INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

Curtis G. Benesch, MD

BACTERIAL INFECTIONS

Meningitis (suppurative, purulent)

Epidemiology

- Approximately 5-10 cases/100,000/year in developed countries
- Three most common organisms: Hemophilus influenzae, Neisseria meningitidis, and Streptococcus pneumoniae (For neonates: Escherichia coli, Group B streptococci, Listeria monocytogenes)

- Risk factors (U.S.)
  - Age (70% < 5 years old)
  - Blacks > whites
  - Native Americans
  - Overcrowding, day-care, barracks, chronic care facilities
  - Contact with infected individuals

Pathogenesis

- Blood-borne (usually respiratory source)
- Direct extension (sinusitis, mastoiditis, facial cellulitis, middle ear infection)
- Direct implantation (penetrating wounds, neurosurgery)

Pathophysiology

- Organisms multiply rapidly in cerebrospinal fluid (CSF) with inflammation of meninges
- Predominantly polymorphonuclear cells (neutrophils) which release chemicals
- Brain edema from bacterial toxins and inflammatory response
- Inadequate tissue perfusion from increased metabolic demand and reduced blood flow
- Raised intracranial pressure, systemic effects of infection (sepsis)

Clinical features

- Symptoms may develop over hours or several days
- Headache – severe, bilateral with photophobia, painful eye movements, vomiting
- Neck stiffness – seen in 80% overall; often absent in children and the elderly
- Fever – present in 85%
- Altered sensorium – rarely with seizures, cranial nerve palsies, focal signs
- Other signs – rash: purpuric with meningococcal meningitis, erythematous with viral meningitis; arthritis
Diagnosis

- CT – LP – Focal mass lesions must be ruled out before proceeding with lumbar puncture
- Confirmed by CSF findings: high cell count (PMN’s), high protein, low glucose, high opening pressure, positive gram stain, positive culture
- Countercurrent immunoelectrophoresis (CIE) and latex agglutination may also be useful

Treatment

- Life supportive therapies: airway, volume status, seizure control, control of raised intracranial pressure, monitoring of electrolytes, especially Na⁺
- Antibiotics – must be administered as soon as possible; high dose, prolonged treatment
- Establish bactericidal effects
- Corticosteroids in children
- Surgery for shunt placement, drainage of fluid collections

Complications

- Focal deficits, seizures, mental retardation
- Hearing loss in children (*H. influenzae*)
- Fluid collections
- Hydrocephalus

Prevention

- General measures to decrease overcrowding
- Isolation
- Immunizations (Pneumovax, *H. influenzae* vaccine)
- Chemoprophylaxis (Rifampin for *N. meningitides*)
- Identify special risks (neonates, immunocompromised patients, skull fractures with CSF leaks)

Brain Abscess

- Suppurative necrosis of brain parenchyma
- Most commonly seen in young adults, especially males
- Leading organisms: Streptococci (anaerobic and microaerophilic), Staphylococci and Bacteroides species; opportunistic in immunocompromised patients.

Pathology

- Direct extension: sinusitis (frontal lobes), mastoiditis (temporal lobes and cerebellum)
- Direct implantation: trauma, neurosurgery
- Blood-borne: deep in the brain, or at gray-white junction; often multiple
Pathogenesis

- Early cerebritis with PMN infiltration and edema followed by invasion of macrophages and fibroblast with increasing edema and early gliosis
- Capsule formation with surrounding edema

Clinical features

- Raised intracranial pressure (headache, nausea and vomiting, papilledema, altered sensorium)
- Focal neurologic signs
- Fever and evidence of systemic infection in some cases
- Symptoms usually present for less than one month

Diagnosis

- CT scan, possibly MRI
- Lumbar puncture is contraindicated due to risk of herniation
- CSF would likely show lymphocytic pleocytosis, increased pressure, increased protein and normal glucose

Treatment

- Antibiotics, usually for 6-8 weeks
- Management of raised intracranial pressure
- Surgical drainage
- Use of corticosteroids remains controversial
- Treatment of predisposing condition

Complications

- Seizures
- Focal neurologic deficits
- Hydrocephalus
- Recurrent abscess formation (10%)

