NEUROPATHOLOGY

Saccular (Berry) aneurysm (Fig. 14-8)
Rupture of a saccular aneurysm can occur at any time, but in one-third of the cases it is associated with acute increases in intracranial pressure, e.g. straining at stool or sexual orgasm. Blood under arterial pressure is forced into the subarachnoid space, and individuals suffer a sudden, severe headache and rapidly lose consciousness. Up to 50% of individuals die with the first rupture. Recurring bleeding is common in survivors. The prognosis worsens with each episode of bleeding.

About 90% of saccular aneurysms occur in the anterior circulation near major arterial branch points; multiple aneurysms exist in up to 30% of cases. They are not present at birth but develop over time because of underlying defects in the vessel media. The probability of rupture increases with the size of the lesion, such that aneurysms greater than 1.0 cm have a roughly 50% risk of bleeding per year. With the occurrence of a subarachnoid hemorrhage, there is an additional risk of ischemic brain injury from vasospasm involving nearby vessels. Healing of subarachnoid hemorrhage may be associated with meningeal fibrosis and scarring, sometimes leading to obstruction of CSF flow as well as interruption of the normal pathways of CSF resorption i.e. hydrocephalus.

Gross features
- An unruptured saccular aneurysm is outpouching of an artery.
- It may measure up to 3 cm in diameter and has a bright red, thin, translucent wall.
- Rupture usually occurs at the apex of the sac with extravasation of blood into the subarachnoid space and/or the substance of the brain.

Microscopic features
- The muscular wall and intimal elastic lamina are absent from the aneurysm sac itself.
- The sac is made up of thickened hyalinized intima covered by the adventitia.

While saccular aneurysms are the most common type of intracranial aneurysm, other types include atherosclerotic (fusiform) (mostly of the basilar artery), mycotic, traumatic, and dissecting aneurysms. These latter three, as with saccular aneurysms, are most often found in the anterior circulation. They usually present with cerebral infarction from vascular occlusion instead of subarachnoid hemorrhage.

INFECTIONS OF THE NERVOUS SYSTEM
An infectious agent must use one of several routes of entry to reach the CNS & cause a disease.

1. Hematogenous spread via the arterial blood supply is the most common mode of entry. There can also be retrograde venous spread, through the anastomoses between veins of the face and the venous sinuses of the skull.
2. Direct implantation of microorganisms is almost invariably post-traumatic, with introduction of foreign material.
3. Local extension from an established infection in the skull or the bony spine can occur. The infection may originate from
   a. air sinus, most often the mastoid or frontal
   b. infected tooth
   c. surgical operation on the cranium or spine causing osteomyelitis
   d. congenital malformation, such as meningomyelocele.
4. Peripheral nerves can also serve as the path of entry for rabies and herpes zoster.
Epidural and Subdural Infections
These spaces can be involved with bacterial or fungal infections, usually as a consequence of direct local spread. **Epidural abscess**, commonly associated with osteomyelitis, arises from an adjacent focus of infection, such as sinusitis or a surgical procedure. When the process occurs in the spinal epidural space, it may cause spinal cord compression and constitute a neurosurgical emergency. Infections of the skull or air sinuses may also spread to the subdural space, producing **subdural empyema**. A large subdural empyema may produce a mass effect. In addition, thrombophlebitis may develop in the bridging veins that cross the subdural space, resulting in venous occlusion and infarction of the brain.

Meningitis
This is an inflammatory process of the leptomeninges and CSF within the subarachnoid space. **Meningoencephalitis** develops with spread of the infection from the meninges into the underlying brain. Infectious meningitis is broadly classified into

1. **Acute pyogenic** (usually bacterial),
2. **Aseptic** (usually viral), and
3. **Chronic** (usually tuberculous, spirochetal, or cryptococcal)

