of a low-grade glioma. **A**, T2-weighted image. **B**, T1-weighted image, gadolinium contrast with minimum enhancement. The images are typical of this tumor, which is being detected with increasing frequency by MRI in seizure patients. Many are invisible on computed tomographic scans. (From Goldman LM, Ausiello D, eds: *Cecil textbook of medicine*, ed 22, Philadelphia, 2004, Saunders.)

Gliomas are tumors of the glial cells, the group of cells that support, insulate, and metabolically assist the neurons. Glial cells are derived from glioblasts. It is of interest to note that neurons, despite their prevalence in the CNS (100 billion in the adult brain, according to some authors), are rarely the cellular basis of neoplastic transformation.

Glial cells, which numerically exceed the number of neurons, are subdivided into astrocytes (star-shaped cells, sometimes termed *long arms*), which provide nutrition for

Table 30-3 Signs Associated with Localized Brain Lesions

Location of Lesion	Associated Signs
Prefrontal area	Loss of judgment, failure of memory, inappropriate behavior, apathy, poor attention span, easy distractibility, release phenomena
Frontal eye fields	Failure to sustain gaze to opposite side, saccadic eye movements, impersistence, seizures with forced deviation of the eyes to the opposite side
Precentral gyrus	Partial motor seizures, jacksonian seizures, generalized seizures, hemiparesis
Superficial parietal lobe	Partial sensory seizures; loss of cortical sensation including two-point discrimination, tactile localization, stereognosis, and graphism
Angular gyrus	Agraphia, acalculia, finger agnosia, allochiria (right-left confusion) (Gerstmann's syndrome)
Broca's area	Motor dysphasia
Superior temporal gyrus	Receptive dysphasia
Midbrain	Early hydrocephalus; loss of upward gaze; pupillary abnormalities; third nerve involvement—ptosis, external strabismus, diplopia; ipsilateral cerebellar signs; contralateral hemiparesis; parkinsonism; akinetic mutism
Cerebellar hemisphere	Ipsilateral cerebellar ataxia with hypotonia, dysmetria, intention tremor, nystagmus to side of lesion
Pons	Sixth nerve involvement—diplopia, internal strabismus; seventh nerve involvement—ipsilateral facial paralysis; contralateral hemiparesis; contralateral hemisensory loss; ipsilateral cerebellar ataxia; locked-in syndrome
Medial surface of frontal lobe	Apraxia of gait, urinary incontinence
Corpus callosum	Left-hand apraxia and agraphia, generalized tonic-clonic seizures
Thalamus	Contralateral thalamic pain, contralateral hemisensory loss
Temporal lobe	Partial complex seizures, contralateral homonymous upper quadrantanopsia
Paracentral lobule	Progressive spastic paraparesis, urgency of micturition, incontinence
Deep parietal lobe	Autopagnosia, anosognosia, contralateral homonymous lower quadrantanopsia
Third ventricle	Paroxysmal headache, hydrocephalus
Fourth ventricle	Hydrocephalus, progressive cerebellar ataxia, progressive spastic hemiparesis or quadriplegia
Cerebellopontine angle	Hearing loss, tinnitus, cerebellar ataxia, facial pain, facial weakness, dysphagia, dysarthria
Olfactory groove	Ipsilateral anosmia, ipsilateral optic atrophy, contralateral papilledema (Foster-Kennedy syndrome)
Optic chiasm	Incongruous bitemporal field defects, bitemporal hemianopsia, optic atrophy
Orbital surface frontal lobe	Partial complex seizures, paroxysmal atrial tachycardia
Optic nerve	Visual failure of one eye, optic atrophy
Uncus	Partial complex seizures with olfactory hallucinations (uncinate fits)
Basal ganglia	Contralateral choreoathetosis, contralateral dystonia
Internal capsule	Contralateral hemiplegia, hemisensory loss, homonymous hemianopsia
Pineal gland	Loss of upward gaze (Parinaud's syndrome), early hydrocephalus, lid retraction, pupillary abnormalities
Occipital lobe	Partial seizures with elementary visual phenomena, homonymous hemianopsia with macular sparing
Hypothalamus, pituitary	Precocious puberty (children), impotence, amenorrhea, galactorrhea, hypothyroidism, hypopituitarism, diabetes insipidus, cachexia, diencephalic autonomic seizures

From Gilroy J: Basic neurology, ed 2, Elmsford, NY, 1990, Pergamon Press, pp 228-229.

Table 30-4 Cell of Origin and Distribution of Primary Central Nervous System Tumors by Histologic Type

Tumor	Cell of Origin	Frequency (%)
Meningioma	Arachnoidal fibroblast	27.4
Glioblastoma	Astrocyte	23.0
Astrocytoma	Astrocyte	11.3
Ependymoma	Ependymal cell	2.2
Oligodendroglioma	Oligodendrocyte	4.0
Embryonal, including primary neuroectodermal tumor (PNET)/medulloblastoma	Unknown	1.9
Pituitary adenoma	Pituitary	6.6
Craniopharyngioma	Cells from Rathke's pouch	0.8
Nerve sheath	Schwann cell	7.5
Lymphoma	Lymphocyte	2.7
All others	Choroid epithelial cell	12.6
Choroid plexus papilloma or carcinoma	Endothelial cell	
Hemangioblastoma	Primitive germ cell	
Germ cell tumor	Pineal parenchymal cell	
Pineocytoma	Notochordal remnant	
Chordoma		

From Abeloff MD, Armitage JO, Niederhuber JE, et al: *Clinical oncology*, ed 3, Philadelphia, 2004, Churchill Livingstone. Data from Central Brain Tumor Registry of the United States, 2002-2003 statistical report, Chicago, 2002, The Registry; analysis of data collected from 1995 to 1999 ($n = 37,788$).

neurons; oligodendrocytes (glial cells with few processes, sometimes termed *short arms*), which produce the myelin sheath of the axonal projections of neurons; and ependymal cells, which line the ventricles and produce cerebral spinal fluid.⁵² Gliomas are subdivided into *astrocytomas*, *oligodendrogliomas*, and *ependymomas*, named for the cell of origin of the tumor. A combination glial cell tumor may occur as well, such as an oligoastrocytoma. *Medulloblastomas* are tumors of the vermis of the cerebellum and are classified by some authors as gliomas and by some as PNETs or embryonal tumors. Medulloblastoma is grouped with the PNETs because of common features, but some pathologists and clinicians prefer to distinguish these two; currently the debate continues.¹⁰¹

Astrocytomas are given histologic grades of I through IV to indicate the rate of cell division (mitosis), nuclear atypia, endothelial proliferation, and necrosis. Grade I and II astrocytomas are the slowest-growing, and grades III and IV astrocytomas are progressively faster growing with higher rates of mitosis.⁹⁶ Astrocytomas are capable at any time of converting to a higher grade.⁸⁹ Refer to Table 30-1. (See the section on Grading of Tumors in Chapter 9.)

Etiologic and Risk Factors. Relatively little is known about the cause of gliomas. They are characterized by a significant genetic heterogeneity, which makes the basic biology of glial neoplasms difficult to understand. A relationship may exist with chromosome abnormalities. Advances in the fields of molecular biology have allowed identification of mutated genes that increase the cell's susceptibility to the development of certain cancers.⁸⁹ These mutated genes that lead to the development of cancer are known as *oncogenes*.¹⁰⁰ (See Chapter 9.) Another type of chromosome abnormality leads to deletion of the cell's defense mechanism or its normal tumor-suppressing activity. This tumor suppressor gene, when altered, is unable to inhibit or limit in its normal ability to inhibit cellular proliferation.¹⁰⁰ The presence of an oncogene and/or the absence of a tumor suppressor gene may be only one step toward tumor formation. Tumorigenesis is thought to be a multistep process, with other contributing factors in addition to chromosome abnormalities.²¹

Certain specific chromosome abnormalities have been linked to specific brain tumor types.¹¹⁷ The oncogene *c-sis* has been identified with GBM. The oncogene *C-erbB* has been identified in 30% of malignant gliomas and is associated with the transforming growth factor receptor. Chromosome 17 abnormalities have been demonstrated to be present in all grades of astrocytomas.¹¹⁷ Oncogenes may have some bearing on other genetic disorders associated with brain tumors. Neurofibromatosis, or von Recklinghausen's disease (a familial condition involving the nervous system, muscles, bones, and skin and characterized by multiple soft tumors over the entire body associated with areas of pigmentation), is associated with spinal neuromas, acoustic neuromas, meningiomas, and gliomas. Tuberous sclerosis is associated with astrocytomas. Von Hippel-Lindau disease, a hereditary condition characterized by angiomas of the retina and cerebellum, is associated with hemangioblastomas.¹³⁹ The best-described tumor suppressor genes are *Rb* and *p53*, associated with retinoblastoma and Li-Fraumeni syn-

drome, a familial breast cancer associated with soft tissue sarcomas and other tumors.

No risk factors have been identified for the development of brain tumors, other than exposure to ionizing radiation.^{103,109,143} The effects of carcinogenic viruses or agents are unclear. Associations have been made between certain viruses and brain tumors, such as the Epstein-Barr virus and primary CNS lymphoma, but they are insufficient to constitute direct cause-and-effect relationships. Sustained exposure to certain pesticides, vinyl chloride, nitrosoureas, and polycyclic hydrocarbons has been implicated in astrocytic tumors, but epidemiologic surveys of workers in the farming, petrochemical, and rubber industries have produced conflicting results.¹²⁶ Certain industries such as synthetic rubber processing, vinyl chloride production, and petrochemical and oil refining do show increased risk.^{101,120} Infection, trauma, and immunosuppression are other suspected triggers. Radiation treatment for scalp ringworm in children is associated with an increased rate of developing brain tumors late in life.⁴⁵ A history of frequent exposure to full-mouth dental x-rays, particularly at an early age, also is associated with certain brain tumors.²¹ Most of the extensive research in the area of nonionizing radiation exposure such as that from cellular phones, household appliances, and high-voltage electrical lines does not support an association with cancer.²⁴ Although some of the studies may show an association with exposure to electromagnetic fields, either many other confounding variables, such as exposure to other carcinogens, may account for the association²¹ or a direct causal relationship cannot be proven.¹⁰¹ (See Chapter 4.) Increased risk of childhood tumors also has been associated with maternal diet, including consumption of cured meats containing nitrates during pregnancy.^{21,101}

Low-Grade Astrocytoma—Grades I and II

Incidence. Low-grade astrocytomas make up 10% to 12% of primary brain tumors in adults.

Pathogenesis. Low-grade astrocytomas include grades I and II. Grade I includes pilocytic astrocytoma (composed of fiber-shaped cells), sometimes termed juvenile astrocytoma, and is considered benign by some and malignant by others.^{73,133} Grade I astrocytoma grows slowly and often becomes cystic. It is composed of astrocytes with densely staining nuclei and scanty cytoplasm and is usually relatively acellular. The cells are uniform and closely resemble mature resting or reactive nonanaplastic astrocytes (well differentiated). Mitoses are absent or very rare.^{59,73} Although these are slow-growing tumors, they may become large.⁴ See Fig. 30-4 for a photograph of a well-differentiated astrocytoma. Grade II astrocytomas may be diffuse, infiltrative, and/or fibrillary, and have more anaplastic features. *Fibrillary* refers to the neuroglial fibrils. Other types are protoplasmic (cells that consist largely of protoplasm) and gemistocytic (large, densely packed cells with a globoid appearance).¹³³ There is moderate cell density. Fig. 30-5 shows the appearance of computed tomographic (CT) and MRI astrocytoma scans with and without the use of contrast. The contrast agent, such as gadolinium, distinguishes the edema from the actual tumor. The larger the extent of the edema after

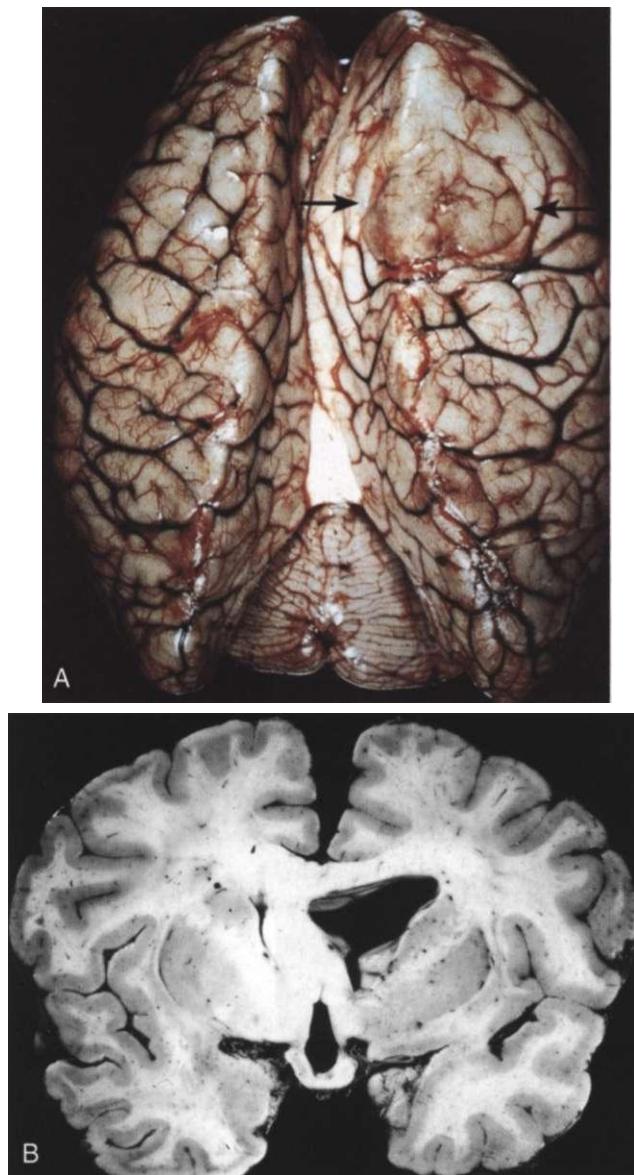


Figure 30-4

Well-differentiated astrocytoma. **A**, The right frontal tumor has expanded gyri, which led to flattening (arrows). **B**, Expanded white matter of the left cerebral hemisphere and thickened corpus callosum and fornices. (From Kumar V, Abbas AK, Fausto N, eds: *Robbins and Cotran pathologic basis of disease*, ed 7, Philadelphia, 2005, Saunders.)

administration of an intravenous contrast agent, the more malignant the lesion is likely to be.⁸³ Cerebral astrocytoma presents as a solid, grey mass with indistinct boundaries. Differentiation falls somewhere within a spectrum from well-differentiated (grade I) tumors to more anaplastic (grade II) tumors.⁴⁵ Astrocytomas in the cerebellum are often cystic and well circumscribed.

Clinical Manifestations. In adults, astrocytomas typically occur in the third and fourth decades of life and are usually located in the cerebrum, most commonly in the frontal lobes, but also may be found in the temporal lobes, parietal lobes, basal ganglia, and occipital lobes. Astrocytomas usually appear in the cerebellum in children.

In adults typical initial symptoms are unilateral or focal headaches that become generalized as ICP increases. Frontal lobe tumors may produce personality disorders with changes in behavior and emotional state. Parietal and temporal lobe tumors may cause seizures on one side of the body. Occipital lobe tumors produce visual changes. Involvement of the optic apparatus or optic pathways also may produce visual changes. Refer to Table 30-3 for more details of signs associated with tumor location. In time, astrocytomas, like other gliomas, tend to become more malignant.

In children, cerebellar astrocytomas lead to symptoms of unilateral cerebellar ataxia involving the limbs and trunk followed by signs of increased ICP.

Prognosis. Individuals with low-grade astrocytomas treated optimally have 5- to 10-year survival rates of 100% for completely excised lesions, and a 60% 5-year survival and 35% 10-year survival for partially excised lesions with radiation therapy. For many there will be a period of relative clinical stability that averages 5 to 7 years.^{98,133} Untreated low-grade astrocytomas have a 5-year survival rate of 32% and a 10-year survival rate of 11%.¹²⁶ Despite the benign categorization, it must be understood that astrocytomas are nearly always infiltrative lesions and generally progressive.

High-Grade Astrocytoma—Grades III and IV

Incidence. High-grade malignant astrocytomas, grades III and IV, are much more common in adults than low-grade astrocytomas. Grade III is often termed anaplastic astrocytoma and grade IV is termed glioblastoma multiforme (GBM), although both are highly anaplastic. Grade III and IV astrocytomas make up 20% to 30% of primary brain tumors.

Pathogenesis. Anaplastic astrocytomas, grades III and IV, are diffusely infiltrative tumors that invade into the cerebral parenchyma. They typically involve the white matter of the cerebral hemispheres but may occur primarily in grey matter as well as in other areas of the CNS.¹³⁰ They often contain a mix of cells and cell grades but are graded by the highest-grade cell seen in the tumor. GBM is a particularly rapidly growing, aggressive, infiltrative tumor that tends to invade both cerebral hemispheres via the corpus callosum. See Fig. 30-6 for a GBM MRI and intraoperative pictures. A GBM is a pinkish grey or multicolored, well-demarcated mass with scattered areas of grossly visible hemorrhage. The blood vessels show endothelial proliferation: it is a highly vascular tumor, with vascular endothelial growth factor (VEGF) implicated, suggesting that the malignant progression from low-grade astrocytoma to GBM includes an "angiogenic switch."¹³⁰ There may be areas of cystic degeneration and a central area of creamy necrosis. The histologic distinction of an anaplastic astrocytoma from a glioblastoma is based largely on the absence or presence of tumor necrosis¹³⁹ and microvascular proliferation.¹³⁰ Microscopically, the tumor is pleomorphic (having various distinct forms) and hypercellular, with the cells showing hyperchromatic nuclei. There are many mitoses, giant cells, and young glial forms.