VIRAL INFECTIONS

Meningitis (Aseptic)

Epidemiology

- Viral meningitis is the most common cause of aseptic meningitis
- 11/100,000/year, most often in children less than one year old
- causative agent identified in 10% of cases
most common agents are: Enterovirus (polio, Coxsackie, echo), arbovirus, herpes simplex virus

Pathogenesis

infection with many viruses is asymptomatic but respiratory tract infections, gastrointestinal infections or skin rashes may precede neurological involvement
Meningeal inflammation with predominantly lymphocytic CSF pleocytosis
Self-limited

Clinical features

Insidious onset of headache, fever, stiff neck (meningismus)
May mimic acute bacterial meningitis in more severe cases
Sensorium generally preserved
Presence of systemic viral illness

Diagnosis

Lumbar puncture, provided there is no mass lesion
CSF with lymphocytes (usually < 1000 cells/mm³), slightly elevated protein, normal glucose
Viral cultures (acute and convalescent)

Treatment

May require antibiotics until bacterial cultures are negative
Supportive care with symptomatic treatment (analgesia, antiemetics, fluids)
Prevention by immunization (mumps, polio)

Encephalitis

Inflammation of the brain parenchyma; organisms usually present within brain
Often associated with meningitis
Etiology is usually viral; may be acute or chronic

Epidemiology

Can be grouped into acute and chronic categories

Acute" epidemic – often seasonal in late fall, winter and early spring (arbovirus – "equine"; tick-borne)

Sporadic (herpes simplex (HSV), mumps, Epstein-Barr, adenovirus)
Zoonotic (animal reservoir – rabies)
• Chronic: Measles, rubella, human immunodeficiency virus (HIV), papova
  (progressive multifocal leukoencephalopathy)

Other unconventional viruses: prions are viral-related agents that are associated with
Creutzfeldt-Jakob disease, kuru, and Gerstmann-Straussler disease

Pathogenesis

• Varies depending on agent
• HSV usually enters via respiratory mucosa and resides in trigeminal ganglion where
  it may remain latent for extended periods of time
• Upon reactivation, HSV may travel along the trigeminal nerve back to the brain or
  may also enter through the olfactory tract, thus accounting for the high frequency of
  involvement of the temporal and mesial frontal lobes, respectively
• Other viruses may reach the brain through the blood supply; rabies virus also travels
  through neurons into the spinal cord and in some cases, the brain

Clinical features

• Symptoms usually begin insidiously
• Mild behavioral alterations progressing to delirium, stupor, coma
• Focal signs such as dysphasia, hemiparesis
• Memory loss, malaise
• Occasional fever and headache

Diagnosis

• History, especially regarding travel, animal exposure, occupational habits
• CSF examination with lymphocytic pleocytosis, mildly elevated protein, normal
  glucose, normal pressure initially, negative gram stain and bacterial culture
• Brain imaging with either CT or MRI
• EEG – "PLEDS": periodic lateralizing epileptiform discharges in HSV
• Viral cultures

Treatment

• Supportive care
• Acyclovir, especially in HSV, possibly in Epstein-Barr virus and cytomegalovirus as
  well
• Control of raised intracranial pressure
• Anticonvulsants for seizures

Prognosis

• Depends on agent
• Mortality rate of treated HSV is 30%; untreated is 80%
• Survivors often left with cognitive impairment, amnesia, seizures and focal neurologic
  deficits (hemiparesis, aphasia)
AIDS AND THE NERVOUS SYSTEM

The human immunodeficiency virus (HIV) infects the immune system, resulting in a progressive immune deficiency.

HIV appears to enter the central nervous system early on in the disease, however, its most profound effects occur later in the disease; HIV also affects the peripheral nervous system.