**Acute Pyogenic Meningitis (Bacterial Meningitis) (Fig. 14-17)**
While a wide range of bacteria can cause acute pyogenic meningitis, there is a relationship between the age of a patient and the most likely organisms. In neonates, common organisms are *Escherichia coli* and the group B streptococci; at the other extreme of life, *Streptococcus pneumoniae* and *Listeria monocytogenes* are more common. Among adolescents and in young adults, *Neisseria meningitides* is the most common pathogen. Regardless of the organism, patients typically show systemic signs of infection superimposed on clinical evidence of meningeal irritation and neurologic impairment-including headache, photophobia, irritability, and neck stiffness. Lumbar puncture reveals an increased pressure, abundant neutrophils, elevated protein, and reduced glucose. Bacteria may be seen on a smear stained with Gram stain or can be cultured.

**Pathological features**
- In acute meningitis, an exudate is evident within the leptomeninges over the surface of the brain.
- The meningeal vessels are engorged and prominent.
- When the meningitis is fulminant, the inflammatory cells infiltrate the walls of the leptomeningeal veins and may spread into the substance of the brain (**focal cerebritis**), or the inflammation may extend to the ventricles.
- On microscopic examination, neutrophils fill the entire subarachnoid space in severely affected areas or may be found predominantly around the leptomeningeal blood vessels in less severe cases.

Bacterial meningitis may be associated with abscesses in the brain. Phlebitis may also lead to venous occlusion and hemorrhagic infarction of the underlying brain.

**Aseptic Meningitis (Viral Meningitis)**
The clinical course is less fulminant than in pyogenic meningitis & is usually self-limiting. *The CSF shows an increased number of lymphocytes, the protein elevation is only moderate, and glucose content is normal.* The most common offending agent is an enterovirus. (Fig. 14-18)
Chronic Meningitis

*Tuberculous Meningitis*
There is only a moderate increase in cellularity of the CSF made up of mononuclear cells, or a mixture of neutrophils and mononuclear cells; the protein level is elevated, often strikingly so, and the glucose content typically is moderately reduced or normal. Infection with *Mycobacterium tuberculosis* may also result in a well-circumscribed brain mass (*tuberculoma*), which may be associated with meningitis. Tuberculous meningitis is a cause of arachnoid fibrosis, which may produce hydrocephalus. The subarachnoid space contains a gelatinous or fibrinous exudate, most often at the base of the brain. There may be discrete white granules scattered over the leptomeninges. *Microscopically*, there are well-formed granulomas, often with caseous necrosis and giant cells. Similar findings are observed in tuberculomas within the brain.

Neurosyphilis
This is a tertiary stage of syphilis and occurs in only about 10% of individuals with untreated infection. One of the major manifestations is meningeal. As with other chronic infections, there can be parenchymal disease as well that eventuates in severe dementia. *Tabes dorsalis* is another form of neurosyphilis, resulting from damage to the sensory nerves in the dorsal roots producing impaired joint position sense and resultant ataxia (locomotor ataxia); loss of pain sensation, leading to skin and joint damage (Charcot joints); other sensory disturbances. *Individuals with HIV infection are at increased risk for neurosyphilis, and the rate of progression and severity of the disease seem to be accelerated.*

Parenchymal Infections

1. **Brain Abscesses** are nearly always caused by bacterial infections; these can arise by
   - *Direct implantation of organisms*
   - *Local extension from adjacent foci* (mastoiditis, paranasal sinusitis)
   - *Hematogenous spread* (usually from a primary site in the heart (bacterial endocarditis), lungs (abscess or bronchiectasis), or distal bones (osteomyelitis) or even after tooth extraction).

   Patients present clinically with progressive focal deficits with the general signs of raised intracranial pressure. The CSF white cell count and protein level are raised, but the glucose content is normal. The increased intracranial pressure and progressive herniation can be fatal, and abscess rupture can lead to ventriculitis, meningitis, and venous sinus thrombosis. *Grossly*, abscesses are discrete lesions with central liquefactive necrosis and a surrounding fibrous capsule (*Fig. 14-19*). *Microscopically*, there is exuberant neovascularization around the pus that is responsible for the marked edema and formation of granulation tissue.