Of interest is the advance in molecular genetics in astrocytoma. Two moderately common genetic

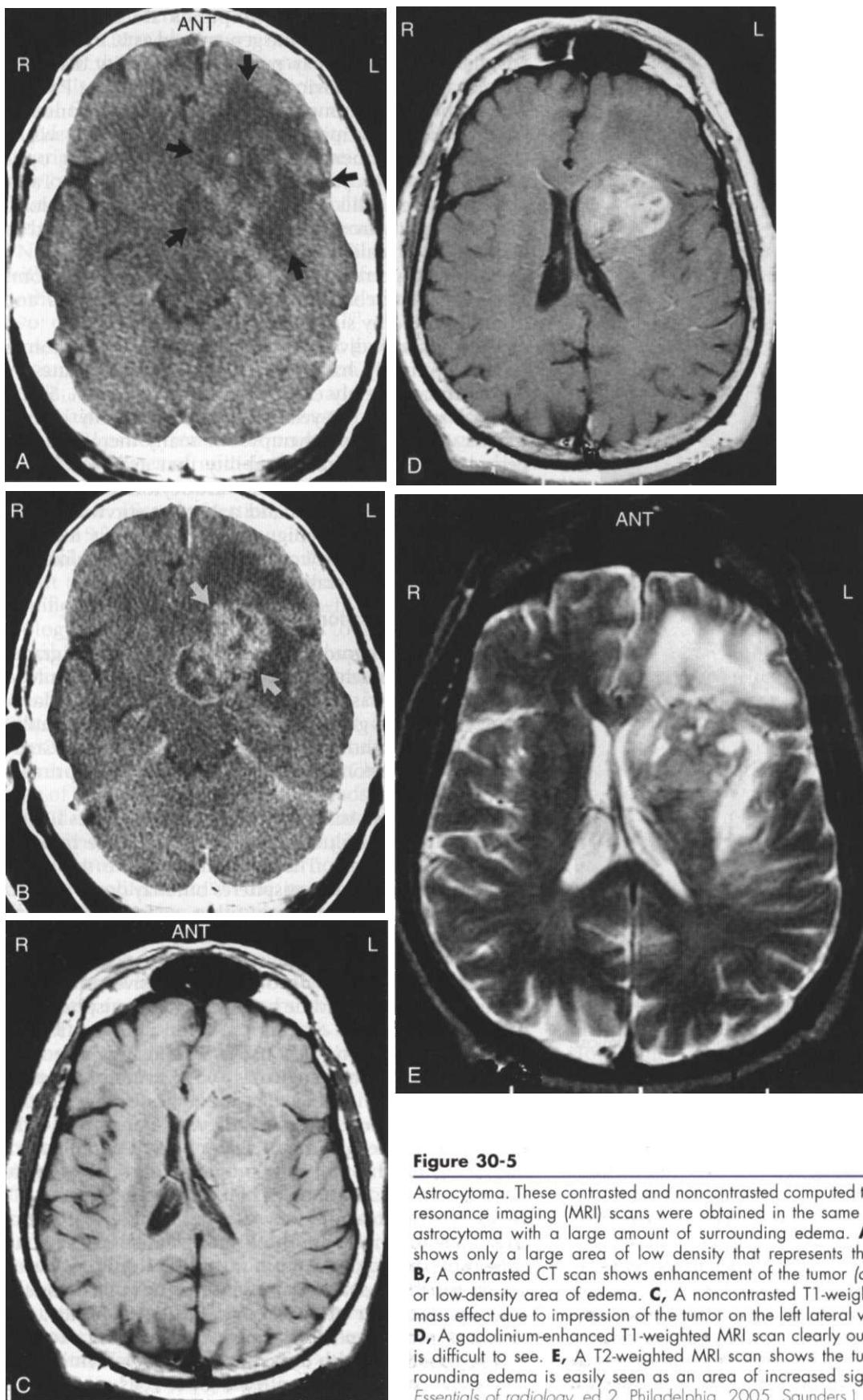


Figure 30-5

Astrocytoma. These contrasted and noncontrasted computed tomographic (CT) and magnetic resonance imaging (MRI) scans were obtained in the same patient and demonstrate a left astrocytoma with a large amount of surrounding edema. **A**, The noncontrasted CT scan shows only a large area of low density that represents the tumor and edema (arrows). **B**, A contrasted CT scan shows enhancement of the tumor (arrows) surrounded by the dark or low-density area of edema. **C**, A noncontrasted T1-weighted MRI scan clearly shows a mass effect due to impression of the tumor on the left lateral ventricle and some midline shift. **D**, A gadolinium-enhanced T1-weighted MRI scan clearly outlines the tumor, but the edema is difficult to see. **E**, A T2-weighted MRI scan shows the tumor rather poorly, but the surrounding edema is easily seen as an area of increased signal (white). (From Mettler FA Jr: Essentials of radiology, ed 2, Philadelphia, 2005, Saunders.)

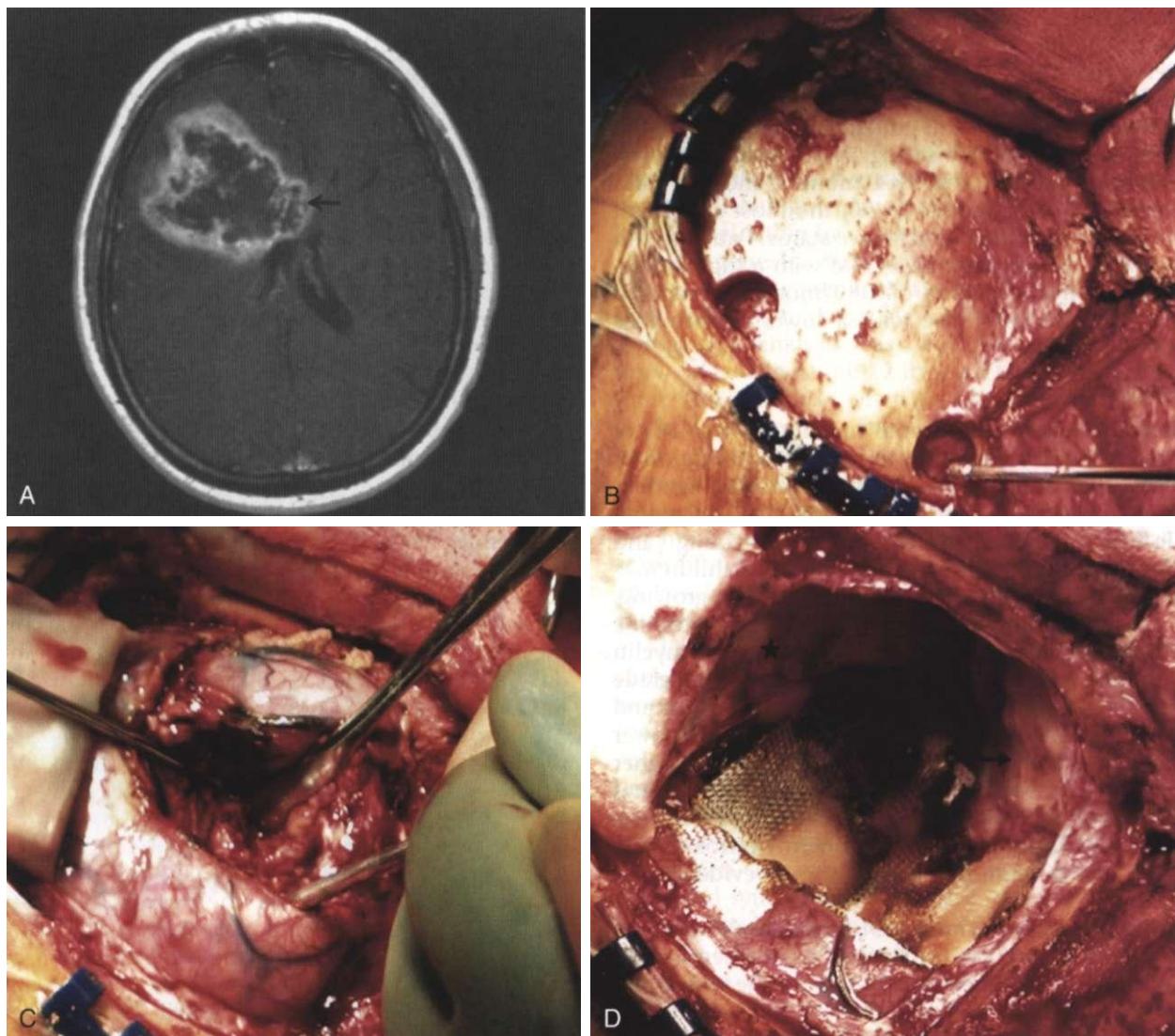


Figure 30-6

Magnetic resonance imaging (MRI) and intraoperative pictures of a patient with a right frontal glioblastoma multiforme. **A**, An axial T1-weighted MRI scan. The enhancing lesion demonstrates central necrosis and is causing mass effect. Infiltration along the corpus callosum is also shown (arrow). **B**, A frontal craniotomy is being performed. Burr holes have been placed and will be connected for bony removal. **C**, The brain has been incised and the tumor is being removed using a combination of suction and blunt dissection. **D**, The tumor and frontal lobe have been resected. The cut edge of the brain is seen at the lower left. The resection cavity has been lined with carmustine polymer (Gliadel) wafers and covered with a layer of Surgicel for hemostasis. (From Townsend CM Jr: *Sabiston textbook of surgery*, ed 17, Philadelphia, 2004, Saunders.)

alterations are found to occur: inactivation of the TP53 tumor suppressor gene and loss of chromosome 22q.⁷¹ Further inactivation of tumor suppressor genes on chromosomes 9p, 13q, and 19q leads to anaplastic astrocytomas.⁷¹ Many further mutations occur, and an understanding of the complexity of these mutations is beginning to suggest methods to intervene therapeutically. Also, understanding tumor stem cells that are responsible for populating and repopulating the tumors may also have therapeutic implications, as therapies that do not ablate the tumor stem cells will be ineffective in eradicating the tumor.^{41,74,75,130}

Clinical Manifestations. Anaplastic astrocytoma and GBM most frequently arise in the frontal and temporal

lobes, with the cerebellum, brainstem, and spinal cord being rare sites for adults. They most frequently occur in the fifth and sixth decades of life. Signs and symptoms progress rapidly, with grade IV GBM being particularly aggressive. The presentation may be of unilateral headache that is followed by generalized headache, indicating an increase in ICP. The development of seizures is not unusual. Lethargy, memory loss, motor weakness, and personality changes may occur.

Prognosis. All malignant astrocytomas will eventually recur. With optimal treatment (excision, radiation therapy) clients with anaplastic astrocytoma (grade III) have a 70% 1-year survival rate, a 40% 2-year survival rate, and a 10% to 20% 5-year survival rate. GBM (grade

IV) has a grimmer prognosis with a 50% 1-year survival rate, a less than 15% 2-year survival rate, and rare long-term survival.¹²⁶ The relationship between genetic alterations and prognosis is complex and may be age dependent.^{54,130} For patients under 50, the most significant prognostic factor is histology, with median survival for anaplastic astrocytoma 49.4 months and for GBM 13.7 months. For patients over 50, the most significant prognostic factor is the performance status. Patients with an anaplastic astrocytoma or a GBM with a high performance status live a median of 10.3 months, compared with 5.3 months for those with a lower performance status.^{88,101}

Oligodendrogioma

Incidence. Oligodendrogliomas make up 2% to 3% of gliomas. It is not uncommon to have a combination of cell types, such as astrocytes, creating a mixed oligodendrogloma/astrocytoma, or oligoastrocytoma. Oligodendrogliomas occur most frequently in young and middle-aged adults but can also be found in children.

Pathogenesis. Oligodendrogloma is a slow-growing, solid, calcified tumor arising from oligodendrocytes, the myelin-producing cells of the CNS. It stains for myelin basic protein. It can be either low grade (II) or high grade (III). It is a grey-pink to red cystic area in the brain and has a honeycomb appearance at low microscopic power due to the presence of a fibrovascular stroma. On higher power the cells have a uniform appearance, with a central nucleus surrounded by a clear cytoplasm, or a fried egg appearance. Mitotic figures are infrequent. Approximately 70% of these tumors show some evidence of calcification.

Clinical Manifestations. Oligodendrogliomas are located predominantly in the cerebral hemispheres, often in the frontal lobes. They expand toward the cortex and may spread through it and eventually attach to the dura.⁴⁵ A history of partial or generalized seizures, usually of long duration and sometimes with chronic headache, is the typical presentation pattern of oligodendrogliomas. They tend to bleed spontaneously and may present with a strokelike syndrome.¹¹⁷ The hallmark of this tumor radiologically is calcification, which can be identified in the vast majority of people by CT. It is usually nonenhancing with gadolinium, meaning that the surrounding edema is limited.¹³³ If an oligodendrogloma contains astrocytoma cells, it is graded at the highest level of anaplasia present.

Prognosis. With optimal treatment, 5- and 10-year survival rates are 80% to 100% and 45% to 55%, respectively. The median overall survival is 17 years.⁹² Although after treatment a long interval of quiescence may occur, oligodendrogliomas eventually recur, often as a more aggressive tumor with progressing symptoms.¹²⁶

Ependymoma

Incidence. Ependymomas have a low incidence, comprising only about 2% of gliomas. Ependymoma is much more prevalent in children than adults and is the third most frequent posterior fossa neoplasm of children.

Pathogenesis. An ependymoma is a neoplasm derived from the ependymal cell lining of the ventricular system

and the central canal of the spinal cord. It is graded I to IV, depending on the degree of anaplasia. It is usually reddish, lobulated, and well circumscribed, resembling a cauliflower in shape. Pseudorosette formation, in which the cells are arranged about a clear space or a blood vessel, may occur, and blepharoplasts (small round or rod-shaped intracytoplasmic bodies) may be seen.

Clinical Manifestations. Ependymoma is more common in the fourth ventricle and is likely to be detected early because of the signs and symptoms of increased ICP in the posterior fossa (e.g., headache, nausea, vomiting, and papilledema). However, supratentorial ependymomas often grow large before detection. Fig. 30-7 depicts an ependymoma of the fourth ventricle.

Prognosis. The prognosis for ependymomas is improving: 5-year survival rates exceed 80% and 10-year survival rates are 40% to 60%.¹²⁶

Medulloblastoma

Incidence. Medulloblastomas make up 3% to 5% of primary brain tumors. The age of peak incidence is 45 to 55 years in adults. In children, the tumor occurs mainly between the age of 2 and 10 years. Medulloblastoma is the most common malignant primary CNS tumor in children and the second most common posterior fossa tumor in children.

Pathogenesis. Medulloblastoma is a rapidly growing malignant tumor. The cell of origin is unknown, but it is presumed to arise from the embryonal external granular layer of the cerebellum. It is considered to belong to a group of tumors known as *primitive neuroectodermal tumors* (PNETs). It characteristically metastasizes to the surface of the remaining CNS via the subarachnoid spaces. Grossly it is red and soft and is composed of many closely packed cells, with oval nuclei and many mitoses. Pseudorosette formations are common. It is highly vascular, containing numerous small blood vessels.¹²⁶

Clinical Manifestations. Medulloblastoma often develops in the cerebellar vermis and is very aggressive in younger children. Because of its proximity to the fourth ventricle, early development of hydrocephalus is common, along with other signs of cerebellar dysfunction, such as ataxia. Medulloblastomas tend to metastasize through CSF pathways, more predominantly into the spine but also into the supratentorial compartment.

Prognosis. Early in the century medulloblastomas were uniformly fatal tumors. Improvement in therapeutic strategies during the past 30 years has dramatically improved the prognosis.¹²⁴ Favorable prognostic factors include age greater than 2 years, undisseminated local disease, and greater than 75% tumor resection. In these clients, the 5-year disease-free survival rate exceeds 60% to 70% in most studies.^{51,126} In poorer-risk cases, the 5-year disease-free survival rate is about 45%.¹²⁶

Tumors Arising from Supporting Structures in the Brain

Meningioma

Overview. Meningiomas are slow-growing, usually benign lesions that occur most commonly along the dural folds and cerebral convexities, although they may

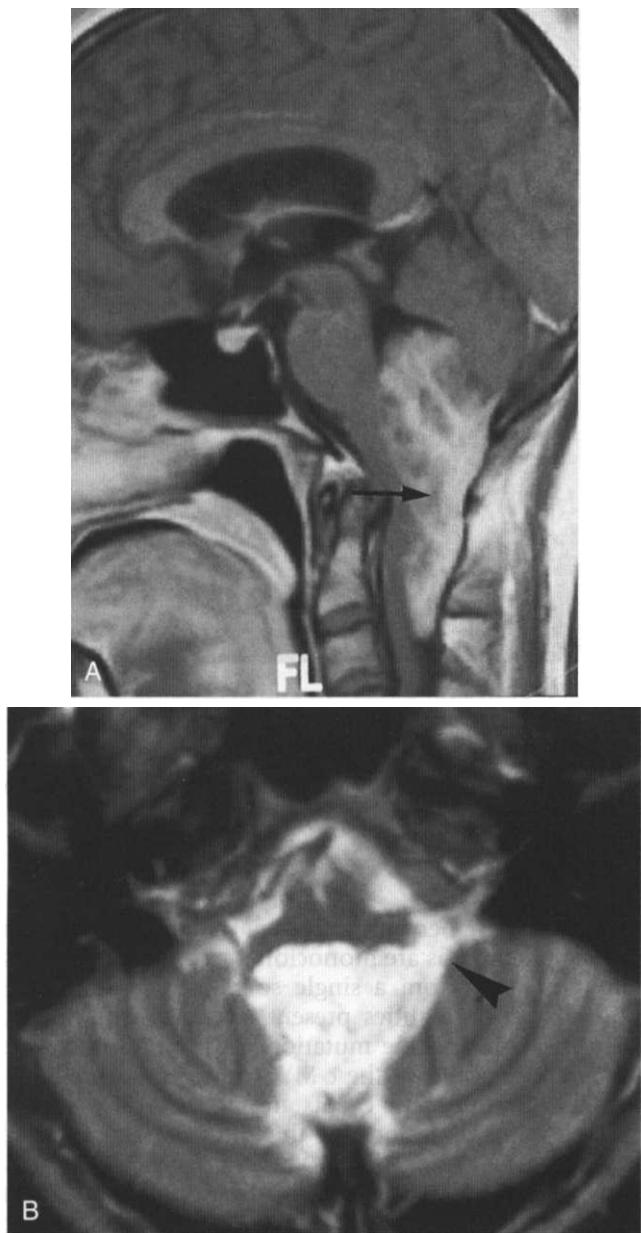


Figure 30-7

Ependymoma of the fourth ventricle. Sagittal gadolinium-enhanced T1-weighted (**A**) and axial T2-weighted (**B**) magnetic resonance images. A heterogeneously enhanced mass (arrow) fills the lower half of the fourth ventricle and extends through the foramina of Luschka (arrowhead) and Magendie to lie posterior to the medulla oblongata and upper cervical spinal cord, which are compressed from behind. There is obstructive hydrocephalus. [From Grainger and Allison's diagnostic radiology: a textbook of medical imaging, ed 4, Philadelphia, 2001, Churchill Livingstone.]

occur in the spinal cord as well. The WHO classification recognizes three groups, grade I or benign, grade II or atypical, and grade III or malignant (anaplastic).¹³⁹

Incidence. Meningiomas represent up to 27% of all intracranial neoplasms and are the second most common primary intracranial tumor in adults and the most common of benign brain neoplasms. Ninety percent are considered benign and about 5% are grade III. Most are

single lesions, but multiple meningiomas also occur. They are most common between the ages of 40 and 70, and are two to three times more prevalent in females than in males. They are increased in neurofibromatosis, in women who use postmenopausal hormone replacement therapy, and in patients who have had breast cancer.³¹ Prognostication and treatment rely on differentiation between a benign meningioma and a metastatic brain lesion originating from a breast cancer.¹³⁹

Pathogenesis. Meningiomas originate in the arachnoid layer of the meninges and are believed to be derived from the cells and vascular elements of the meninges. Cytogenetic analysis has demonstrated multiple deletions on chromosome 22 in most people with meningioma. They are most often located between or over the cerebral hemispheres, at the skull base, or in the posterior fossa. Meningiomas are typically well-circumscribed globular masses. They may infiltrate the dura, the dural sinuses, or bone, but generally do not invade the underlying brain parenchyma. See Figs. 30-8 and 30-9 for CT scans of meningiomas. Most meningiomas grow as well-encapsulated tumors, but others develop in relatively thin sheets along the dura.