Clinical features

Neuromuscular

- Neuropathic
  - Acute and chronic inflammatory demyelinating polyneuropathy
  - Distal sensory polyneuropathy
  - Mononeuritis multiplex
  - Polyradiculopathy

- Myopathic
  - Polymyositis
  - Nemaline rod body-like myopathy
  - AZT-induce myopathy

Central nervous system

- Primary HIV syndromes
  - Acute aseptic meningitis
  - Vasculitis
  - AIDS dementia complex (ADC) – gradual cognitive, motor and behavioral impairment characterized initially by forgetfulness, apathy, psychomotor retardation, and leg weakness followed by progressive deterioration leading to frank dementia; CT/MRI may show atrophy; metabolic abnormalities, drug intoxication and depression must be excluded

- Opportunistic infections
  - Toxoplasma gondii
  - Lymphoma
  - Cryptococcal meningitis
  - Progressive multifocal leukoencephalopathy
  - Treponema pallidum (syphilis)
  - Cytomegalovirus
Pathology

- Subacute encephalitis – direct HIV infection of the brain
- AIDS-dementia complex – includes subacute encephalitis without clear-cut viral invasion; also includes vacuolar myelopathy of the spinal cord, primarily affecting the white matter

Treatment

- AZT, DDI and protease inhibitors for HIV infection per se
- AZT may also help with cognitive impairment
- Antimicrobial therapy for specific opportunistic infections
- Supportive services
THE NEUROLOGY OF HIV-1 INFECTION
ROBERT G. HOLLOWAY, M.D.

Epidemiology

Neurological complications occur in 39-70% of patients with the acquired immunodeficiency syndrome (AIDS). In 1991, 50,000 - 100,00 AIDS patients experienced neurologic complications in the U.S. Considering the estimate that the human immunodeficiency virus (HIV-1) infects over 20 million people worldwide, 1.5 million of which have AIDS, the worldwide neurological burden caused by this infection is enormous.

Neuroinvasion

HIV-1 invades the central nervous system (CNS) early after infection, and evidence of infection is found in the CSF of most asymptomatic seropositive individuals. Macrophages and microglia are the predominant cells infected within the nervous system. Despite this early entry, the most profound neurological manifestations occur in the later stages of the disease along with the progressive immune decompensation.1

Causes of Neurological Disease in HIV-1 infection

When confronting HIV-1 infected patients, it is essential to establish their level of immunocompetence and their past infectious disease history as well as to catalog all their past and present medications. The following pages highlight the essential aspects of HIV-1 neurology based on the etiologic classification below:

- HIV-1
- Opportunistic Infections
- Tumor
- Treatment
- Other

Primary HIV-1 related Neurological Diseases

One of the commonest causes of neurological disorders in young Americans with 65,000 new cases annually.

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1Early stage disease (CD4+ count > 500 cells/mm³), Middle stage disease (CD4+ count 200-500 cells/mm³) and Later stage disease (CD4+ count <200 cells/mm³). Most neurological manifestations occur in the later stage disease; however, exceptions occur which will be highlighted in the text.
HIV-1 associated dementia

The most common HIV-1 related neurological disease accounting for 40,000 cases annually. The clinical manifestations of HIV-1 dementia suggest predominantly subcortical involvement characterized primarily by memory loss selective for impaired retrieval, impaired manipulation of acquired knowledge, personality changes characterized by apathy and irritability and a general slowing of all thought processes. Examination reveals slowed motor skills, abnormal ocular pursuits, leg ataxia and hyperreflexia. Magnetic resonance imaging (MRI) and computed tomography (CT) may reveal atrophy and diffuse white matter changes. Early in the disease it is important to identify patients with reversible causes of cognitive decline, most notably depression, drug intoxication and infection. If these causes are not present, zidovudine (ZDV) at maximum doses is indicated. There is preliminary evidence that ZDV will transiently improve cognitive function and may retard subsequent cognitive decline. HIV-1 dementia is evident in up to one 1/3 of patients with AIDS by the time of death. Without treatment, the dementia is rapidly progressive with a mean survival of about 6 months.

HIV-1 associated myelopathy

Clinically affects up to 20% of patients with AIDS. The clinical features include the progressive development of spastic paraparesis, with variable sensory ataxia and bladder involvement. The arms are usually spared and there is no truncal sensory level. ZDV is not effective in reversing the myelopathy, which progresses inexorably.

Acute meningitis, encephalitis

Often in early stage disease at the time of seroconversion.