2. **Viral Encephalitis and myelitis** (*Fig. 14-20*)
Viral encephalitis is a parenchymal infection of the brain that is almost invariably associated with meningeal inflammation (*meningoencephalitis*). *The most characteristic histologic features are perivascular and parenchymal mononuclear cell infiltrates*. Certain viruses may form inclusion bodies. The nervous system is particularly susceptible to viruses such as rabies and polio. Intrauterine viral infection may cause congenital malformations, as occurs with rubella.

*Herpes Simplex Virus Type 1* produces encephalitis mostly in children and young adults. Only some patients have prior oral herpetic lesions. There is a predilection for the lesions to occur in the frontal and temporal lobes. The infection is necrotizing and often hemorrhagic.

*Herpes Simplex Virus Type 2* usually manifests in adults as meningitis. Disseminated severe encephalitis occurs in many neonates born vaginally of women with active HSV genital infections.

*Varicella-Zoster Virus (Herpes Zoster)* causes chickenpox during its primary infection. The virus institutes a latent infection in neurons of dorsal root ganglia. Reactivation in adults
manifests as a painful, vesicular skin eruption in the distribution of one or a few dermatomes (shingles). In immunosuppressed patients, acute herpes zoster encephalitis can occur. 

**Cytomegalovirus** infects the nervous system in fetuses and immunosuppressed individuals. It is especially common in individuals with AIDS.

**Poliovirus** causes paralytic poliomyelitis. Infection with poliovirus mostly causes mild gastroenteritis; in a small fraction of cases it secondarily invades the nervous system and damages motor neurons in the spinal cord and brain stem. With loss of motor neurons, it produces a flaccid paralysis in the corresponding region of the body. In the acute disease, death can occur from paralysis of respiratory muscles.

**Rabies** is severe encephalitis transmitted to humans by the bite of a rabid animal. Virus enters the CNS by ascending along the peripheral nerves from the wound site.

**Human Immunodeficiency Virus (HIV)** can affect the CNS in three ways
1. Direct effects on the nervous system 
2. Predisposes for opportunistic infections 
3. Setting the stage for tumors 

Up to two-thirds of AIDS patients develop neurologic dysfunctions. Patterns of direct injury to the CNS include:
   a. Aseptic HIV-1 meningitis
   b. HIV-1 meningoencephalitis causing AIDS-dementia complex.
   c. Vacuolar myelopathy involving the tracts of the spinal cord can resemble subacute combined degeneration, although serum levels of vitamin B_{12} are normal.

**Progressive Multifocal Leukoencephalopathy (PML)** is caused by JC (Jacob Creutzfield) virus. The virus preferentially infects oligodendrocytes, so demyelination is its principal pathologic effect. The disease occurs mostly in immunosuppressed individuals in various clinical settings, including
1. Chronic lymphoproliferative or myeloproliferative illnesses
2. Immunosuppressive therapy
3. AIDS.

Most patients show serologic evidence of exposure to JC virus during childhood; it is believed that PML results from virus reactivation because of immunosuppression. Patients develop focal and progressive neurologic symptoms and signs. The lesions consist of irregular, ill-defined demyelination patches within the white matter that enlarge as the disease progresses. At the edge of the lesion are greatly enlarged oligodendrocyte nuclei whose chromatin is replaced by viral inclusion.

**3. Fungal Encephalitis**

*Candida albicans, Mucor, Aspergillus fumigatus, and Cryptococcus neoformans* are the most common fungi that can cause encephalitis, but in endemic areas, *Histoplasma capsulatum, and some other fungi* can also infect the CNS, especially in the setting of immunosuppression.

*Parenchymal granulomas or abscesses* can occur with most of the fungi and often coexists with meningitis. Although most fungi invade the brain by hematogenous dissemination, direct extension may also occur, particularly with *Mucor infections* of the nose & paranasal sinuses, most commonly in diabetics with ketoacidosis. *Aspergillus* tends to cause a distinctive pattern of widespread septic hemorrhagic infarctions because of its marked predilection for invasion of blood vessel walls and subsequent thrombosis.
4. Other Meningoencephalitides

*Cerebral Toxoplasmosis* is one of the most common causes of neurologic symptoms and morbidity in persons with AIDS. The brain shows multiple abscesses, most often involving the cerebral cortex and deep gray nuclei. Both free tachyzoites and encysted bradyzoites may be found at the periphery of the necrotic foci.