Meningiomas, because of their proximity to or invasion of the bone, are known to provoke a local osteoblastic response termed *hyperostosis*. This may cause a profuse local thickening of the skull. Fig. 30-10 shows diffuse reactive hyperostosis as well as facial distortion from the growing meningioma.

Clinical Manifestations. Meningiomas are more common in the later years of life and are more frequent in women. Because they are slow growing, abnormal signs and symptoms may evolve over a period of many years. When located in silent brain areas, some meningiomas can become very large before causing clinical symptoms. Also, they can be discovered incidentally as masses that show little or no growth over time. Neurologic abnormalities depend on the location of the tumor; seizures are a common finding with skull-based lesions.

Prognosis. Meningiomas, when completely resected (surgical accessibility determines excision capabilities), have excellent prospects of long-term cure. Patients with completely excised lesions experience a 10-year survival rate of 80% to 90%. Partially resected meningiomas have a 50% to 70% 10-year progression-free survival. Malignant meningiomas, about 1% to 10% of meningiomas, have a shorter disease-free interval¹²⁶ and a tendency to recur.

Pituitary Adenoma

Overview. Pituitary adenomas are benign tumors derived from cells of the anterior portion of the pituitary gland. The pituitary gland, located at the base of the brain, sits in the sella turcica, the saddle-shaped transverse depression on the superior surface of the body of the sphenoid bone. Fig. 30-11 gives the anatomic relations of the pituitary gland, optic chiasm, and surrounding parasellar structures. Although pituitary adenomas are the most common of the pituitary tumors, infrequently other types of pituitary tumors may occur in the location of the pituitary gland and may be primary or metastatic. See also the section Pituitary Gland in Chapter 11.

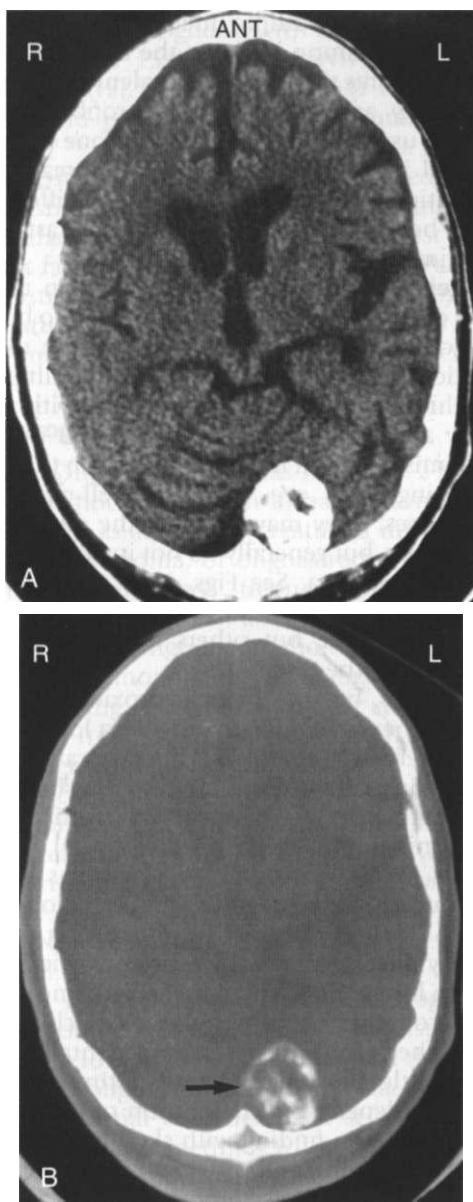


Figure 30-8

Meningioma. **A**, A noncontrasted computed tomographic scan shows a very dense, peripherally based lesion in the left cerebellar area. **B**, A bone window image obtained at the same level shows that the density is due to calcification within this lesion. (From Mettler FA Jr: Essentials of radiology, ed 2, Philadelphia, 2005, Saunders.)

Incidence. Pituitary adenomas are common lesions, accounting for about 5% to 15% of all intracranial tumors, making them the third most common primary brain tumor in adults after meningiomas and the gliomas. They are usually found in middle-aged or older people. Women are more affected than men, particularly during childbearing years. Almost 70% are functional, or secreting, tumors, and these tend to occur in younger adults. Nonfunctioning tumors (nonsecreting), also called nonfunctioning adenomas or NFAs, tend to occur in older adults.

Pathogenesis. With recent advances in molecular techniques, genetic abnormalities associated with pitu-



Figure 30-9

Computed tomographic scan with contrast of a meningioma in a patient who presented with mild cognitive deficits, illustrative of the size a slow-growing tumor can attain in the brain. The tumor was completely resected. (From Goldman LM, Ausiello D, eds: Cecil textbook of medicine, ed 22, Philadelphia, 2004, Saunders.)

itary tumors are becoming clearer. The great majority of pituitary adenomas are monoclonal in origin, suggesting that most arise from a single somatic cell. Additional molecular abnormalities present in aggressive pituitary adenomas and include mutations of the RAS oncogene and overexpression of the c-MYC oncogene, which suggests that these genetic events are linked to disease progression.⁶⁷ Small lesions of the pituitary gland called *microadenomas* are less than 10 mm in diameter, and may be asymptomatic. Most grow in the front two thirds of the pituitary gland. Larger tumors, or *macroadenomas*, may compress the adjacent normal pituitary gland. Fig. 30-12 shows a pituitary tumor extension down into the sphenoid sinus. Extension of the tumor above the sella turcica compresses the optic chiasm.

Clinical Manifestations. In the majority of pituitary tumors, the release of excess pituitary hormones or pituitary insufficiency results in dramatic and unique clinical syndromes. Galactorrhea and amenorrhea, gigantism and acromegaly, and the symptoms of Cushing's disease (hypertension, facial and truncal obesity, osteoporosis, muscle weakness, menstrual abnormalities, and female hirsutism) are among the hormonal symptoms. Pituitary insufficiency, or hypopituitarism, can lead to symptoms such as fatigue, weakness, and hypogonadism. A second pattern of presentation consists of regression of secondary sexual characteristics and hypothyroidism. The third pattern of presentation is one of neurologic findings, including headache, bitemporal visual loss, and ocular palsy. Fig. 30-13 localizes masses such as a pituitary tumor by the pattern of visual field loss. Fig. 30-14 illus-



Figure 30-10

A, Upper eyelid edema, mild proptosis, and downward displacement of the eye due to en plaque sphenoid wing meningioma. **B**, Computed tomographic scan of the same patient demonstrating lytic bone lesions and diffuse reactive hyperostosis due to bone infiltration by meningioma. (From Abeloff MD, Armitage JO, Niederhuber JE, et al: *Clinical oncology*, ed 3, Philadelphia, 2004, Churchill Livingstone.)

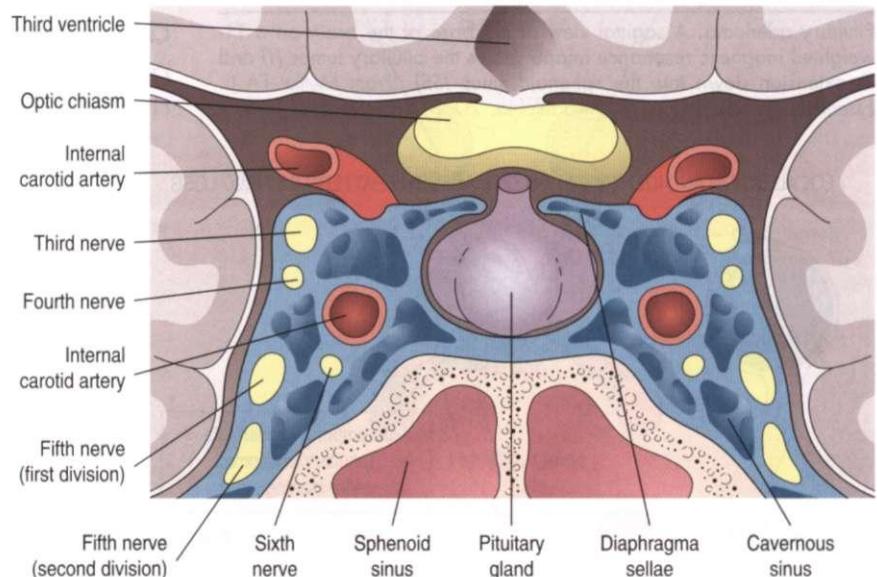


Figure 30-11

Anatomic relations of pituitary gland and surrounding parasellar structures. (From Yanoff M: *Ophthalmology*, ed 2, St. Louis, 2004, Mosby; adapted from Warwick R. The orbital vessels. In Warwick R, ed: *Eugene Wolff's anatomy of the eye and orbit*, ed 7, Philadelphia, 1976, WB Saunders, pp 406-417.)

trates the local effects of an expanding pituitary tumor causing visual field defects.

MEDICAL MANAGEMENT

Nonfunctioning tumors usually require no treatment. Functional tumors may respond to hormonal therapy. Malignant tumor treatment is by surgery, transsphenoidal whenever possible, and conventional and stereotactic radiotherapy.⁶³

PROGNOSIS. Tumors of the pituitary have become very treatable, with the majority of people enjoying long-term

survival or cure. Because visual compromise is a complicating feature of many pituitary tumors, serial recording of visual field deficits can document disease progression in addition to responses to treatment.

Neurinoma, Neuroma

Overview and Incidence. Neurinomas are slow-growing, benign tumors originating from Schwann cells. In the brain they most commonly develop on the vestibular component of the eighth cranial nerve and are also called *acoustic neurinomas*, *acoustic neuromas*, or *schwannomas*. Acoustic neurinomas account for 3% to 10% of all brain

tumors. They occur mainly in the fourth to sixth decades of life, with a 2:1 female to male occurrence ratio. About 5% occur in the context of neurofibromatosis. Bilateral lesions are most likely to occur in neurofibromatosis.

Pathogenesis. Acoustic neurinomas typically originate in the internal auditory canal in the transition zone of the oligodendroglial cells and peripheral nervous

system Schwann cells. Neurinomas also may be found attached to other cranial nerves, such as the trigeminal nerve. The tumor grows into the cerebellopontine angle, eventually compressing the facial nerve, and encroaches on the brainstem. Some lesions may remain relatively quiescent for long periods of time, but the majority are slow-growing, progressive lesions. The tumor is thickly encapsulated, often highly vascular, and microscopically consists of spindle-shaped cells with rod-shaped nuclei often lying in parallel rows.

Clinical Manifestations. Acoustic neurinomas typically present with progressive unilateral sensorineural hearing loss. Other symptoms include tinnitus, vertigo, and unsteadiness. Facial numbness, difficulty swallowing, impaired eye movement, and taste disturbances may occur. Weakness of the facial muscles is generally a late feature. Deformity and obstruction of the fourth ventricle leads to hydrocephalus with headache, vomiting, and other symptoms of increased ICP. See Fig. 30-15 for a surgical view of a large acoustic neuroma.

Prognosis. In the majority of cases cure is achieved with surgical resection. Stereotactic radiotherapy may be possible, reducing surgical side effects.⁵ As acoustic neurinomas are slow growing, and surgery often accelerates hearing loss, the decision to delay surgery until necessary maybe made. However, because the likelihood of hearing retention is greatest when the tumor is small, surgery may be done as soon as possible.

Choroid Plexus Papilloma

Choroid plexus papilloma is a low-grade neoplasm of the choroid plexus, the vascular coat along the ventricles car-



Figure 30-12

Pituitary adenoma. A sagittal view of the base of the brain on a T1-weighted magnetic resonance image shows the pituitary tumor (*T*) and its extension down into the sphenoid sinus (*SS*). [From Mettler FA Jr: Essentials of radiology, ed 2, Philadelphia, 2005, Saunders.]

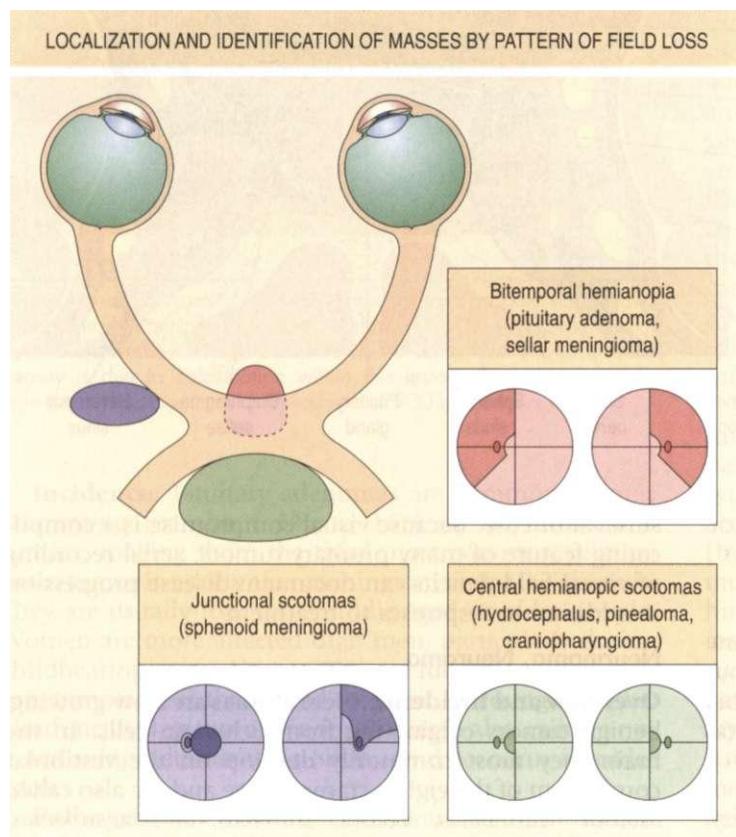


Figure 30-13

Localization and probable identification of masses by pattern of field loss. Junctional scotomas occur with compression of the anterior angle of the chiasm (sphenoid meningioma). Bitemporal hemianopia results from compression of the body of the chiasm from below (e.g., because of pituitary adenoma, sellar meningioma). Compression of the posterior chiasm and its decussating nasal fibers may cause central bitemporal hemianopic scotomas (e.g., because of hydrocephalus, pinealoma, craniopharyngioma). [From Yanoff M, Duker JS, Augsburger JJ, et al, eds: Ophthalmology, ed 2, St Louis, 2004, Mosby.]

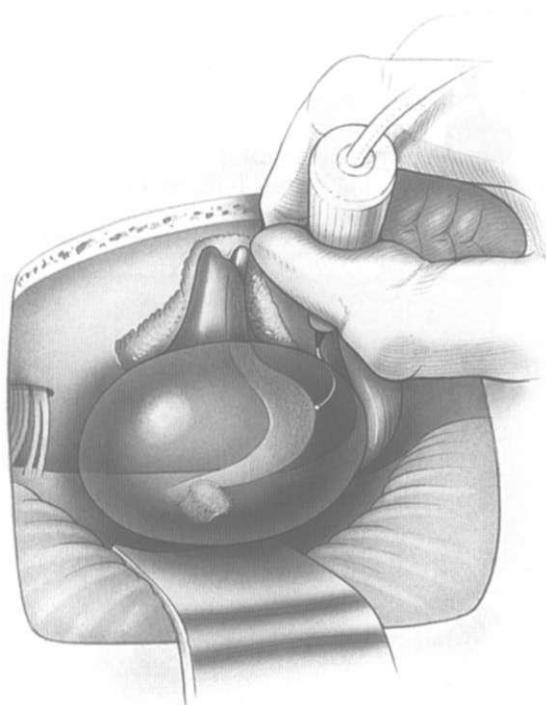


Figure 30-15

Surgical view of a large acoustic neuroma (retrosigmoid approach) showing use of a flexible-tipped probe to locate the facial nerve on the medial surface of the tumor out of direct view. Early identification of the facial nerve "around the corner" on the ventral surface of the tumor helps speed the procedure by allowing rapid removal of the remaining capsule. Tumor is drawn as if transparent to show details of anatomy on the hidden surface. [From Yingling CD, Gardi JG: *Otolaryngol Clin North Am* 24:413, 1992.]

embryonal basis, and although some are very radiosensitive, others are aggressive, highly malignant, and generally incurable. Pineal parenchymal tumors have a tendency to craniospinal dissemination.

Clinical Manifestations and Prognosis. Pineal region tumors typically result in obstructive hydrocephalus because of the proximity of the pineal gland to the ventricular system. Symptoms include headache, nausea, vomiting, and ocular abnormalities. Management is by shunting the hydrocephalus, if present; radiation therapy; and/or surgical excision. Individuals with responsive tumors have a 5-year survival rate of 70%.¹²⁶ Those with nonresponsive tumors have a 1-year survival rate of only 33%.

Craniopharyngiomas

Overview. Craniopharyngiomas are histologically benign congenital tumors and occur most commonly in the suprasellar region in the pituitary stalk adjacent to the optic chiasm.