Chronic meningitis

Probably an under-recognized cause of chronic headache in the early and middle stages of disease. Dramatic symptomatic improvement can occur with a short course of oral steroids.

HIV-1 associated vasculopathy

Neuromuscular complications

Neuromuscular diseases occur in as many as 50% of patients infected with HIV-1. All forms of neuromuscular disease have been reported, including demyelinating neuropathies (Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy), axonal neuropathies, mononeuritis multiplex, polyradiculitis, and myopathies. The most common etiologies causing neuromuscular complications include HIV-1, opportunistic infections (most often CMV, see page 3) and medication side effects (see pages 5-6). Here we will restrict the discussion to the most common HIV-1 related neuromuscular complications.
Neuropathy

A characteristic distal symmetric axonal neuropathy occurs in patients with declining CD4+ cell counts and advancing systemic disease. The typical symptoms are tingling, numbness or burning of the toes and feet. Examination shows loss of sensory function more than motor; distal greater than proximal. The ankle muscle stretch reflexes are usually depressed or absent. Anti-retroviral treatment does not alter the natural history of this disease that is treated symptomatically with tricyclic anti-depressant agents. A reversible toxic axonal neuropathy associated with ddI, ddC and D4T can mimic this syndrome.

Myopathy

An inflammatory myopathy can occur at any stage of the illness. Patients present with symmetric proximal weakness of the upper and lower limbs, and an elevated creatine kinase. EMG studies reveal typical myopathic changes. The majority of patients improve with oral steroid treatment. Zidovudine, by inhibiting mitochondrial DNA polymerase, can cause a similar myopathic picture; these symptoms improve upon withdrawal of the drug. Therefore, if a patient presents with proximal weakness while on ZDV, the medication should be discontinued to assess if symptoms improve -- evidence that the myopathy is secondary to ZDV rather than HIV-1.

Opportunistic Infections

The spectrum of opportunistic infections causing neurological complications in HIV-1 infection is extensive, with representatives from the viruses, bacteria, fungi and parasites. The more common infections will be described here.

Opportunistic Viral Infections

Cytomegalovirus (CMV)

CMV now represents the most common opportunistic infection in AIDS. Just as with other DNA-containing herpesviruses, infection with CMV occurs as a reactivation of a primary infection during periods of immunosuppression. The two most important neurological complications from CMV include CMV encephalitis and CMV polyradiculopathy. Therapy is available with either ganciclovir or foscarnet, both antiviral agents.

CMV encephalitis

This presents with headache, fever, stiff neck and diminished level of consciousness. The examination is generally non-focal. MRI may show ependymal enhancement representing ependymitis, and cerebrospinal fluid (CSF) may show a polymorphonuclear pleocytosis and a depressed glucose level. Although helpful, these findings are not diagnostic.
CMV polyradiculopathy

A striking peripheral neurological manifestation characterized by low back pain, rapid paraplegia and sphincteric dysfunction. Important diagnostic clues include CSF polymorphonuclear pleocytosis and depressed glucose levels. Early recognition is important since early treatment may retard progression.

Papovavirus (JC virus)

In severely immunocompromised patients, this virus infects oligodendrocytes and causes a demyelinating disease termed Progressive Multifocal Leukoencephalopathy (PML). It occurs in 3-4% of AIDS patients and presents, in descending order of frequency, with limb weakness, cognitive dysfunction, visual loss, gait disturbance, limb incoordination, speech or language disturbance and headache. CT and MRI scanning reveal non-enhancing white matter lesions without mass effect. No therapy is available and prognosis is poor with a median survival of four months.

Opportunistic Fungal Infections

Cryptococcal meningitis

This is the most common fungal infection in patient with AIDS, with an incidence that varies between 1.9-11%. Headache is an almost universal feature of this infection. Other symptoms include nausea, vomiting, photophobia, blurred vision, fever, mental status changes and meningismus. Seizures and focal findings are uncommon. CSF examination invariably shows a mononuclear pleocytosis and a depressed glucose. Diagnosis is firmly established by CSF antigen detection or culture. Treatment is with intravenous amphotericin B followed by long-term suppressive therapy with oral fluconazole or itraconazole.