*Amebic meningoencephalitis* has different patterns of disease with different species of the parasite. *Naegleria* species, associated with swimming in nonflowing warm fresh water, causes rapidly fatal necrotizing encephalitis.

**Prion Diseases**

This group of diseases includes forms of Creutzfeldt-Jakob disease (CJD). Several animal diseases from this group are also known, including scrapie in sheep and goats and bovine spongiform encephalopathy in cattle ("mad cow" disease). All these disorders are associated with abnormal forms of a normal cellular protein, termed prion protein (PrP\(^\beta\)). The abnormal form of this protein can act as an infectious agent, since it propagates itself and injures the cells in which it is present. Most cases of prion disease are either sporadic or associated with mutations in the gene that encodes PrP\(^\beta\).

*Creutzfeldt - Jakob disease (CJD)* is a rare but well-characterized prion disease that manifests clinically as a rapidly progressive dementia. The disease has a peak incidence in the elderly 60 to 70 years of age. The clinical presentation is characterized by rapidly progressive dementia. The disease is uniformly fatal, with an average duration of only 7 months.

On microscopic examination, the pathognomonic finding is a spongiform transformation of the cerebral cortex and deep gray matter structures (caudate, putamen) (Fig. 14-21).

*Variant Creutzfeldt-Jakob Disease (vCJD)*

In 1995, cases with a CJD-like illness have been reported in the UK. The disease affected young adults with more slow progression of the neurologic features than in individuals with CJD. *Evidences indicate that this new disease is a consequence of exposure to the prion disease of cattle, bovine spongiform encephalopathy.* vCJD has a similar pathologic appearance to CJD i.e. spongiform change and absence of inflammation.

**TUMORS**

The incidence of CNS tumors is generally low; about 50% to 75% are primary, and the rest are metastatic. In children, they constitute 20% of all tumors with a predilection for the posterior fossa (in adults they are most tumors are supratentorial).

*Tumors of the nervous system differ from neoplasms elsewhere in the body*

1. *Low-grade lesions may diffusely infiltrate large areas* of the brain, thus associated with poor prognosis.
2. *The anatomic site of the tumor can affect the prognosis*
   a. *it may have lethal consequences* irrespective of the histopathologic type; for example, a benign meningioma, by compressing the medulla, can cause cardiorespiratory arrest.
   b. through influencing the extent of respectability.
3. *Even the most highly malignant gliomas rarely metastasize outside the CNS*, however, the subarachnoid space does provide a pathway for spread so that seeding along the brain and spinal cord can occur.
GLIOMAS
Gliomas are tumors of the brain parenchyma that histologically resemble different types of glial cells. The major types of gliomas are astrocytomas, oligodendrogliomas, and ependymomas.

1. Astrocytomas: the most common of these are fibrillary and pilocytic astrocytomas.
   Fibrillary Astrocytoma account for 80% of adult primary brain tumors. They are most frequent in the ages of 30 to 60 years. Their usual location is the cerebral hemispheres. They show a spectrum of histologic differentiation that correlates well with clinical course and outcome. Based on the degree of differentiation, they are classified into three groups:
   a. Astrocytoma (infiltrating astrocytoma) (WHO grade II)
   b. Anaplastic astrocytoma (WHO grade III)
   c. Glioblastoma multiforme (WHO grade IV)
For well-differentiated astrocytomas, which are slow growing, the mean survival is more than 5 years. Eventually, however, a more rapid growth occurs due to the appearance of anaplastic features. However, many patients present with glioblastoma from the outset. The prognosis of glioblastoma is very poor (mean survival 8 to 10 months despite treatment).