Incidence. Craniopharyngiomas are rare and account for 1% to 3% of all intracranial tumors.^{13,22} They are the third most common intracranial tumor in children, accounting for 10% of all intracranial tumors in this age group.

Pathogenesis. Craniopharyngiomas presumably arise from embryonic remnants of Rathke's pouch and grow

slowly from birth. They vary in size from small, solid, well-circumscribed masses to huge multilocular cysts that invade the sella turcica, reaching a large size before they are diagnosed. They often involve the pituitary gland, optic nerve, and third ventricle. Three basic histologic subtypes have been described: mucoid epithelial cysts, squamous epitheliomas, and adamantinomas.¹³⁴

Clinical Manifestations. Based on the location, craniopharyngiomas can compromise a number of important intracranial structures and produce multiple signs and symptoms. The most common presentations are pituitary hypofunction, visual difficulties, and severe headaches. Other signs are increased ICP, neuroendocrine disorders, hypothalamus involvement, cranial nerve palsies, hydrocephalus, and progressive dementia. Sexual dysfunction is the most common endocrine problem in adults, with 90% of men complaining of erectile dysfunction and most women having amenorrhea. Depression may occur, presumably because of extension of the tumor into the frontal lobes, striocapsulothalamic areas, or limbic system.¹³⁴

Prognosis. Optimal treatment is controversial, but radiation and/or surgical resection are used. Intracavitary radiation is used in select tumors. With complete resections or resections followed by radiation therapy, 10-year survival rates of 78% have been reported. The tumors do have a tendency to recur, and even though histologically they are benign, they may be better thought of as low-grade malignancies.

Epidermoid and Dermoid Tumors (Cysts)

Incidence. Epidermoid and dermoid tumors are rare benign tumors that arise from imperfect embryogenesis of the CNS and account for 2% of intracranial tumors. The most common cysts in the brain are epidermoid, arachnoid, colloid, and dermoid.

Pathogenesis. Cysts are fluid-filled spheres composed of desquamated epidermal cellular debris, keratin, and cholesterol. During embryologic development, groups of cells are diverted from the areas of the face or skin to the neural tube. They grow in basal regions of the brain and tend to enlarge along CSF pathways. Most cysts are benign and grow slowly, and may not cause symptoms for many years.

The epidermoid cyst often contains remnants of skin cells or tiny pieces of cartilage and occurs near the cerebellopontine angle or the pituitary gland. The arachnoid cyst is found in the subarachnoid space, often in the Sylvian fissure, the cerebellopontine angle, the cisterna magna, or the suprasellar region of the brain, and may cause increased ICP. The colloid cyst is most frequently found in the third ventricle and may block CSF, causing headache, seizures and increased ICP. The dermoid tumor has epidermal cellular debris, but it is mixed with additional dermal elements such as hair, hair follicles, sweat glands, and sebaceous glands. Dermoid cysts are usually located in the posterior fossa or the adjacent meninges, or in the lower spine.

Prognosis. In most cases complete surgical excision of the tumor capsule and contents is curative.¹²⁶ If the tumor is unable to be totally removed it may recur, although growth is slow.²

Hemangioblastoma

Incidence. Hemangiomas make up 2% of all intracranial tumors, are the most common adult intraaxial tumor of the posterior fossa, and occur more frequently in males. They most commonly occur in people about 40 years old.

Pathogenesis. Hemangiomas are benign slow-growing tumors typically arising in the posterior fossa, primarily in the cerebellar vermis or pons, as solitary lesions with clearly indicated borders. The origin is thought to be cells in the blood vessel lining. Hemangioblastomas are a vascular conglomerate of endothelial cells, pericytes (peculiar elongated cells with the power of contraction, found wrapped about precapillary arterioles), and stromal cells. These highly vascular tumors attached to the wall of a surrounding cyst are often associated with von Hippel-Lindau syndrome.

Clinical Manifestation and Prognosis. Blockage of the CSF results in ICP and hydrocephalus. Common symptoms include headache, nausea and vomiting, balance and gait disturbances, and poor coordination. Complete surgical excision for tumors arising in the cerebellum is curative.

Chordoma

Chordomas rarely arise in the brain and represent less than 1% of all intracranial neoplasms. They are much more typical in the axial skeleton, preferring the clivus (in the posterior cranial fossa), sacrum, and nonsacral spine. They are tumors of bone, presumed to arise from the embryonal notochord remnants. They are considered histologically benign but have a locally destructive nature, progressive course, and metastatic behavior.¹²⁶ Cranial chordomas typically involve the skull base with a destructive process that invades rostrally into the optic chiasm, into the brainstem, or ventrally into the sinuses. Because of surgical inaccessibility, curative resections are difficult, if not impossible. Median survival ranges from 4.2 to 5.2 years, with recurrences likely.¹²⁶

Primary Central Nervous System Lymphoma

Overview and Incidence. Primary CNS lymphoma (PCNSL) is a non-Hodgkin's lymphoma and occurs in the absence of systemic lymphoma. It is also called an extranodal lymphoma. This tumor was formerly quite rare, but from 1973 to 1985 tripled in frequency in immunocompetent patients and also increased in the immunosuppressed population—that is, clients with acquired immunodeficiency syndrome (AIDS) and collagen vascular disorders, organ transplant recipients, and the congenitally immunodeficient.^{4,139} There was a decrease in incidence in young men and patients with AIDS from 1995 to 1998, explained by the introduction of highly active antiretroviral therapy for patients with human immunodeficiency virus (HIV) infection.¹⁴² It currently accounts for 4% to 7% of all primary brain tumors.^{1,26,28,58,91}

Pathogenesis. The pathophysiologic basis for development of these tumors is unclear, particularly in immunocompetent patients. PCNSL most commonly originates from B lymphocytes and is associated with cytokines. In

immunosuppressed patients it is almost always associated with latent infection of neoplastic B cells by Epstein-Barr virus. B cells infected with Epstein-Barr virus are immortalized and able to replicate spontaneously.⁵⁸ The lymphoma cells typically assume a periventricular pattern, involving the deep white matter, basal ganglia, corpus callosum, and thalamus. PCNSL may also involve the CSF, the eyes, or the spinal cord. A large percentage of PCNSLs begin as solitary cerebral lesions but eventually develop into multiple lesions. Lesions in immunocompetent patients more often may be a single brain lesion, in a supratentorial location, and with frontoparietal lobe involvement. The diagnostic procedure of choice is a stereotactic (x-ray guided) biopsy, because patients derive no clinical benefit from surgical resection.⁵⁸

Clinical Manifestations. Symptoms and signs generally evolve over several months, including personality and behavioral changes, confusion, generalized seizures, and symptoms associated with increased ICP (headaches, nausea and vomiting). The most frequent presenting symptom in 30% to 40% of patients is impaired cognition.³² Focal neurologic signs such as hemiparesis or blurred or double vision may occur. The appearance on MRI or CT of multiple deep cerebral and periventricular lesions, along with an immunodeficient state, contributes to the diagnosis.⁶⁵ Differential diagnosis includes infections, other tumors, and inflammatory disorders.

Prognosis. The prognosis is generally poor, with median survival of 10 to 14 months, although adding systemic chemotherapy (methotrexate and cytosine arabinoside) to radiation has improved median survival to 32 to 60 months.^{58,126}

Other Miscellaneous Brain Tumor Types

Other infrequent brain tumors bear mention. They are as follows:

- **Chondromas** tend to arise at the base of the skull, are slow growing, and are composed of cartilage-like cells often attached to the dura mater.
- **Chondrosarcomas** are the malignant variant of chondromas.
- **Atypical teratoid rhabdoid tumors (ATRTs)** are high-grade tumors occurring most commonly in the cerebellum in children and are aggressive with frequent metastasis through the CNS.
- **Dysembryoplasticneuroepithelial tumors (DNETs)** are slow-growing, benign, grade I tumors, often containing a mix of neurons and glial cells, and typically found in the temporal or frontal lobe.
- **Gangliocytomas** and **gangliogliomas** arise from ganglia-type cells (groups of neurons), and are most commonly located in the temporal lobe and third ventricle.
- **Germ cell tumors** include the germinoma, teratoma, embryonal carcinoma and yolk sac tumor, and choriocarcinoma. These tend to arise in the pineal or suprasellar regions and occur primarily in children and young adults. Teratomas are composed of various tissue types within the tumor, often containing calcium, cysts, fat, and other soft tissues.

More details on these CNS tumors, as well as further information on the numerous other infrequent CNS tumors, are available in various references.*

Diagnosis of Primary Brain Tumors

When a brain tumor is suspected on clinical evaluation, a thorough neurologic examination as well as brain imaging studies are done to confirm its presence and exact location.

MRI has evolved as the most informative brain imaging study because of its superior imaging capabilities and lack of artifact from the temporal bones. With the addition of gadolinium contrast enhancement, which distinguishes tumor from surrounding edema, MRI detects tumors even a few millimeters in size. MRI also defines critical anatomic relationships between the tumor and surrounding neurovascular structures. The multiplanar capability of MRI allows optimal visualization of the anatomy. MRI is particularly useful in visualizing the brainstem and other posterior fossa structures.¹³⁹ New MRI techniques are being developed to investigate the biochemical basis of tumors, such as the proton magnetic resonance spectroscopy (MRS), which measures the signals from nuclei other than water.¹⁰¹

Although MRI has many advantages over CT, CT scanning is widely accessible, convenient, and effective in revealing most brain tumors if they are large enough. The increased vessel formation or neovascularization accounts for the enhancement of these tumors and allows them to be visualized. Although its brain imaging capabilities are inferior to those of MRI, CT can identify cerebral edema, midline shift, and ventricular compression of obstructive hydrocephalus. In intraventricular masses, CT is highly sensitive in detecting calcification. CT also is better than MRI for demonstrating bone destruction. CT imaging may be needed when a patient has precautions for a magnetic study (e.g., pacemaker or other metallic implants). Intravenous contrast greatly increases the sensitivity of CT scan for brain tumors.

Once a tumor has been detected with MRI or CT, other particular parameters may help to characterize it further. For example, establishing the location of an intracranial neoplasm in either the extraaxial or intraaxial compartment is valuable in differential diagnosis.¹³⁹ For example, astrocytomas are intraaxial, and meningiomas are extraaxial. The MRI or CT may detect a cleft between the brain parenchyma and the tumor, which indicates a possible extraaxial mass such as a meningioma.

There are numerous new techniques to image tumors. Single-photon emission computed tomography (SPECT) imaging uses preoperative thallium 201 emission CT in which the maximum uptake area of the brain tumor distinguishes benign from malignant tumors and localizes the area for biopsy. Iodine-123- α -methyl-L-tyrosine single-photon emission tomography (IMT-SPET) imaging uses a radioisotope to distinguish glioma recurrence from benign posttherapeutic change. The positron emission tomography (PET) scan is able to localize the areas of maximum glucose utilization within a tumor, guiding the

neurosurgeon to perform biopsy of locations with the most aggressive biologic behavior and differentiating viable tumor from necrosis.^{26,47,101} The PET scan also maps functional areas of the brain prior to surgery or radiation in order to minimize injury to eloquent areas.¹³⁹ Presurgery motor and somatosensory cortex mapping with functional MRI and PET is possible. Fluorodeoxyglucose PET (FDG-PET) measures glucose utilization and helps to differentiate recurrent tumor from radiation necrosis. It also is not influenced by corticosteroid therapy. Echo planar MRI is a new technique of functional MRI imaging that provides maps of tumor blood flow and may allow better resolution of tumor versus surrounding edema at the tumor borders. MRS may show pathologic spectra outside the area of contrast enhancement, suggesting infiltrative lesions.^{110,129}

Additional tests may be indicated to further delineate the tumor and identify possible surgical hazards. Cerebral angiography delineates the vascularity within the brain and can help determine the best surgical approach. Visual field and funduscopic examination identifies visual defects that are specific to a particular area. Audiometric studies determine hearing loss. Chest films help to rule out lung cancer with metastatic lesions to the brain, and other studies are used to rule out a primary lesion outside the brain when a metastatic lesion is suspected. Endocrine studies are done when a pituitary adenoma or craniopharyngioma is suspected.⁵²

A needle biopsy using CT-guided stereotactic (x-ray guided) technique through a burr hole in the cranium may be performed to identify the specific tumor type and grade. A needle biopsy may not be possible, however, with vascular tumors or tumors near vital centers for fear of precipitating bleeding or respiratory distress. As tumors may have variation in grading throughout the tumor, a needle biopsy may potentially miss the higher-graded area, limiting the accuracy of the diagnosis.

MEDICAL MANAGEMENT

Surgery, radiation therapy, chemotherapy, and immunotherapy are the treatment options for brain tumors. Management of symptoms and side effects is a major component of medical management.

TREATMENT

Surgery. Surgical excision is the most important form of initial therapy, because it provides histologic confirmation of the tumor and a basis for determining the treatment and prognosis. The new stereotactic neurosurgical techniques have had a profound impact on neurosurgery efficacy and safety. Intraoperative magnification and the operating microscope have allowed stereoscopic visualization of otherwise inaccessible tissues and have reduced the morbidity and mortality of brain surgery.¹⁰¹ MRI scanning combined with computer-aided navigation tools helps the neurosurgeon map the exact tumor location and track its removal during the procedure. Surgery reduces tumor load and quickly relieves the ICP and mass effect, thereby reducing symptoms and improving neurologic function. The surgical cytoreduction also enhances the effectiveness of adjuvant therapy (e.g., radiation therapy).

*References 1, L6, 24, 59, 66, and 77.

A traditional operative technique is the *craniotomy*, a resection of the skull overlying the tumor, removal of the tumor, and replacement of the bone flap (Fig. 30-16). *Stereotactic biopsy* of the lesion without craniotomy is used when deep mass lesions are surgically unresectable or when the risk of craniotomy outweighs the benefits. Stereotactic procedures involve creating a burr hole in the brain at an exact location using a computer, radiologic equipment, and a special head-fixation device.

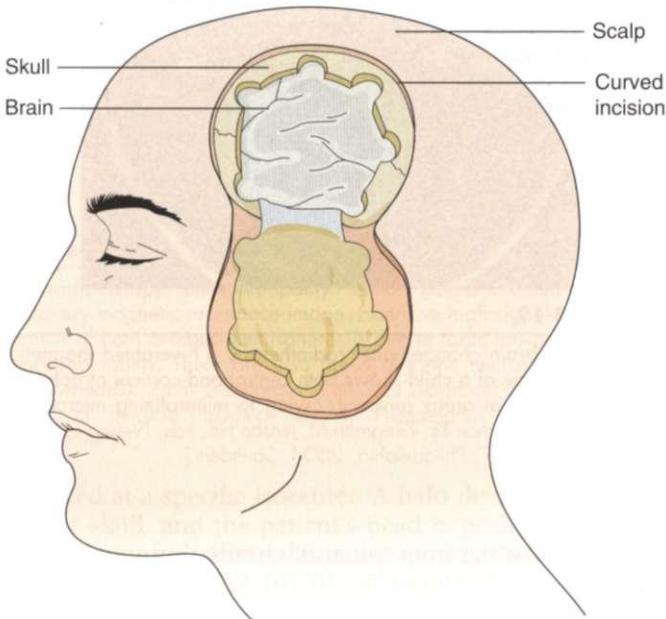


Figure 30-16

Craniotomy with osteoplastic bone flap. (From Schnell SS: Nursing care of clients with cerebral disorders. In Black JM, Matassarin-Jacobs E, eds: *Luckmann and Sorensen's medical-surgical nursing*, ed 4, Philadelphia, 1993, Saunders, p 734.)

The technologic and conceptual advances in neurosurgery (e.g., intraoperative magnification, ultrasonic aspirators, microinstrumentation, computer-based stereotactic resection procedures) have allowed safer and more precise approaches to previously inaccessible tumors.^{118,126} Awake cortical mapping before and during surgery identifies critical areas of brain functioning to avoid and/or reduce damage to these areas.^{18,38} Endoscopic surgery for pituitary adenomas, tumors of the orbit, vestibular (acoustic) neuromas, meningiomas, and other skull-based tumors utilizes endoscopes attached to an endocamera and a video monitor system.¹¹⁹ Transsphenoidal resections are possible through the nose (transnasal), which avoid an external craniotomy. See Fig. 30-17. Actual short videos of endoscopic brain surgeries are available for viewing on the Internet.⁶² Facial craniotomy or endoscopy utilizes incisions positioned between facial cosmetic subunits as shown in Fig. 30-18.

The goal of surgery is total excision, while minimizing trauma to vital neural structures. The survival rates of patients undergoing total resections for brain tumors are significantly higher than those of patients undergoing partial resections.⁸⁸ In infiltrative intraaxial lesions, in which total excision is not possible, the goal is to provide a measure of temporary control by reducing mass effect and ICP. If the preoperative neurologic deficit is due to destruction of brain tissue by tumor, surgical resection will not improve the situation. However, if the deficit is related to compression from the tumor, excision may relieve the compression and allow the deficit to improve. In the case of many benign extraaxial tumors (e.g., meningiomas, schwannomas, pituitary adenomas), cure can be achieved.

Operative complications include hemorrhage, infection, seizures, hydrocephalus resulting from an impairment of CSF absorption, and neuroendocrine disturbances, especially if surgery is in the region of the pituitary. Brain edema, usually present before surgery, may be severely

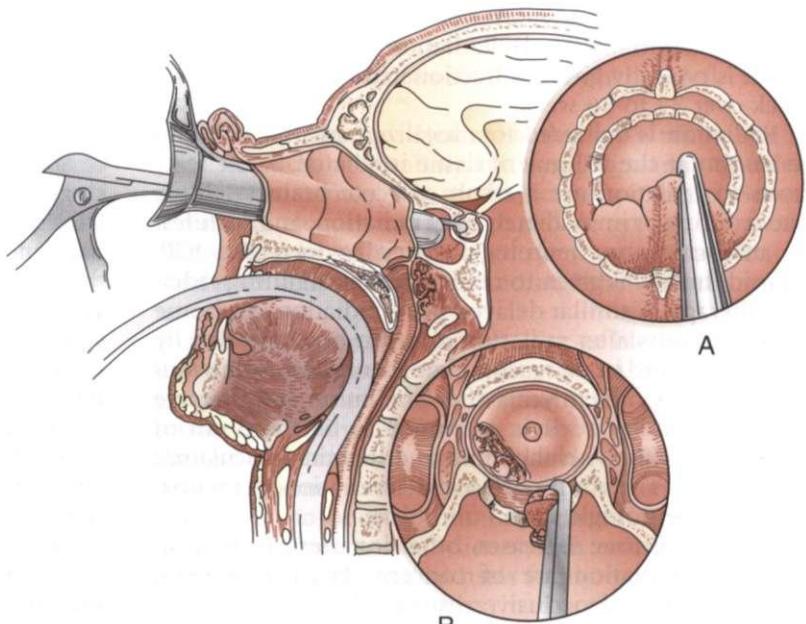


Figure 30-17

Endonasal transsphenoidal resection of the pituitary tumor. **A**, Removal of the sella floor with small rongeurs. **B**, Exposed inferior aspect of a pituitary adenoma. (From Tindall GT, Barrow DL: *Disorders of the pituitary*, St Louis, 1986, Mosby.)