Opportunistic Parasitic Infections

Toxoplasmosis encephalitis

Toxoplasma gondii, an intracellular protozoan, causes a diffuse meningoencephalitis, but can also result in focal or multifocal disease. This infection occurs in 10%-30% of patients with AIDS, making it one of the most common neurological complications associated with HIV-1 infection. Presenting symptoms are focal in nature, superimposed on a global encephalopathy. MRI or CT will often reveal focal or multifocal lesions, with ring enhancement on contrast injection. Although positive serum anti-toxoplasma IgG antibodies are almost always present, their absence does not exclude the diagnosis. Acute treatment is effective with pyrimethamine and sulfadiazine or pyrimethamine and clindamycin and ongoing maintenance therapy is required to prevent relapse.
Opportunistic Bacterial Infections

Treponema pallidum

Co-existent infection with Treponema pallidum is increasingly common in HIV-1 infected patients. HIV-1 infection alters the natural history of neurosyphilis, hastening the onset of meningovascular syphilis that presents with focal stroke-like symptoms and seizures. The diagnosis is difficult and usually based on CSF analysis. When clinical suspicion is high, therapy with intravenous penicillin for ten days is indicated.

Mycobacterium tuberculosis

HIV-1 infected patients with tuberculosis are at increased risk for meningitis, but infection with HIV-1 does not appear to change the clinical manifestations or the outcome of tuberculous meningitis. The commonest clinical manifestations include seizures, altered mental status and fever with meningismus. Despite the high frequency of tuberculosis in some populations, CNS involvement is rather uncommon and usually occurs in the later stages of HIV-1 disease. Mortality of tuberculous meningitis is 20%-35%.

Malignancies Associated with HIV-1 Infection

Primary CNS Lymphoma

Primary CNS lymphoma is a substantially different disease in persons with and without AIDS with regard to patient characteristics, clinical and radiographic presentation, and prognosis. The disease is much more common in the presence of HIV-1 infection, occurring in up to 6% of AIDS patients. Initial symptoms and signs may be quite variable, although the majority of patients present with seizures, headache and focal dysfunction. MRI reveals focal or multifocal lesions anywhere in the brain; ring or homogenous enhancement with contrast administration may be seen. The radiographic picture of lymphoma is not specific, and to distinguish among several of the opportunistic infections described above, a brain biopsy is often required. Prognosis is poor and even with radiation therapy, the median survival is only increased from six weeks to four months.

Treatment-Associated Neurological Disease

Brief mention is made of the neurological complications associated with the anti-retroviral agents used to treat advancing HIV-1 infection. The importance of recognizing these complications lies in their reversibility once the drug is discontinued.

Zidovudine (ZDV)

A thymidine analog that inhibits the replication of HIV-1 by interfering with HIV-1 RNA-dependent DNA polymerase (reverse transcriptase). An association exists between long-term ZDV therapy (>six months) and the development of a myopathy characterized by myalgias, proximal weakness, wasting and elevations in serum creatine kinase. Controversy presently exists over the distinction between ZDV myopathy and HIV-1 myopathy. However, if a patient presents with myopathic disease and is taking ZDV, the...
drug should be discontinued and the patient monitored for improvement prior to considering a trial of oral steroids.

2',3'-Dideoxyinosine (ddl), 2',3'-Dideoxycytidine (ddC), and Stavudine (D4T)

These nucleoside analogs cause a painful dose-dependent predominantly sensory polyneuropathy. There is no reliable clinical or electrodiagnostic means to distinguish these toxic neuropathies from the neuropathy associated with HIV-1. The diagnosis is based on the temporal association with drug treatment, and clinical improvement on drug removal.