Gross features
- Low-grade (infiltrating) astrocytoma is a poorly defined, gray, & infiltrative mass lesion that leads to expansion and distortion of the affected regions of the brain. (Fig. 14-22). The cut surface of the tumor is either firm, or soft and gelatinous; cystic degeneration may be seen.
- In glioblastoma, variation in the gross appearance of the tumor from region to region is characteristic. Some areas are firm and white, others are soft and yellow (the result of tissue necrosis), and yet others show regions of cystic degeneration and hemorrhage. (Fig. 14-23).

Microscopic features
- Low-grade (infiltrating) astrocytomas are characterized by a mild to moderate increase in the number of glial cells, slight nuclear pleomorphism, and an intervening feltwork of fine, GFAP-positive astrocytic cell processes that give the background a fibrillary appearance.
- The tumor cells can be seen infiltrating surrounding normal tissue for some distance from the main lesion.
- Anaplastic astrocytomas are more densely cellular with greater nuclear pleomorphism; increased mitoses are often observed.
- Glioblastoma, have a histologic appearance similar to anaplastic astrocytoma with additional features of necrosis surrounded by pseudo-palisaded nuclei &/or prominent vascular endothelial cell proliferation.

Pilocytic Astrocytoma (WHO grade I) is a relatively benign tumor, often cystic, that typically occur in children and young adults and are usually located in the cerebellum. In the cystic variant, there is usually a mural nodule in the wall of the cyst. The tumor is composed of areas with bipolar cells with long, thin "hair-like" processes that are GFAP positive. Rosenthal fibers, eosinophilic granular bodies, and microcysts are often present. Necrosis and mitoses are absent. (Fig. 14-24)

2. Oligodendrogliomas are most common in the 30 to 50 years of age. It is mostly located in the white matter of cerebral hemispheres. The prognosis is generally better than that of astrocytoma.
Oligodendrogliomas are infiltrative gelatinous, gray tumors. Microscopically, the tumor is composed of sheets of regular cells with spherical vesicular nuclei surrounded by a clear halo of cytoplasm. It typically contains a delicate network of anastomosing capillaries (chicken wire– type vasculature). Calcifications are frequently present; these range from microscopic foci to massive depositions. (Fig. 14-25) The current WHO classification grades
oligodendrogliomas into 2 different categories as WHO grade 2 and anaplastic WHO grade 3. Prominent mitotic activity and microvascular/endothelial proliferation are the 2 features that define anaplastic tumors.

3. Ependymoma most often arises next to the ependyma-lined ventricular system, including the central canal of the spinal cord. In the first two decades of life, they typically occur near the fourth ventricle. In adults, the spinal cord is their most common location. Because ependymomas usually grow within the ventricles, CSF dissemination is a common occurrence. In the fourth ventricle, ependymomas are typically solid or papillary masses projecting from the floor of the ventricle. These tumors are composed of cells with regular, round to oval nuclei. Between the nuclei there is a fibrillary background. Tumor cells may form round or elongated structures (rosettes) with long, delicate processes extending into a lumen; more frequently present are perivascular pseudo-rosettes in which tumor cells are arranged around vessels with an intervening zone consisting of thin ependymal processes. (Fig. 14-26)

NEURONAL TUMORS

Central neurocytoma is a low-grade neuronal neoplasm that is typically but not exclusively a periventricular lesion i.e., found within and adjacent to the ventricular system (most commonly the lateral or third ventricles). It is characterized by evenly spaced, round, uniform nuclei and often islands of neuropil.

Gangliogliomas are tumors with a mixture of glial elements (looking like a low-grade astrocytoma) and mature-appearing neurons. Most of these tumors are slow growing.