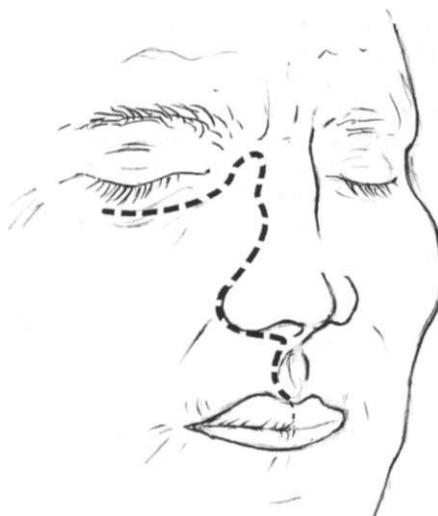


Figure 30-18

Illustration of standard location for facial incisions, with craniofacial resection completed using traditional methods. These incisions are positioned between facial cosmetic subunits (dashed lines). (From Cummings CW Jr, Haughey BH, Thomas JR, et al, eds: *Cummings otolaryngology—head and neck surgery*, ed 4, Philadelphia, 2005, Mosby.)

aggravated during surgery. Corticosteroids usually are given for several days before craniotomy to reduce pre-operative edema. Improved surgical techniques have reduced the complications of hemorrhage, infection, and permanent neurologic injury to less than 10% of cases.¹²⁶

Radiation Therapy. Radiation therapy following surgical resection is of proven effectiveness for most malignant brain tumors.³³ Various brain tumors have different susceptibilities to radiation therapy, but the survival advantage is unquestionable. A greater degree of tumor anaplasia and a younger age may result in a better response to radiation.¹¹ Unresectable or incompletely resected tumors in particular are candidates for radiation therapy. Established radiation doses that avoid exceeding thresholds of CNS tolerance are in the range of 40 to 60 Gy (4000 to 6000 rad). Radiation using a linear accelerator is typically given in fractionated doses five times a week over 34 to 36 weeks.

Radiation is delivered to a localized area of the brain to minimize the volume of tissue irradiated. Acute reactions to radiation are a result of acute brain swelling, occur during or immediately after radiation, and manifest as an increase in neurologic deficit or increased ICP. Steroid therapy is given to reduce this effect during radiation therapy. A similar delayed postirradiation syndrome 1 to 3 months after radiation also can be controlled by steroids. A third brain reaction known as *radiation necrosis* may occur months to years after irradiation and is severe and irreversible.^{64,123} It is presumed to be the result of direct toxic effects on the brain and its microvasculature (Fig. 30-19). There is progressive deterioration, dementia, and focal neurologic signs.

As survival time increases, other long-term complications of irradiation are of concern. Hypopituitarism, radiation-induced occlusive disease of cerebral vessels, radiation-induced oncogenesis, leukoencephalopathy,



Figure 30-19

Generalized brain changes after radiotherapy. T1-weighted magnetic resonance image of a child shows both central and cortical atrophy as well as high-signal areas (arrows), owing to mineralizing microangiopathy. (From Behrman RE, Kliegman M, Jenson HB, eds: *Nelson textbook of pediatrics*, ed 17, Philadelphia, 2004, Saunders.)

and myelopathies from spinal axis irradiation are included in these complications (Fig. 30-20). White matter injuries have been shown to correlate significantly with radiation dose in long-term survivors (greater than 18 months). These changes correlate with functional neurologic status,³⁰ including altered mental status, speech impairments, motor deficit, cranial nerve deficit, personality changes, altered memory, and other neurologic signs.⁶

Advances in radiation therapy have led to newer methods of radiation delivery. Interstitial radiation therapy, or *brachytherapy*, involves the placing of the radiation source, such as radium seeds, within the tumor for a period of several days. Brachytherapy has shown promise in treating GBM and other primary brain tumors.

Stereotactic radiosurgery is a technique to deliver a large single fraction of highly focal radiation to a brain tumor.⁷² It originally was used to treat functional disorders (e.g., pain and movement disorders) but is now being used in the treatment of primary and metastatic brain tumors.¹¹⁶ There are several methods: The linear accelerator-based systems, which are the most widely available, deliver high-energy photon beams using converging arcs, which intersect at the target site. Various modifications in the linear accelerator, or LINAC, are available. Three-dimensional conformal radiation therapy (3D-CRT) allows shaping the radiation beams to match the tumor's contours. Intensity-modulated radiation therapy (IMRT) is a refinement of 3D-CRT which ensures that maximum intensity is directed at a specific site, reducing the dose to the surrounding tissues. Gamma knife radiotherapy uses high-energy photon beams from cobalt 201 sources, each

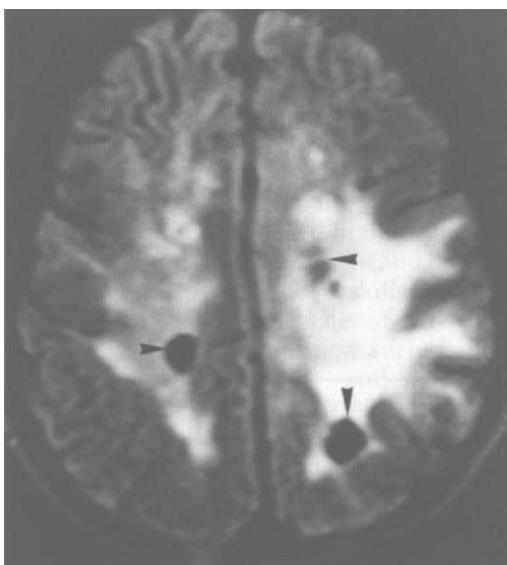


Figure 30-20

Postradiotherapy encephalopathy. Axial fluid-attenuated inversion recovery magnetic resonance image. Extensive high signal in the white matter of both cerebral hemispheres is due to radiation-induced leukoencephalopathy. There are also areas of cystic necrosis in this case (arrowheads). (From Grainger and Allison's diagnostic radiology: a textbook of medical imaging, ed 4, Philadelphia, 2001, Churchill Livingstone.)

directed at a specific isocenter. A halo device is attached to the skull, and the patient's head is positioned into a collimator that delivers focused gamma beams to the targeted tumor.

Synchrocyclotron proton beam therapy delivers heavy charged particle beams through a small number of portals in the skull.¹²⁶ The *CyberKnife* is a frameless robotic radiosurgical device with increased fractionation flexibility and the ability to treat extracranial lesions. It is capable of changing the target of the beam delivery instantaneously.^{107,116}

In some specific primary and metastatic brain cancers, radiosurgery may be the first line of treatment, instead of surgery. The advantages of radiosurgery compared to surgery are avoiding the risk of hemorrhage, infection, and tumor seeding; linking treatment directly to three-dimensional visualization, which reduces the chances of a marginal miss; and requiring minimal hospitalization.^{56,116}

Although gamma knife, proton beam, and CyberKnife equipment is expensive, and treatment requires collaboration between radiation oncologists and neurosurgeons, the use of these modalities is rapidly increasing, and data on their effectiveness and neurotoxicity are becoming available. Radiotherapy may prove increasingly to be a beneficial modality of client care¹¹⁴ as it becomes more available and easier to deliver. Brain metastases are ideal lesions to be treated with stereotactic radiation because they can be optimally covered by the radiation distribution, which can be easily designed by radiosurgical treatment planning.^{28,29,128} In time, technologic modifications will allow treatment at other sites, such as the spine.

Chemotherapy. Chemotherapy has been extensively studied in brain tumors and may have an impact on both

survival and quality of life in those who have primary brain tumors, particularly for certain pediatric neoplasms such as medulloblastoma.¹²⁶ The early studies in the 1960s involved the nitrosoureas (carmustine or BCNU, and lomustine or CCNU) and hydroxyurea, because of their in vitro sensitivity and lipophilic characteristics allowing them to cross the blood-brain barrier. BCNU has been the most effective cytotoxic agent against malignant glioma.¹³⁹

Newer agents with antitumor activity include diaziquone, procarbazine, imidazole carboxamide (DTIC), vincristine, cisplatin, carboplatin, tamoxifen, CPT-11 (irinotecan or Camptosar), and temozolamide (Temozol or TMZ).^{101,139} TMZ is emerging as the chemotherapy drug of choice for high-grade gliomas in the adjuvant setting, associated with significant improvements in median progression-free survival.^{8,57,121,122,125} It is thought that TMZ may be especially useful for elderly patients with glioblastomas as an alternative to radiation therapy to maintain a reasonable performance status.²⁰ A three-drug regime of procarbazine, lomustine, and vincristine (PCV) also has been shown to benefit patients with anaplastic glioma but offered no survival benefit for those with GBM.¹⁰¹ Current clinical trials are investigating paclitaxel (Taxol), phenylacetate acid, and other novel techniques such as the thymidine-kinase gene, continuous infusion chemotherapy, and the use of antiangiogenesis drugs such as thalidomide. Trials of intracavitary placement of carmustine polymer wafers (Gliadel) are demonstrating prolonged survival without the systemic side effects of chemotherapy.¹³⁹

To bypass the blood-brain barrier, intrathecal delivery (through an Ommaya reservoir surgically placed in the scalp with its tube inserted into the lateral ventricle) can be done. Another technique is an intraarterial (intracarotid) delivery allowing much higher concentration of drugs such as methotrexate, vincristine, or cisplatin than intravenous injection, which overcomes molecular resistance. Intrathecal chemotherapy may be given when leptomeningeal involvement occurs with tumor or to increase the CSF concentration. Addition of chemotherapy to surgery and irradiation for malignant gliomas does provide some increases in 24-month survival, up to 23.4% from 15.9%.¹²⁶

Hormonal Therapy. Hormonal therapy is often used to treat functioning pituitary tumors. Dopamine agonists are used to control the production of prolactin. Somatostatin analogues are used to reduce growth hormone levels and relieve the associated symptoms. If satisfactory results are achieved, surgery and/or radiation may not be necessary.

Immunotherapy. Immunotherapy or biotherapy is the most infrequently used and least proven therapy for brain tumors. Immunotherapy, originally the use of donor serum containing preformed antibodies, now includes the use of interferons and interleukin-2 (see the section on Interferons in Chapter 7 and Immunotherapy in Chapter 9) to boost immune function.⁵² The depressed immunocompetence of clients with malignant glioma gives at least a theoretical basis for the potential roles of biologic response modifiers in the treatment of these tumors. Preliminary studies have shown some promise.¹²⁶

Table 30-5 Emergency Treatment of Elevated Intracranial Pressure in Acutely Decompensating Patients

Therapy	Treatment	Onset (Duration of Action)	Other
Hyperventilation	Lower PaCO ₂ to 25-30 mm Hg	Seconds (minutes)	Usually requires intubation and mechanical ventilation
Osmotherapy	Mannitol 0.5-2 g/kg IV, repeat as necessary	Minutes (hours)	Brisk diuresis
Corticosteroids	Dexamethasone 50-100 mg IV, followed by 50-100 mg/day in divided doses	Hours (days)	Requires Foley catheter Requires strict attention to electrolytes Most effective on vasogenic edema (tumors, abscesses) Less effective on cytotoxic edema (stroke)

From DeAngelis, LM: Tumors of the central nervous system. In Goldman LM, Ausiello D, eds: *Cecil textbook of medicine*, ed 22, Philadelphia, 2004, Saunders.

PaCO₂, Arterial partial pressure of carbon dioxide; IV, intravenous.

SYMPTOM MANAGEMENT. Brain tumors lead to edema of tissue surrounding the tumor, and brain swelling can be massive and extend the neurologic deficits caused by the tumor alone. Antiinflammatory drugs (corticosteroids, such as dexamethasone [Decadron], prednisone, hydrocortisone) are used to provide prompt and effective reduction in peritumoral edema. Improvement in symptoms of ICP and in focal neurologic signs begins within 24 to 48 hours after steroid initiation, and by the fourth and fifth day the maximum degree of improvement is obtained.¹³⁹

Corticosteroids generally are used perioperatively and are tapered gradually after tumor resection, because long-term high-dose corticosteroids precipitate undesirable side effects. Corticosteroids also may be used periirradiation because radiation also precipitates edema. Upon tumor recurrence or progression, corticosteroids may again be instituted to temporarily maximize residual neurologic function.

It is possible for a brain tumor to cause an acute increase in ICP that may be life-threatening because of imminent cerebral herniation. Emergency treatment is required if ICP reaches 20 mm Hg or more. Quick-acting agents are needed to lower the pressure. Mannitol is used as a temporary agent to quickly reduce brain water and relieve the pressure. Steroids are used in conjunction with mannitol to decrease edema. Table 30-5 lists emergency treatments for elevated ICP in acutely decompensating patients.

Anticonvulsants also may be needed to prevent or control seizure activity. These drugs also are used before and after surgery to control symptoms and are continued as long as they are indicated.²⁶ One of the most common anticonvulsant therapies used today in the brain tumor population is phenytoin (Dilantin).⁹³

Brain tumors also cause a variety of motor, speech, hearing, visual, and other neurologic signs and symptoms. While control of the tumor and edema through medical management is the first priority, residual neurologic problems can significantly lower the quality of life. Timely referral to rehabilitation specialists for management of these functional deficits can improve performance status and quality of life. Strengthening, motor

and balance evaluation and training, splinting, bracing, fatigue and pain management, incontinence training, home adaptation, activities of daily living (ADL) retraining, speech therapy, hearing adaptations, auditory retraining, and vision programs are available to improve and alleviate these functional deficits.

Other specialists are also part of the rehabilitation team. Enterostomal therapists provide help with ostomies; pharmacists provide assistance with pain management; the oncology nurse provides symptom management, psychosocial support, and education; the nutritionist provides diet and nutrition counseling; the social worker assists with community resources and placement in settings for necessary further care; and clergy provide assistance with personal and spiritual issues.

The psychosocial implications of brain tumors are enormous. Referral to psycho-oncologic specialists for alleviation of psychologic distress and family disruption, and promotion of role reorganization and adaptation are often of great value. Brain tumor support groups, psychotropic medications, oncology educational classes for the client and family, and enrollment in one-on-one support programs can be very helpful.

SPECIAL IMPLICATIONS FOR THE THERAPIST 30-1

Primary Brain Tumors

PREFERRED PRACTICE PATTERNS

5A: Primary Prevention/Risk Reduction for Loss of Balance and Falling

5D: Impaired Motor Function and Sensory Integrity Associated with Nonprogressive Disorders of the Central Nervous System—Acquired in Adolescence or Adulthood

5E: Impaired Motor Function and Sensory Integrity Associated with Progressive Disorders of the Central Nervous System

5I: Impaired Arousal, Range of Motion, and Motor Control Associated with Coma, Near Coma, or Vegetative State

6B: Impaired Aerobic Capacity/Endurance Associated with Deconditioning

Rehabilitation Referrals

Therapists will undoubtedly encounter clients with brain tumors in any practice arena because of the significant neuromuscular and cardiopulmonary impairments. Neurologic or orthopedic practices may see patients with brain tumors presenting with gait and balance instability or cervical pain. When the signs and symptoms of a yet undiagnosed brain tumor bring the person to therapy (e.g., unsteady gait and poor balance, weakness), differential diagnosis skills are needed by the therapist to determine a cluster of signs and symptoms indicating a possible tumor, such as headache, nausea and vomiting, lethargy, and so on (refer to Boxes 30-2 and 30-3 and Table 30-3) or a progression of symptoms despite physical therapy intervention requiring referral to the physician.

Knowledge Needed for Rehabilitation

Brain tumor studies are beginning to demonstrate rehabilitation effectiveness.^{14,46,86} As the survival of those with brain tumors increases, rehabilitation needs become more prominent.¹⁴ A general knowledge of primary brain tumor and medical treatment is needed to provide the therapist with skills for differential diagnosis, examination and evaluation, treatment planning, and goal setting. Knowledge of malignant versus benign status, disease progression expectations, complications, prognosis, and precautions such as seizures and deep vein thromboses (DVTs) are needed to plan intervention and establish goals. The therapist should also be aware of expected focal symptoms in relation to tumor location to anticipate functional changes that may require treatment modifications, as well as possible paraneoplastic syndromes that may complicate rehabilitation. In geriatric populations, managing the patient with brain cancer may require comprehensive geriatric assessment (CGA) to identify comorbidities.^{9,10}

It is important to be knowledgeable about the more prevalent brain tumor types and be able to differentiate, for example, between a meningioma (a benign, potentially curable tumor) and a malignant glioma (a rapidly growing fatal tumor), in order to set goals, to interact with the family, and to provide appropriate intervention. The advancements in brain tumor medical management (e.g., the promising effectiveness of TMZ for malignant gliomas) and the developing precision of radiation therapy, sparing brain damage, brings longer survival and opportunities for better quality of life.¹²¹ The therapist must be aware, prepared, and hopeful that, as the demand for rehabilitation grows, the rehabilitation outcomes will improve.

In addition, knowledge of medical treatment complications from surgery, radiation, chemotherapy, and other interventions will give the therapist the ability to adjust the rehabilitation program as needed, to accommodate, for example, myelosuppression from chemotherapy or fatigue from radiation therapy.

Acute Postoperative Management

When a referral is received for acute postoperative rehabilitation therapy, awareness of general postoperative complications, including atelectasis, pneumonia, cardiac arrhythmias, fluid and electrolyte imbalances, infection, meningitis, intracranial hemorrhage, and renal and gastrointestinal disorders, is important. Potential symptoms after brain surgery include confusion, pain, weakness, and headache. Observing the client closely during therapy intervention for any significant signs and symptoms, and making appropriate adaptations during therapy, are part of the role of the therapist.¹¹³

Postoperative Complications of Intracranial Surgery

Potential complications of intracranial surgery may be very serious, even fatal, because of the significant functions performed by the structures involved. Some post-operative complications may improve; others may be permanent.

Increased ICP (resulting from cerebral edema or bleeding) is the major complication of intracranial surgery. Findings may include decreased level of consciousness with headaches, visual and speech disturbances, muscle weakness or paralysis, pupil changes, seizures, vomiting, and respiratory changes (see Box 30-3).

In at-risk patients, there are several methods that can be used to continuously measure ICP, including intraventricular catheters, subarachnoid or subdural screws or bolts, epidural sensors, and intraparenchymal catheters. The ICP is often displayed in the bedside monitor. Other monitored parameters include mixed venous oxygen saturation (SvO_2) and jugular oxygen saturation (SjO_2), which reflects oxygen saturation of the blood returning from the brain. Normal ICP ranges from 0 to 15 mm Hg, with a midrange of 8 mm Hg and fluctuations occurring with active movement of the extremities and trunk, coughing, suctioning, noxious touch, and other physical stress maneuvers. Use of pleasant sensations such as music and therapeutic touch to reduce ICP are being investigated.⁷⁰ Sustained ICP above 20 mm Hg requires emergency treatment. A therapist noting a rise in ICP above 15 mm Hg should contact the nurse or physician.

Because of increased ICP, further surgical intervention may be needed to release excess fluid. A catheter may be inserted to drain excess fluid from a ventricle or other fluid-filled space, called a shunt, or a Jackson-Pratt suction drain may be needed. CSF postoperative leaks are evidenced by saturation of the surgical head dressing or leaking of a clear, thin fluid from the ear or nose that dries in concentric circles.

Management of the postoperative client with increased ICP typically includes, among other things, elevation of the head. A position with the client's head elevated about 20 to 30 degrees is often prescribed. The client should be protected from any position that allows stasis of the CSF drainage and should be taught

Continued.

to observe the drainage and to be aware of signs of infection. The client also should be instructed against coughing, sneezing, or blowing the nose.

An erratic body temperature may occur after intracranial surgery. Either hypothermia or hyperthermia may be present. The therapist should check with the nursing staff before beginning therapy if concern exists regarding abnormal temperature.

DVT occurs in one third of patients who have surgery. Seizures,⁵³ CSF leakage, and wound infection are also risks. Periocular edema is common, as are temporary visual field deficits. Patients may have other temporary deficits resulting from cerebral edema, such as communication, motor, and sensory deficits; diminished gag and swallowing reflexes; diplopia; loss of corneal reflex; and personality changes.⁵² *Pneumocystis carinii* pneumonia (PCP) is a life-threatening opportunistic infection that occurs in immunocompromised hosts, such as with corticosteroid used. Signs of PCP are fever and dyspnea with or without a prominent dry cough, though the onset may be subtle. The risk of PCP is increased while steroids are being tapered.^{93,112}

Meningitis also may occur, caused by irritation of the meninges by infection or blood in the subarachnoid space. If it develops, meningitis typically appears 2 or 3 days after surgery. Chills, fever, nuchal rigidity, headache, irritability, increased sensitivity to light, and decreased level of consciousness are signs of meningitis. It is essential that all care providers practice infection prevention measures such as thorough handwashing when caring for clients who have had intracranial surgery.

Other signs to be aware of include ecchymosis, stress ulcer, swallowing difficulties and aspiration, and impaired airway. Respiratory changes should be monitored carefully. An abnormal respiratory rate and depth may indicate rising ICP. By carefully observing the client during therapy, protecting the client from harm, and alerting medical staff of seizure activity or other adverse signs and symptoms, the therapist can provide a valuable adjunct to postoperative care.

Positioning in the Acute Postoperative Phase

If there is any question about positioning of a client during therapy, the therapist should communicate with the nursing staff. Incorrect positioning may have serious, possibly fatal, consequences. In the acute phase after surgery above the tentorium, orders may be given to avoid lowering the head, to avoid extreme flexion of the legs, and to keep the neck in a neutral position. After surgery below the tentorium, the client may be kept flat and turned every 2 hours or have orders for elevation of the head of the bed. It is recommended that the neck not be angulated anteriorly or laterally, but there are usually no restrictions placed on turning. For infratentorial tumors that may cause dizziness on arising, elevating the head of bed gradually while concurrently monitoring vital signs is recommended. The dizziness is caused by transient edema in the area of the eighth cranial nerve. For posterior fossa surgery, the client is typically positioned on the side with a pillow under the head. This protects the

operative site from pressure and minimizes tension on the suture line.⁵²

If a bone flap was removed for decompression, the orders may be to place the client only on the nonoperated side or the back. This facilitates brain expansion. If a large tumor has been removed from a cerebral hemisphere, there may be an order to avoid positioning on the operative site to prevent shifting of the cranial contents due to gravity.

If a client is neurologically unstable, and with ICP in a critical range (more than 20 mm Hg), therapy procedures that require a flat position (e.g., lowering the head of the bed for range-of-motion [ROM] exercises) should be avoided. Placing a pillow under the head facilitates good venous outflow. When the client is side lying, protecting the hips from sharp flexion avoids an increase in intrathoracic pressure, which can in turn increase cerebral ICP.

Intervention Preparation

Before physical therapy intervention, examination should include a review of the medical chart; the surgical, radiologic, and pathologic reports; laboratory values; and nursing and other reports. If indicated, physicians should be contacted for pertinent information and guidelines. Hematologic values may be of critical importance for exercise training plans. Anemia causes fatigue, leukopenia increases infection susceptibility, and thrombocytopenia increases bleeding susceptibility and is of particular concern because it may lead to intracranial hemorrhage.^{90,93}

Familiarity with cancer terminology and the behavior of the particular tumor aids communication with others on the team. For example, knowledge of tumor staging and grading, the prognosis, the medical management such as the surgical procedure, presence of an Ommaya reservoir, and the various types of central lines and monitoring devices facilitates interdisciplinary care planning and intervention. The ICP levels, blood pressure, and other vital signs are typically available on the bedside monitor. Knowledge of the Karnofsky scale (Table 30-6), a functional performance scale used by many oncologists to indicate the client's activity level in the hospital, home, or community, is helpful. It can facilitate communication among the team on issues such as a client's candidacy for home discharge with home health assistance or need for more supervised care. The ECOG (Eastern Cooperative Oncology Group) 1-4 Scale is another tool that may be used to identify functional performance.

Initial outcomes expected for clients with brain surgery include full ROM, active where possible, of all extremities and optimal functioning of respiratory, cardiovascular, and other systems within the precautions indicated. When the client's condition is stable, functional outcomes include independent bed mobility and transfers, ambulation, and self-care skills (ADLs).

Rehabilitation Examination for Postoperative Care

During the acute postoperative phase, a thorough examination within the constraints of the precautions,

Table 30-6 Karnofsky Performance Status Scale

Condition	Percentage	Comments
Able to carry on normal activity and to work. No special care is needed.	100 90 80	Normal; no complaints; no evidence of disease Able to carry on normal activity; minor signs or symptoms of disease Normal activity with effort; some signs or symptoms of disease
Unable to work. Able to live at home, care for most of personal needs. A varying degree of assistance is needed.	70 60	Cares for self; unable to carry on normal activity or to do active work Requires occasional assistance but is able to care for most needs
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	50 40 30 20 10 1 0	Requires considerable assistance and frequent medical care Disabled; requires special care and assistance Severely disabled; hospitalization is indicated, although death is not imminent Hospitalization is necessary; very sick; active supportive treatment necessary Moribund; fatal processes progressing rapidly Unconscious Dead

From Baird SB, McCorkle R, Grant M: *Cancer nursing: a comprehensive textbook*, Philadelphia, 1991, Saunders.

including strength, joint ROM, sensory and perceptual status, neurologic signs, pain patterns, presence of fatigue, and mobility, helps to identify treatable impairments that affect function.⁷⁹ During examination and intervention, the therapist should avoid any Valsalva maneuver that would increase intrathoracic pressure, thus increasing ICP. The therapist also should avoid jarring the client's bed or causing sudden movements that would increase pain.

Rehabilitation Intervention

After intracranial surgery bed rest precautions may be initiated, usually for 24 hours, and should be observed by the therapist. If the client is stable, passive ROM exercises may begin.

Position changes are important, and use of a draw sheet and adequate help ensure that the patient will not strain with position change and increase ICP. When movement to the bedside chair is safe but ICP precautions preclude active supine to sitting movements, lifting the client to a reclining chair by a draw sheet with the help of several caregivers and then gradually raising the client's back and head in the chair protects him or her from straining. Bedside sit-and-dangle exercises also may be requested. Blood pressure checks for postural hypotension, close assessment for dizziness and faintness, and monitoring of respiratory rate, heart rate, and ICP during activities are essential. General conditioning activities early in the recovery are valuable to address the fatigue cycle typical of cancer.

Subacute and Ambulatory Rehabilitation

As the patient becomes more stable and is moved into lower levels of acuity, including inpatient and ambulatory care, continued monitoring is imperative. The therapist must monitor vital signs and observe for any neurologic change; any adverse indications such as

seizures, bleeding at the operative site, or signs of a DVT; or sudden changes in mental status.

Reviewing diagnostic information, laboratory reports, and medical treatment continues to be important as the patient moves into new phases of care. Medical treatment modalities and side effects have a pronounced effect on the client's participation in therapy. Chemotherapeutic and radiation side effects, such as myelosuppression, nausea, and fatigue, may temporarily lower energy levels, requiring adjustment of the therapy program. Irradiated areas should be protected against skin injury. No heat or cold or topical agents should be used in the irradiated area during the treatment series or for several weeks after the treatment series until the skin damage has cleared. The radiation oncologist will determine the topical agent(s) to be used. If persistent trophic change occurs to the skin with obvious circulatory impairment, heat or cold should not be applied over the site because of poor dissipation effects.

Examination and intervention are based on the impairments and disabilities identified. Safety in mobility, gait and balance training, protection from falls, strengthening, equipment decisions, functional training and aerobic capacity training are important rehabilitation interventions.¹¹⁸ Written educational materials are increasingly requested.

The efficacy of increasing the activity level has been demonstrated, and functional training, gait training, and exercise are well-accepted postoperative interventions.¹⁰² Long-term management may include family training and education and more advanced treatment aimed at self-care and safety, return to family roles, and work and leisure activity.

More attention is being paid at the present time to cancer-related fatigue (CRF), identifying possible causes such as myelosuppression, anorexia, pain, sleep

Continued.

deprivation, and somnolence. Treatment modalities including surgery, radiation therapy, and chemotherapy are associated with fatigue. Understanding fatigue and the ameliorating factors is becoming the subject of more studies. In a recent glioblastoma study, fatigue was associated with decreases in almost all aspects of quality of life.⁷⁶ Addressing fatigue with a structured progressive exercise program has been shown to have some efficacy.^{35,36,84,85} Although there is no consensus on the ideal type of exercise, frequency, intensity, duration, or mode, there is good cardiopulmonary response to interval training at 50% to 70% of heart rate reserve or working at an exertion level of 11 to 14 on the 6 to 20 rate of perceived exertion (RPE) scale. While treatment is being given, most studies recommend decreasing the intensity to the lower end of the heart rate range.²⁷ Careful monitoring to avoid overstressing the immune system has been suggested by some studies.⁶⁵ Throughout the rehabilitation process, activities that increase ICP, such as vigorous resistive exercises or isometrics, should be avoided.

Recent studies support the benefits of comprehensive and interdisciplinary rehabilitation for patients with primary and metastatic brain tumors.^{55,85,33} Outcomes of physical therapy intervention may be measured by standardized tools, such as the Karnofsky scale, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTCQ-30), the Psychosocial Adjustment to Illness Scale, the Functional Living Index—Cancer (FLIC) Scale, the Functional Assessment of Cancer Therapy—Brain (FACT) tool,^{43,78} and the Functional Assessment of Chronic Illness Therapy (FACIT) Scale. Fatigue measures include the 1 to 10 analogue scale, the Brief Fatigue Inventory (BFI),¹⁹ the Piper Fatigue Scale, and numerous other new fatigue measures. Some studies have used the Functional Independence Measure (FIM) to evaluate changes in function with inpatient rehabilitation^{55,78,85,90} and have demonstrated improvements. Considerations of quality of life are increasingly part of medical oncologic studies.

Steroid Effects

Corticosteroids are prescribed during surgery and again during radiation to reduce cerebral edema. Long-term effects include many adverse problems, including proximal weakness, behavioral changes, osteoporosis, increased appetite, bloating, hypertension, opportunistic infections, night sweats, hyperglycemia, yeast stomatitis, and many more. Long-term steroid use is avoided, and the drugs are typically discontinued after the acute surgical or radiation management is completed. However, with steroid tapering and discontinuation, there may be a possible increase in cerebral edema and a recurrence of symptoms previously present before surgery or radiation. For example, a person receiving brain radiation taking dexamethasone during the radiation series may demonstrate improved hemiparesis as a result of the steroid. However, when radiation therapy is completed and steroid therapy is tapered and discontinued, the hemiparesis may worsen. The therapist needs to be aware

of decreasing function related to steroid tapering during this time and report it to the physician. The decision may be made to continue the steroid at a low dose. If corticosteroids are tapered too rapidly after surgery or radiation therapy, causing peritumoral edema, a bolus dose of dexamethasone followed by a more gradual weaning schedule may alleviate the symptoms.⁴⁴ Edema fluctuations from the tumor effect itself may cause a puzzling improvement and regression in neurologic status. Mobility issues and goals should be planned with the client and family, keeping in mind this potential of variable symptoms from edema fluctuations. The therapist must avoid creating either false hope or pessimism when patient performance varies because of edema fluctuations.

Psychosocial Impact

The impact of the diagnosis may be difficult for the client to comprehend. The client who does comprehend may demonstrate extreme behavioral responses or a profound sense of hopelessness. The client should be encouraged to ask questions and express his or her feelings about the situation. Depression is difficult to distinguish from apathy caused by the brain tumor,⁶⁰ but a differential diagnosis, if possible, through depression testing, is important to help the therapist to advocate for improved management of depression. Managing cognitive effects of radiation therapy is difficult for the client and family.²³ The caregiver's support, realistic reassurance, and inclusion of the client and family in the decision-making process will have a positive impact on the quality of life.⁵²

Because the diagnosis of a brain tumor is so devastating to the client and family, causing fear and uncertainty, the therapist must have sufficient maturity and psychosocial skills to be supportive and understanding. The challenge is not necessarily to provide solutions to these psychosocial problems but to provide support and validation and to facilitate referrals to appropriate professionals while addressing the physical problem for which the person was referred.

The Rehabilitation Team

The therapist involved in rehabilitation of the person with a brain tumor is part of a rehabilitation team of professionals that also may be involved in the care. The team may include representatives from nursing, nutrition, respiratory therapy, speech therapy, social work, psychology, the chaplain's office, durable medical equipment (DME) suppliers, hospice staff, and the physician office staff. An interdisciplinary approach allows access to needed resources.

The therapist must understand that the term *cancer rehabilitation* is used by many specialists and community programs that provide services for the person with cancer and may mean different things in different contexts. The American Cancer Society has a rehabilitation program that includes support groups and services such as rides to medical appointments and supplies like wigs. Oncology nurses have become increasingly supportive of cancer rehabilitation and an interdisciplinary approach⁸⁰ and include symptom control and

psychosocial issues in their definition of rehabilitation. Many local groups, such as church and synagogue support groups, provide another aspect of rehabilitation. The National Cancer Institute has identified four objectives for cancer rehabilitation: psychologic support, optimal physical functioning, vocational counseling, and optimal social functioning.⁸² Financial issues, nutrition, spousal relationships, sexual counseling, vocational rehabilitation, employment opportunities, physician-patient communication, patient education, and coping skills are broader aspects of rehabilitation.

In some acute care and outpatient settings, the therapist may be fortunate enough to be part of a more formalized cancer rehabilitation program that includes these broader aspects of rehabilitation. The advantages for the client with access to such a program include early and appropriate referrals to skilled professionals and resources, coordination of care and information, and a smooth transition across the continuum of care. Other benefits include enhancement of program development resulting from collaboration of professionals, outcome studies that will improve the quality of care, and the potential for rehabilitation research.

PRIMARY INTRASPINAL TUMORS

Primary spinal cord tumors are about one sixth as common as primary brain tumors. The histologic types of tumor cells in the spinal cord are the same as those found in the brain, although the prevalence of certain types may differ. The most common tumor in the spinal

cord is the schwannoma or neurinoma, followed by the meningioma and glioma.⁸³

A convenient anatomic classification system of spinal cord tumors is based on the relationship of the tumor to the spinal cord and dura. Fig. 30-21 diagrams the location and relative incidence of spinal tumors. Intradural-intramedullary tumors arise within the spinal cord substance. Intradural-extramedullary tumors arise outside the spinal cord but within the dura. Extradural spinal cord tumors arise outside the spinal cord and the dura (Fig. 30-22).

The specific spinal cord tumor types and their incidence are discussed first, followed by the clinical presentation and medical management.

Intradural-Intramedullary Tumors

Incidence

Intradural-intramedullary tumors are the least common type of primary intraspinal tumors in adults but the most common type in children. These tumors account for 5% to 10% of intraspinal tumors. The dominant tumor types are astrocytomas and ependymomas.

Pathogenesis

Because they are located within the cord itself, intradural-intramedullary tumors generally are derived from the cellular substrate of the spinal cord, such as the astrocytes and ependymal cells, or from the primitive embryonal cells. Astrocytomas may occur anywhere along the spinal cord and may span several cord segments longitudinally. In children they may run the entire length of the cord.