Medulloblastoma occurs predominantly in children and exclusively in the cerebellum. This highly malignant tumor is radiosensitive but without treatment the prognosis is poor. In children the tumor is located typically in the midline of the cerebellum. It is often well circumscribed, gray, and friable. Medulloblastomas are extremely cellular, with sheets of undifferentiated small cells with little cytoplasm and hyperchromatic nuclei; mitoses are abundant. Some tumors show differentiation along neuronal lines in the form of Homer Wright rosettes. The latter consist of tumor cell nuclei disposed in circular fashion about tangled cytoplasmic processes. (Fig. 14-27)

OTHER PARENCHYMAL TUMORS

Primary Central Nervous System Lymphoma are rare but are the most common CNS neoplasm in immunosuppressed individuals (including transplant recipients and persons with AIDS); under these circumstances the CNS lymphomas are nearly all driven by Epstein-Barr virus. Most of these tumors are diffuse large B-cell lymphomas.

Germ-Cell Tumors occur along the midline, most commonly in the pineal and the suprasellar regions. They are a tumor of the young, with 90% occurring during the first two decades. Germ-cell tumors in the pineal region show a strong male predominance. The histologic classification of brain germ-cell tumors is similar to that used in the testis, but the CNS equivalent of testicular seminoma is called a germinoma. It should be noted, however, that CNS involvement by a gonadal germ-cell tumor is not uncommon.

MENINGIOMAS

These predominantly benign tumors of adults arise from the meningotheial cell of the arachnoid & are usually attached to the dura. Meningiomas may be found along any of the external surfaces of the brain as well as within the ventricular system, where they arise from the stromal arachnoid cells of the choroid plexus. They cause symptoms through compression of underlying brain. Multiple meningiomas, especially in association with eighth nerve schwannomas or glial tumors, may be a part of neurofibromatosis type 2 (NF2). About half of meningiomas not associated with NF2 still have mutations in the NF2 gene.
**Gross features (Fig. 14-28)**
- They are well-defined dural-based masses that compress underlying brain but are easily separated from it.
- On sectioning most meningiomas are grayish-tan and soft. Collagenized examples, however, have rubbery texture and whorled or trabeculated cut surface.
- Calcification may impart a gritty sensation on cutting.
- Extension into the overlying bone may be present.

**Microscopic features (Fig. 14-28 B)**
- There are many histologic patterns of meningiomas, including
  1. **Syncytial**, showing whorled clusters of tight groups of cells without visible cell membranes
  2. **Fibroblastic**, with elongated cells and abundant collagen deposition between them
  3. **Transitional**, which shares features of the syncytial and fibroblastic types
  4. **Psammomatous**, with numerous psammoma bodies (NB: psammoma bodies may also occur in the above variants but less heavily).

**Atypical meningiomas** show a higher rate of recurrence, more aggressive local growth. They are recognized by several histologic features including a higher mitotic rate.

**Anaplastic (malignant) meningiomas** are highly aggressive tumors that resemble a high-grade sarcoma.

Although most meningiomas are easily separable from underlying brain, some tumors infiltrate the brain. The presence of brain invasion is associated with increased risk of recurrence.

**METASTATIC TUMORS**
Metastatic lesions, mostly carcinomas, account for 25% to 50% of intracranial tumors. The **five most common primary sites are**
1. Lung  4. Kidney
2. Breast  5. GIT
3. Skin (melanoma)

The meninges are also a frequent site of involvement by metastatic disease. In the brain, metastases form sharply demarcated masses, often at the gray matter-white matter junction, usually surrounded by a zone of edema. The boundary between tumor and brain parenchyma is well defined microscopically as well, with surrounding reactive gliosis. (Fig. 14-29)

In addition to the direct and localized effects produced by metastases, **paraneoplastic syndromes** may involve the peripheral and central nervous systems, sometimes even preceding the clinical recognition of the malignant neoplasm. **These syndromes are most commonly associated with small-cell carcinoma of the lung.** There are several manifestations of paraneoplastic syndromes; some characteristic patterns include: **Subacute cerebellar degeneration** resulting in ataxia, **Limbic encephalitis** causing a subacute dementia; the pathological changes are centered in the medial temporal lobe, and **Subacute sensory neuropathy** leading to altered pain sensation.
DISEASES OF THE PERIPHERAL NERVOUS SYSTEM

Neoplasms of the Peripheral Nervous System
These tumors arise from cells of the peripheral nerve, including Schwann cells, perineurial cells, and fibroblasts. In addition to arising along the peripheral course of nerve, these tumors can arise within the confines of the dura. When they do this, they may cause changes in adjacent brain or spinal cord.