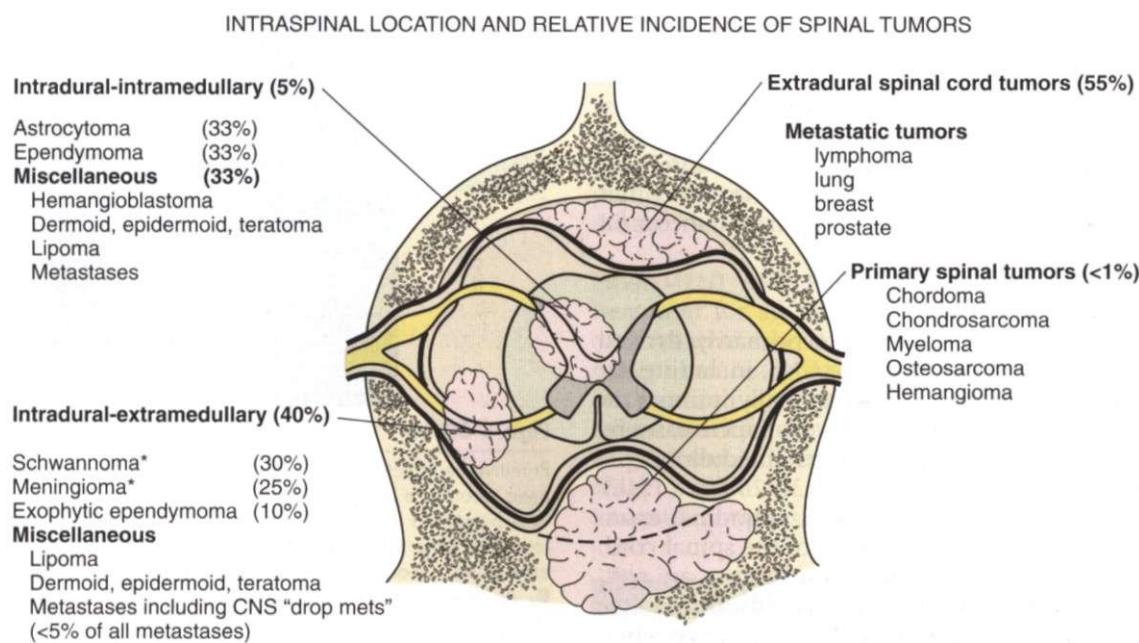


Figure 30-21

Primary and metastatic tumors of the spine and spinal cord. (Adapted from Poirier J, Gray F, Escourelle R: *Manual of basic neuropathology*, ed 2, Philadelphia, 1990, Saunders.)

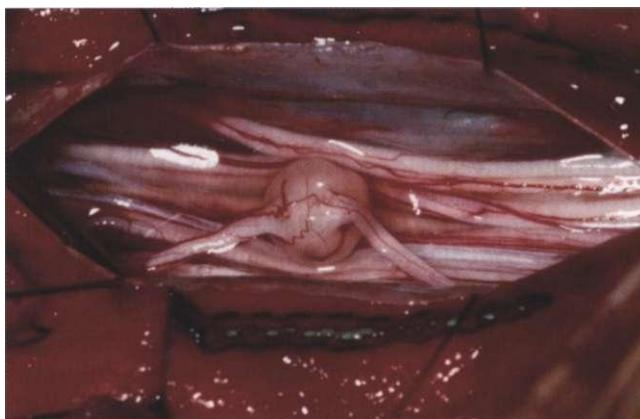


Figure 30-22

Spinal-cord neoplasms are extradural or intradural tumors according to their relation to the thecal sac. (From *Lancet Oncol* 8[1], 2007.)

Although all astrocytomas are infiltrative, most are low grade and slow growing in the spinal cord. Ependymomas are generally slow growing as well and less infiltrative, and therefore more amenable to surgical excision. Other less frequent types of intradural-intramedullary tumors are hemangiomas, epidermoid and dermoid cysts, teratomas, lipomas, and neuroenteric cysts. Of interest to therapists is chemical meningitis with its significant chronic pain that can occur when epidermoid or dermoid cysts leak debris into the CSF. Very infrequently, a primary intramedullary spinal lymphoma (PCNSL) may occur.^{13,127}

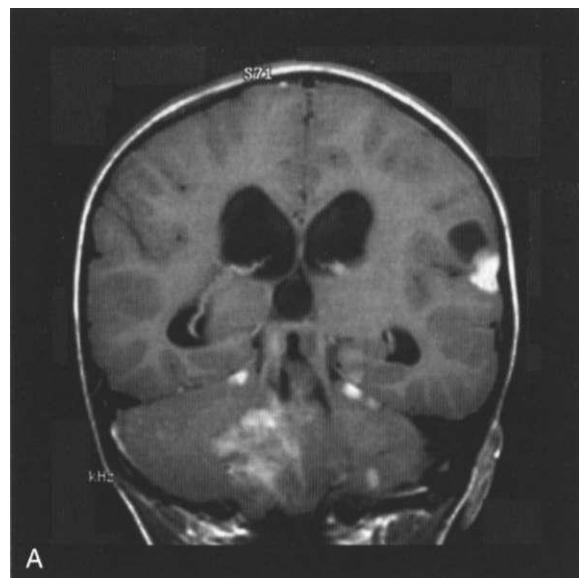
Intradural-Extramedullary Tumors

Incidence

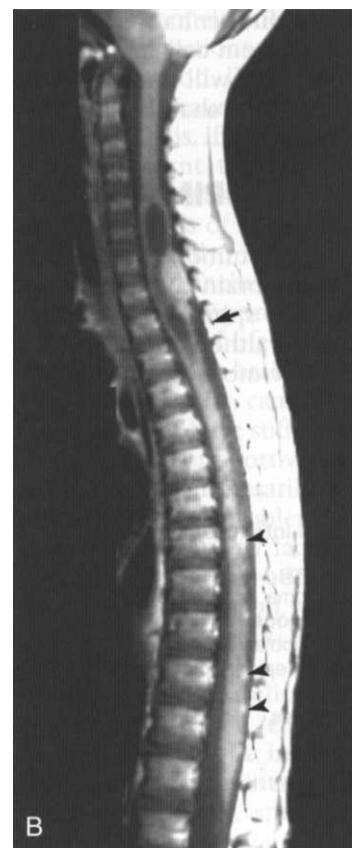
Intradural-extramedullary tumors are the most common type of primary intraspinal tumor in adults, and they account for about 45% of all spinal tumors. Neurinomas (schwannomas) and meningiomas are the dominant tumors in this group. Meningiomas are 10 times more common in women than in men and occur in middle age.

Pathogenesis

Intradural-extramedullary tumors are primarily derived from the supporting elements of the CNS, including the meninges and nerve sheath. Occasionally tumors in this compartment are carried down as drop metastases by the CSF from malignant brain tumors (medulloblastomas, ependymomas, PNETs). See Fig. 30-23 for a PNET in the brain and spinal cord surfaces. Intradural-extramedullary tumors cause compression of the spinal cord, rather than invasion of the cord. Neurinomas are soft, globular masses that arise at the sensory or dorsal nerve root. Occasionally they may straddle the intervertebral foramen and extend outside the foramen, forming the so-called *dumbbell configuration*. Spinal meningiomas are benign, slow-growing globular tumors that often grow in the thoracic, cervical, and foramen magnum regions. They may be present for many years before symptoms occur.



A



B

Figure 30-23

Primitive neuroectodermal tumor (PNET). **A**, T1-weighted coronal magnetic resonance imaging (MRI) scan after injection of contrast medium in a 5-year-old boy. There is a large multifocal tumor in the posterior fossa causing hydrocephalus. There are multiple smaller, contrast-enhancing, tumors along the surface of cerebellum and in the cerebrum. **B**, A T1-weighted sagittal postcontrast MRI scan of the spinal canal shows a large mass (arrow) in the junction of the cervical and thoracic spine with a syrinx and multiple small enhancing nodules (arrowheads) over the surface of the spinal cord. (From Adam A, Dixon AK, Grainger RG, et al, eds: *Grainger and Allison's diagnostic radiology: a textbook of medical imaging*, ed 4, Philadelphia, 2001, Churchill Livingstone.)

Extradural-Extramedullary Tumors

Incidence

Extradural-extramedullary tumors are most often metastatic tumors and are addressed in the section Metastatic Tumors. Extradural-extramedullary tumors represent about 45% of all spinal cord tumors. An occasional meningioma, neurinoma (schwannoma), or spinal chordoma arises extradurally. Spinal chordomas represent less than 1% of spinal cord tumors.

Pathogenesis

Spinal chordomas are primary tumors that arise from the vertebral bodies, usually in the cervical or sacral regions of the axial skeleton. They are prone to metastasize outside the spinal column. Lesions are characterized by expansive destruction of the bone, for example, the sacrum, or by varying degrees of vertebral collapse. Box 30-4 summarizes the type and location of spinal tumors.

Clinical Manifestations of Primary Intraspinal Tumors

Spontaneous pain caused by nerve root irritation is a common clinical feature of primary spinal tumors and is usually worse at night. Intramedullary tumors give rise to a poorly localized, deep, burning type of pain in the spinal region. Extramedullary tumors produce a knifelike radicular type of pain typically radiating to the periphery of the nerve, often aggravated by coughing, sneezing, or straining. The association of asymmetry of reflexes with nerve root pain and an insidious onset is strongly suggestive of a spinal cord tumor.

Nerve root pain may be followed by motor weakness and wasting of muscle supplied by the nerve. The motor changes of intramedullary tumors include lower motor neuron changes at the level of the lesion and may also

include upper motor neuron changes at lower levels. The motor changes of extramedullary lesions begin with segmental weakness at the lesion site and progress to damage to half of the spinal cord (Brown-Séquard syndrome) and later to a transverse cord syndrome.¹²⁶ The weakness is characterized by upper motor neuron signs, including spasticity. Sphincter weakness, increasing urinary frequency, and urgency may develop. In men, the development of sphincter disturbances frequently is followed by impotence.

Sensory changes in extramedullary tumors are usually along the distribution of the involved nerve roots. Intramedullary tumors result in dissociated sensory disturbances in the limbs below the level of the lesion because of their growth pattern of crossing fibers of the spinothalamic tract. People often report a feeling of temperature change, particularly a feeling of cold below the level of the lesion. Pain and temperature sensation are compromised, but proprioception and light touch are preserved.

Syringomyelia-like symptoms of loss of pain and temperature sensation below the level of the lesion on one or both sides of the body may occur from damage to the decussating lateral spinothalamic fibers. This often is accompanied by progressive spastic paraparesis caused by pressure on the descending corticospinal tracts. Anterior growth of the tumor produces anterior horn signs, such as muscle weakness, wasting, and fasciculations in the muscles supplied by the anterior horn cells.

Other symptoms of intramedullary cord tumors are papilledema, hydrocephalus, and elevations in ICP. The reason for development of papilledema is unclear, but it is more common with tumors of the thoracic and lumbosacral regions. Box 30-5 lists signs and symptoms of spinal cord tumors.

MEDICAL MANAGEMENT

DIAGNOSIS. After a history and neurologic examination, MRI is the method of choice for the identification of spinal cord tumors. Gadolinium-enhanced MRI is helpful to differentiate between edema and tumor. Occasionally plain films may be helpful in treatment planning. Lumbar puncture and CSF examination are no longer used as diagnostic tools.

TREATMENT AND PROGNOSIS. Surgery is the principal treatment for all primary intraspinal tumors. Complete and curative resection is the objective. Extramedullary tumors can be cured in most cases. Radiation therapy is not required when lesions are completely excised. Intraspinal astrocytomas have a lower rate of cure, although surgery and radiation may prolong the disease-free survival. Childhood astrocytomas, however, have a more favorable prognosis, with a 5-year survival rate of 90%.

Box 30-4

SPINAL TUMORS

Extradural

- Metastasis
- Primary bone tumors arising in the spine

Intradural and Extramedullary

- Meningiomas
- Neurofibromas
- Neurinomas (schwannomas)
- Lipomas
- Arachnoid cysts
- Epidermoid cysts
- Metastasis

Intramedullary

- Ependymoma
- Glioma
- Hemangioblastoma
- Lipoma
- Metastasis

From DeAngelis LM: Tumors of the central nervous system. In Goldman LM, Ausiello D, eds: *Cecil textbook of medicine*, ed 22, Philadelphia, 2004, Saunders.

SPECIAL IMPLICATIONS FOR THE THERAPIST

30-2

Primary Intraspinal Tumors

PREFERRED PRACTICE PATTERNS

4F: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion, and Reflex Integrity Associated with Spinal Disorders

Continued.

Box 30-5**SIGNS AND SYMPTOMS OF SPINAL CORD TUMORS**

- Pain
- Weakness
- Sensory changes
- Urinary frequency
- Urinary urgency
- Sphincter disturbances
- Syringomyelia-like symptoms
- Brown-Séquard syndrome-like symptoms
- Hydrocephalus
- Increased intracranial pressure
- Papilledema
- Atrophy
- Hyporeflexia
- Spasticity
- Hyperreflexia
- Gait disturbances
- Sexual dysfunction

5E: Impaired Motor Function and Sensory Integrity Associated with Progressive Disorders of the Central Nervous System

5H: Impaired Motor Function, Peripheral Nerve Integrity, and Sensory Integrity Associated with Nonprogressive Disorders of the Spinal Cord

6B: Impaired Aerobic Capacity/Endurance Associated with Deconditioning

6E: Impaired Ventilation and Respiration/Gas Exchange Associated with Ventilatory Pump Dysfunction or Failure

Alertness to Signs and Symptoms

As specialists in motor function, therapists may be involved even before a diagnosis of cancer has been made in observing and identifying the signs of spinal cord tumors. Clients referred to physical therapy because of back pain symptoms who have intractable pain that worsens with recumbency and is not relieved by physical therapy should raise the suspicion of an intraspinal tumor. Progressive neurologic signs should alert the therapist to the need for medical referral. A thorough initial examination and evaluation of any person with back pain, including symptoms, pain patterns, strength assessment, and other neurologic signs such as impaired bowel and bladder function, changes in deep tendon reflexes, and signs of spasticity, should be the standard of practice to rule out tumors and other systemic disorders.

Rehabilitation Referrals

Neurologic deficits from primary spinal cord tumors may result in impairments such as spinal pain, weakness in the extremities and trunk, sensory loss, bowel and bladder dysfunction, spinal instability, and impaired aerobic capacity. Bed mobility limitations, difficulties with transfers in and out of bed, knowledge deficit regarding spinal safety, ambulation limitations, decreased self-care, equipment issues, and difficulties in returning to work, community activities, and leisure

activities all require rehabilitation therapy. Because of a favorable prognosis with completely excised primary tumors, the approach of the therapist should be toward achieving maximal function and support of the client and family toward long-term goals. Medical management, including surgery (resections, kyphoplasty, fusions), chemotherapy, and radiation therapy, causes complications over a prolonged time period that require rehabilitation intervention at numerous time points during recovery.

Knowledge Needed for Rehabilitation

As with primary brain tumors, therapists should know the medical management plan, the prognostic expectations, the side effects of treatment, and precautions to prepare for the rehabilitative approach to a client with an intraspinal tumor. Knowledge of the most common intraspinal tumors, their patterns of growth, and neurologic changes assists the therapist in assessing the patient accurately, setting goals, and providing intervention.

Rehabilitation Evaluation

A thorough examination of the neurologic and musculoskeletal systems is very important to identify impairments that affect function. For example, an anterior tibialis muscle weakness or a lower extremity paraparesis may be the impairment that limits mobility and transfers and may be amenable to therapy. The therapist should review medical records, laboratory and radiologic reports, and other studies. If the treatment is provided on an outpatient basis, blood value determinations should be requested to assist the therapist in planning exercise programs. Communicating with the oncologist, the surgeon, and nurse; keeping abreast of imaging reports and other diagnostic tests; and being alert to other medical management, such as the effect of steroids and chemotherapy, allow the therapist to be more effective in treatment. Postoperative precautions may include protection from spinal torsion and use of an external support. Protection of irradiated skin follows the same guidelines as given under Primary Brain Tumors.

METASTATIC TUMORS

The extended survival in all types of cancer has allowed time for metastasis to occur from primary tumors elsewhere in the body. Metastatic complications are an escalating problem. Metastases to the brain and spinal cord are among the most serious complications of metastatic cancer.^{15,126}

Incidence

The incidence of metastatic CNS tumors is estimated to be 150,000 to 180,000 per year, although exact figures are difficult to ascertain.^{3,104} The number of metastatic brain tumors is estimated to be 100,000 per year, and the number of metastatic spinal cord tumors is estimated to be about 80,000 per year.³ Metastatic tumors are the most

common intracranial tumor in adults.¹³⁵ The incidence of metastatic CNS tumors is on the rise as a result of improved life expectancies from advances in cancer treatment, allowing micrometastases time to develop in the spinal cord and brain. Here they find a safe haven behind the blood-brain barrier through which many chemotherapeutic agents for the primary cancer cannot pass. The blood-brain barrier restricts passage of high-molecular-weight compounds through its tight capillary endothelial junctions.¹⁰⁰ The brain is a metastatic site in about 20% of people with primary cancer elsewhere, and the spinal cord is a metastatic site for 10% of primary cancers.¹²⁶

Pathogenesis*

Metastatic tumors reach the brain generally through the arterial blood system. A smaller number arise by direct extension from extracranial sites such as the neck or paranasal sinuses. The cascade of events for formation of a metastasis includes tumor cells at the primary site reaching a critical volume in proximity to a blood vessel, dislodging from the primary tumor and entering blood vessels, embolizing, traveling, extravasating from the blood vessel, and growing in parenchyma of another organs.^{39,15} Most metastatic tumors arise in the distribution area of the middle cerebral artery to the cerebral hemispheres, with most lesions located in the parietal or frontal lobes. About 20% are found in the posterior fossa, primarily the cerebellum. About half of cases include multiple metastatic lesions in the brain (Fig. 30-24).

Metastatic tumors reach the spine and spinal cord through direct arterial dissemination to the vertebral body, by retrograde spread via the vertebral venous plexus as it perforates into the epidural space and vertebral bodies, or by direct invasion from a paravertebral tumor to the epidural space via the intervertebral foramen. The majority of spinal metastases are extradural-extramedullary, although in less than 5% of cases the location is intramedullary. The thoracic spine is the most frequent site of metastasis (70%), followed by the lumbosacral spine (20%) and the cervical area (10%).¹²⁶

The most common cancers resulting in brain metastases are lung cancers, especially small cell carcinoma; cancers of the breast, kidney, and gastrointestinal tract; and melanoma. Fig. 30-25 shows dural metastasis from breast cancer. The most common cancers metastasizing to the spinal column are lung, breast, prostate, and kidney cancers and lymphomas. In about 10% of cases, the primary tumor is never found.

Clinical Manifestations of Brain Metastasis

Metastatic brain tumors present with headache, seizures, elevated ICP, and similar signs of primary tumors. See Table 30-7 for a more complete listing. However, symptoms may progress much more rapidly, often in days to weeks, as a result of the significant edema that accompanies a metastasis. Cerebellar metastases may cause obstructive hydrocephalus and abrupt deterioration.