Schwannomas are benign tumors arising from Schwann cells. Symptoms are referable to local compression of the involved nerve, or to compression of adjacent structures (such as brain stem or spinal cord). They are often encountered in the cerebellopontine angle, where they are attached to the vestibular branch of the eighth nerve. These patients often present with tinnitus and hearing loss, and the tumor is often referred to as an acoustic neuroma. Elsewhere within the dura, sensory nerves are preferentially involved, including branches of the trigeminal nerve and dorsal roots. When extradural, schwannomas are most commonly found in association with large nerve trunks. Sporadic schwannomas are associated with mutations in the NF2 gene on chromosome 22.

Gross features (Fig. 14-35).
- These tumors are well-circumscribed encapsulated masses that are attached to the nerve.
- They form firm, gray masses sometimes with cystic change.

Microscopically
- There is a mixture of two growth patterns. In the Antoni A pattern of growth, elongated cells are arranged in fascicles with their nuclei palisade along "nuclear-free zones" forming Verocay bodies.
- In the Antoni B pattern of growth, the tumor is less densely cellular with a loose meshwork of cells along with microcysts and myxoid changes.
- In both areas, the cytology of the individual cells is similar, with elongated cell cytoplasm and regular oval nuclei.

Neurofibroma
Solitary neurofibromas are mostly cutaneous or involving a peripheral nerve. These arise sporadically or in association with type 1 neurofibromatosis (NF1). The skin lesions are evident as nodules, sometimes with overlying hyperpigmentation; they may grow to be large and become pedunculated. The risk of malignant transformation from these tumors is extremely small, and cosmetic concerns are their major morbidity. The second type is the plexiform neurofibroma, mostly arising in individuals with NF1. In the latter situation it is not only difficult to surgically remove these plexiform tumors when they involve major nerve trunks but also their potential for malignant transformation. (Fig. 14-36)

Malignant Peripheral Nerve Sheath Tumors (MPNST) are highly malignant sarcomas that are locally invasive, frequently leading to multiple recurrences and eventual metastatic spread. Despite their name, these tumors do not arise from malignant transformation of schwannomas. Instead, they arise de novo or from transformation of a plexiform neurofibroma. These tumors can also occur after radiation therapy.
FAMILIAL TUMOR SYNDROMES are inherited diseases characterized by the development of hamartomas and neoplasms throughout the body with particular involvement of the nervous system. Most of these syndromes are linked to loss of tumor suppressor genes. The following are autosomal dominant disorders.

**Type 1 Neurofibromatosis (NF1)** is characterized by neurofibromas (plexiform and solitary), gliomas of the optic nerve, and cutaneous hyperpigmented macules (*café au lait spots*). Individuals with NF1 have a propensity for the neurofibromas to undergo malignant transformation. This is especially true for plexiform neurofibromas.

**Type 2 Neurofibromatosis (NF2)** is characterized by the development of a range of tumors, most commonly *bilateral vestibular (acoustic) schwannomas and multiple meningiomas*. Ependymomas of the spinal cord also occur.

**Tuberous Sclerosis** is another autosomal dominant syndrome characterized by the development of hamartomas and benign neoplasms involving the brain and other tissues. Seizures, which can be difficult to control with antiepileptic drugs, are associated with the cortical lesion. Extracerebral lesions include renal angiomyolipomas, retinal glial hamartomas, and pulmonary lesions and cardiac rhabdomyomas.

**von Hippel-Lindau Disease** is characterized by the development *hemangioblastomas mostly within the cerebellar hemispheres, and retina*. Patients may also have cysts involving the pancreas, liver, and kidneys and have a high propensity to develop renal cell carcinoma of the kidney.