MEDICAL MANAGEMENT

DIAGNOSIS, TREATMENT, AND PROGNOSIS. MRI is the diagnostic procedure of choice because it is the most

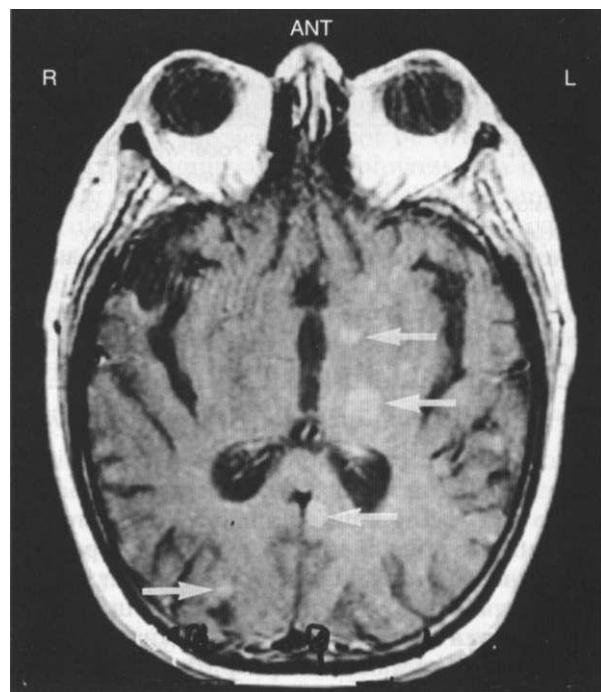


Figure 30-24

Metastatic disease to the brain. A gadolinium-enhanced T1-weighted magnetic resonance image shows multiple metastases as areas of increased signal (arrows). (From Mettler FA Jr: *Essentials of radiology*, ed 2, Philadelphia, 2005, Saunders.)

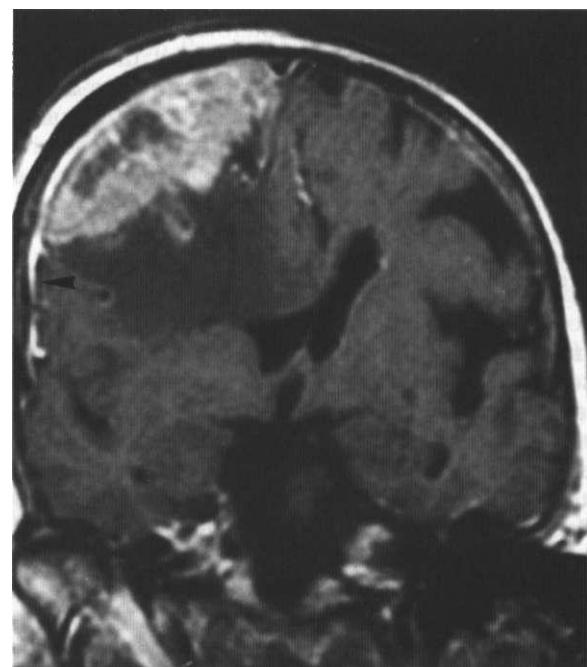


Figure 30-25

Dural metastasis from breast carcinoma. Coronal T1-weighted postcontrast magnetic resonance image. There is a heterogeneously enhancing mass with an irregular surface that arises from the dura over the right cerebral convexity. It displaces the underlying brain and causes considerable low-signal edema within it. There is a dural "tail" extending away from the tumor (arrowhead). (From Grainger and Allison's *Diagnostic radiology: a textbook of medical imaging*, ed 4, Philadelphia, 2001, Churchill Livingstone.)

Table 30-7 Presenting Symptoms and Signs of Brain Metastasis

Symptom	Common Signs
Headache	Focal weakness or unexplained falls
Mental status change	Focal sensory deficits
Altered level of consciousness	Speech difficulty
Seizures occurring when older than 35 yr of age	Aphasia, focal weakness
Papilledema or visual obscurations	Ataxia
Visual complaints or unexplained motor vehicle accidents	Visual field defect

From Goetz CG: *Textbook of clinical neurology*, ed 2, Philadelphia, 2003, Saunders, chap 47.

sensitive in revealing multiple small lesions. A review of the chest film is often enough to give a presumptive diagnosis of lung cancer. With a history of cancer elsewhere in the body, a solitary brain lesion has about a 90% certainty of being a metastatic deposit.¹²⁶ Because meningiomas have a high prevalence in people with breast cancer, metastatic breast lesions in the brain must be differentiated pathologically from meningiomas for optimal treatment.

Medical management includes corticosteroids, surgical excision when solitary or small numbers of metastases are accessible, and irradiation in almost all cases. Of solitary brain metastases associated with non-small cell lung cancer, up to one third may be cured with surgery followed by radiation therapy. Steroids have a dramatic effect in relieving symptoms caused by the significant peritumoral swelling. Radiotherapy provides adequate palliation for many people, because death occurs from the primary cancer, not the brain metastasis.⁶¹

In general, the prognosis for people with brain metastasis is poor, because the metastasis indicates that the primary cancer has already escaped control.

Clinical Manifestations of Spinal Metastasis

Back pain is the most common and prominent symptom of metastasis to the spinal column and cord, and is present in 95% of cases. Anyone with a known cancer history who presents with new-onset back pain of unknown etiology should be considered to have spinal metastasis until proved otherwise.¹²⁶ Pain is due to stretching of the periosteum, tension or traction on the spinal nerve roots and cord, or compression of the cord and meninges. It is usually a dull ache, worse at night in the recumbent position, and may be local in the spine or may be a radicular pain.

Without treatment, pain progresses in weeks or months (sometimes days) to weakness, sensory loss, and bowel and bladder sphincter disturbance. These tumors characteristically progress quickly after onset of weakness to cause paraplegia and permanent loss of sphincter control. Diagnosing and treating the metastasis early is important, because people treated while still ambulatory are likely to remain so, but those who have reached the stage of paraplegia and sphincter loss do not typically regain function.

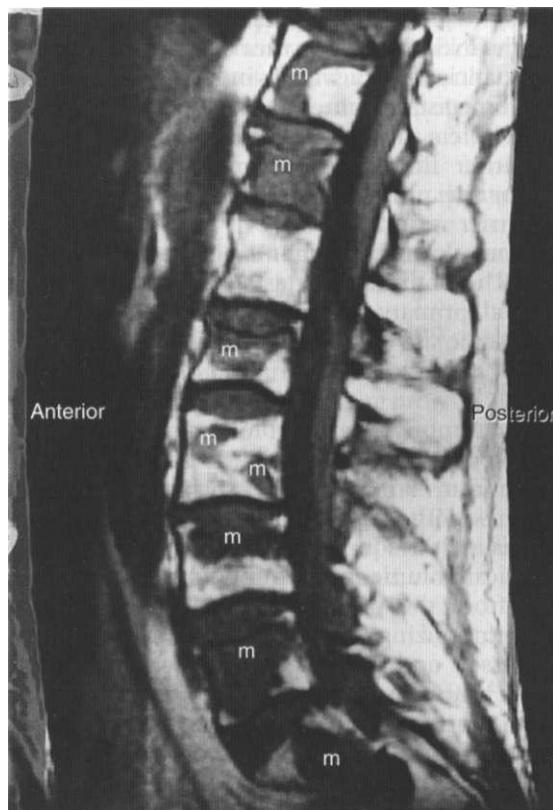


Figure 30-26

Focal spine metastases. A sagittal or lateral T1-weighted magnetic resonance image of the lumbar spine shows the normal white or high signal in fat within the bone marrow. In many of the vertebral bodies, the high signal of normal marrow has been replaced by dark areas of metastatic deposits (*m*). [From Mettler FA Jr: *Essentials of radiology*, ed 2, Philadelphia, 2005, Saunders.]

MEDICAL MANAGEMENT

DIAGNOSIS. A careful neurologic examination, followed by plain films of the spine, is an important first approach and results in a diagnosis in the majority of cases. The most common findings are pedicular erosion, vertebral collapse, pathologic fracture-dislocation, and a soft tissue shadow suggestive of a paraspinal mass.¹²⁶ Bone scans are the next test of choice. If results of any of these tests are positive, MRI or CT is then done for more definitive imaging of the lesion. Fig. 30-26 is an MRI showing focal spine metastases.

TREATMENT. Radiotherapy is typically the treatment of choice for spinal metastasis to reduce pain, reduce tumor compression, and restore neurologic function. Radiotherapy and/or chemotherapy is also helpful in preserving spinal stability. For those tumors that are chemotherapy sensitive, urgent management with chemotherapy is indicated to preserve spinal integrity.

Surgery is reserved for people with a worsening neurologic deficit during radiation therapy, for those with a spinal instability causing cord compression, for tumors known to be radioresistant, and for individuals who already have received the maximum radiation.

It should be noted that past attempts at surgical decompression with laminectomy have proved to be disappointing, with neurologic improvement occurring in only 30% of cases.¹²⁶ Surgical access via laminectomy to the typically anterior tumors compressing the cord from a ventral direction is technically difficult. Evidence exists that very high doses of corticosteroids relieve local spinal edema. Current practice is to begin very large doses of corticosteroids as soon as a spinal cord compression from metastatic tumor is diagnosed. This dose is continued for several days, then reduced, allowing time for decisions to be made for radiation or surgery.¹³⁹

PROGNOSIS. Prognosis for return of neurologic function is based on the degree of loss before radiotherapy. With radiotherapy, 80% of clients who are ambulatory at the time of treatment remain so, and 30% who are nonambulatory regain gait.¹²⁶ Pain and neurologic function improve in a large percentage of people. Because the metastasis indicates loss of containment of the primary tumor, cure is beyond expectation. However, early diagnosis and treatment lead to the optimal result, the prevention of paraplegia.

Radiation to the spinal cord may cause complications of myelopathy. Although radiation has no acute effects on the cord, an early delayed radiation myelopathy after irradiation of the neck is common. Lhermitte's sign (a sudden electric shock sensation brought on by neck flexion), the hallmark of this radiation myelopathy, is present for several months and then abates. It is not a predictor of late delayed radiation spinal cord injury.³⁴ A late effect of radiation to the cord, occurring between 6 and 36 months after radiation, is a chronic progressive myelopathy that begins as a Brown-Squard syndrome and progresses over weeks or months to a spastic paresis. No effective medical treatment exists, but the therapist can provide mobility management, skin precautions, and safety education for these clients.

SPECIAL IMPLICATIONS FOR THE THERAPIST 30-3

Primary Intradural Tumors

Rehabilitation Referrals

Neurologic deficits resulting from metastatic CNS tumors in the brain or spinal cord often require physical and occupational therapy. The neurologic impairments from either intracranial or intraspinal tumors may include weakness, paralysis, decreased sensation, and pain leading to loss of mobility and self-care skills. Paraplegia from spinal metastasis requires much rehabilitative intervention. The incidence of metastatic CNS tumors is increasing.

Prediagnosis Alertness to Signs and Symptoms

Because therapists are often in a position to observe the mobility and neurologic status of clients before a diagnosis of a CNS metastasis is made, being alert to abnormal neurologic signs in anyone with a cancer history is vital. In someone with a cancer history, any

signs of intracranial metastasis, such as visual symptoms or mental status changes, should be reported immediately to the physician. Knowing the signs and symptoms of an intraspinal metastasis and immediate referral to the physician cannot be overemphasized. Spinal cord compression can progress in a matter of hours or days to paraplegia. Spinal pain complaints, particularly in the thoracic spine, and/or progressive strength changes, sensory changes, and/or bowel or bladder function changes in a patient with a cancer history are red flags. A therapist who refers the patient to the physician in time may prevent irreversible paraplegia and sphincter function loss.

Knowledge Needed for Rehabilitation

As with primary CNS tumors, therapists need to know the medical management plan, the prognostic expectations, and the hematologic guidelines for exercise. Goal setting needs to be realistic for noncurable disease, yet not without hope for good management.¹⁷ Families and caregivers may need to have an even greater role in goal setting and training. As with primary brain tumors, the psychosocial implications have a profound impact on the client and family, and the therapist can provide support and even be a sounding board for decision making. It is helpful to realize that in some cases, paraplegia from a metastatic spinal cord tumor may respond to irradiation and improve enough for some return of function, such as limited ambulation. The physical therapists must be alert to any neurologic improvement.

Rehabilitation Precautions

As with primary CNS tumors, clients and their families must have an awareness of the side effects of the various treatment modalities. Postoperative acute care precautions are discussed under Primary Brain Tumors. A general knowledge of metastatic spread and behavior is helpful.^{7,81} Myelosuppression, fatigue, nausea, and precautions need to be understood. Avoiding modalities such as heat or cold or any topical agents over skin being irradiated is important for skin protection, because poor circulation inhibits normal heat and cold dissipation. Once the irradiation sessions are completed and the skin has healed, and depending on skin integrity and adequate circulation, modalities such as heat or cold or transcutaneous nerve stimulation (TNS) may be used. Although ultrasound is not usually recommended for pain management because of concerns about tumor growth, its use for palliation of pain in end-stage disease may be allowed.

PARANEOPLASTIC SYNDROMES

Cancer may cause effects on the nervous system that are not directly related to the primary tumor mass or a metastasis. These so-called *remote effects*, or paraneoplastic syndromes (see Chapter 9), include such problems as paraneoplastic cerebellar degeneration, brainstem encephalitis, myelitis of the spinal cord, and motor

neuron disease.⁴² Paraneoplastic syndromes are also termed paraneoplastic neurologic disorders or PNDs. The cause of most paraneoplastic syndromes is unknown, although an immune mechanism is the most likely hypothesis. The response of the immune system to the antigen may be misdirected and cause neurologic dysfunction. Paraneoplastic syndromes may be the first sign of the presence of cancer.^{12,99,108}

Although paraneoplastic syndromes involving the CNS are rare, they are often severe, often associated with an inflammatory CSF, and leave the person with severe neurologic disability. Treatment effectiveness has been limited. Some syndromes are associated with particular tumors, such as paraneoplastic cerebellar degeneration with lung cancer. In this syndrome, the early symptoms are a slight incoordination in walking, with progressive gait ataxia; incoordination of arms, legs, and trunk; dysarthria; and often nystagmus. After a few months the illness reaches its peak and stabilizes. By this time, most clients must have assistance to walk, handwriting is impossible, many cannot sit unsupported, and speech is with great effort.

It is not within the scope of this chapter to elaborate on CNS paraneoplastic syndromes. However, it is helpful for the therapist to have an acquaintance with these syndromes, because they appear in the practice of caring for people with CNS neoplasms.¹⁵

LEPTOMENINGEAL CARCINOMATOSIS

Infiltration of the meninges and CSF pathways of the CNS by neoplastic cells is a less common complication of cancer and is known as *leptomeningeal carcinomatosis* or *neoplastic meningitis*. This metastatic seeding of the meninges is widespread and multifocal. Neurologic signs depend on location. Brain symptoms may include headache, change in mental status, seizures, double vision, abducens palsy, and hemiparesis; spinal symptoms include radicular pain, numbness, and weakness.¹⁰¹ Meningeal carcinomatosis occurs in approximately 5% of patients with cancer but is being diagnosed with increasing frequency as patients live longer and as neuroimaging studies improve.^{48,99} Cancers of the breast and lung, non-Hodgkin's lymphoma, melanomas, and adult acute leukemias are the most common primary tumors responsible for carcinomatosis. Diagnosis is by CSF studies, which show malignant cells in most cases. MRI is also done to assess bulky disease in the brain or spine. Current therapy includes radiotherapy to symptomatic sites, with concurrent intrathecal chemotherapy.¹²⁶ Survival is measured in months from treatment.

PEDIATRIC TUMORS

Incidence and Pathogenesis

Approximately 2200 primary brain tumors are diagnosed in children and adolescents each year.⁶⁸ The incidence of primary brain and nervous system tumors peaks in the

pediatric population from age 0 to 6, drops at age 7 to 10, remains steady until age 18, then drops. In infants and young children, intracranial tumors are the second most common form of cancer, after leukemia.¹²⁶ The peak incidence of these tumors occurs between birth and age 6 years. Brain tumors are the second leading cause of cancer-related deaths in children below the age of 15. Refer back to Table 30-2 for a comparison of the frequency of childhood tumors compared with adult tumors.

The etiology of pediatric brain tumors is little understood. Cranial exposure to radiation and possible evidence of a heritable syndrome are causes. Other factors being studied include maternal diet and intake of vitamins during pregnancy.

The most frequently encountered types of intracranial tumors in children are the astrocytoma, medulloblastoma, ependymoma, and brainstem glioma.⁴⁵ Brain tumors in children are typically located infratentorially, primarily in the cerebellum and brainstem, although they may occur at any location. See Fig. 30-27 for relative frequency and location.

Astrocytomas are the most common type of pediatric intracranial tumor, accounting for about 47% of all brain tumors in children. They are usually well-differentiated grade I tumors. About half of them occur supratentorially, most commonly in the frontal lobes, but also in the temporal and parietal lobes. The cerebellum is the most common infratentorial site of the astrocytoma in children. Cerebellar astrocytoma is more common in males and usually occurs in the first two decades of life, with the median incidence at age 18. Children with grade I astrocytomas have a 10-year postoperative survival rate of 85%.⁴⁵ Infrequently high-grade astrocytomas occur, with a poorer prognosis.

Medulloblastomas account for 20% to 25% of childhood brain tumors and are the most common malignant tumor in children. These aggressive tumors are most common in males and have a peak incidence at age 5 years in children. Evolution of therapeutic strategies including multimodal chemotherapy followed by surgery has dramatically improved the outlook for children with medulloblastomas.¹²⁶ Medulloblastomas belong to the group of tumors known as *primitive neuroectodermal tumors (PNETs)* and arise in the fourth ventricle. Medulloblastomas have a predilection for meningeal seeding. The 5-year survival rate is about 50%.

Ependymomas usually arise in children from the floor of the fourth ventricle and make up 9% to 20% of childhood tumors. The 5-year survival is 85% when complete resection is possible and about 45% overall.

Brainstem gliomas may be of several tumor types; the most common is astrocytoma, but they also may be glioblastomas or ependymomas. The overall prognosis for brainstem tumors is relatively poor, but occasionally gratifying treatment results are obtained.¹²⁶

Clinical Manifestations

Clinical manifestations of CNS neoplasms in children are more difficult to evaluate because children are less able to relate and report symptoms. Parents, teachers, and caretakers may notice problems before the child is aware