Other

Because neurological complications of HIV-1 infection can involve all levels of the neuraxis, often in dramatic fashion, one easily forgets that these individuals are susceptible to all other non-HIV related neurological conditions as well. Several of the more common HIV-associated systemic disorders which may present with neurological signs and symptoms include vitamin B_{12} deficiency, drug abuse, drug toxicity and depression.
EPILEPSY AND ANTICONVULSANT DRUGS

Margaret C. McBride MD

Advances in medicine over the past 20 years include progress in various aspects of epilepsy. The explosion in understanding of neuroscience has increased knowledge of the mechanisms of epilepsy. New antiepileptic drugs, including some with fewer sedative effects, have led to more effective and acceptable treatment for many individuals. The field of epilepsy surgery has grown and offers cures or marked amelioration of seizure frequency to many individuals with seizures that are intractable to medications. Societal understanding of epilepsy as well as general openness about human differences has led to less social stigma being attached to the diagnosis.

The goals for the two hours of lecture on epilepsy and anticonvulsant drugs are for students to have an understanding of the following:

- The main categories and types of seizures
- The differential diagnosis of seizures
- The main points in evaluating a patient with seizures including the usefulness and misleading aspects of the EEG in diagnosing and managing seizure disorders
- The multiple facets of treating epilepsy (without specific details of each medication)

**DEFINITION**

- **Seizure** - a paroxysmal, involuntary, and excessive discharge of neurons, usually resulting in stereotyped involuntary behavior.

- **Epilepsy** - the tendency to recurrent seizures. This term is usually applied when a person has had two or more seizures not relatable to an acute reversible condition within the CNS.

- Other less specific and unofficial terms often used by health professionals and non-medical persons include "fits", "shakes", "spells" for seizures or "seizure disorder" for epilepsy.

**CLASSIFICATION OF SEIZURES AND OF EPILEPSY**

**Seizures**

Seizures are classified according to the pattern of involvement of the brain. They fall basically into one of two categories:

- **Primary generalized seizures** - involve all of the cortical gray matter from the onset and usually have their maximum clinical expression at the onset.

- **Focal seizures** - begin in one part of the brain and their clinical expression depends on which parts of the brain become involved. If they spread to involve the whole brain they are called "secondarily generalized seizures".
Primary Generalized  Partial  Partial with secondary generalization

These two main categories are further subdivided according to the manifestations of the seizure, which of course are directly dependent on the pattern of involvement of cortical gray matter. Appendix I gives the official classification of seizures as devised by an international group of epileptologists called the Commission on Classification and Terminology. It is important to have an understanding of what the main terms in this classification mean:

Partial Seizures:

- Simple Partial - without loss of awareness or consciousness. These seizures are further subdivided by the phenomena occurring (and hence which part of the cortex they are generated from). Since there is no loss of awareness, the patient is able to describe these phenomena:
  - Motor - twitching or posturing
  - Somatosensory - numbness or tingling in some part of the body
  - Sensory - visual, olfactory, or auditory hallucinations
  - Autonomic - an epigastric sensation, sudden body feelings
  - Psychic - Fear, "deja vu", out of body experience etc.

- Complex Partial - with loss of awareness
  - May begin as simple partial and spread to be complex partial or have loss of awareness and hence be complex partial from the beginning

Generalized Seizures:

- Absence - brief lapses in consciousness with posture maintained
- Myoclonic - quick jerks, usually of the upper body, in flexion
- Clonic - alternating contraction and relaxation of musculature
- Tonic - sustained contraction of musculature
- Tonic-clonic - combining these two features
- Atonic - sudden loss of tone or posture
Other important terms are:

- **Aura** - the feeling that warns the patient that a seizure may be coming. It is essentially a simple partial seizure. Generalized seizures or seizures with loss of consciousness from the onset do not have auras. Patients may have auras that do not progress to their full seizure. Sometimes a patient can stop a seizure after the aura.

- **Ictal** - pertaining to or during the seizure (or paroxysmal event)

- **Postictal** - after the seizure. Typically, any seizure that includes an alteration of consciousness, with the exception of absence seizures, is followed by a period during which the patient is obtunded, lethargic, or at least confused and tired.

**Epilepsy**

The categories of epilepsy parallel somewhat the categories of seizures, but they are based not only on

1. the seizure type involved, but also on  
2. the age of onset and course,  
3. the anatomic substrate and cause, and  
4. the associated clinical findings.

The main categories of epilepsy are:

1. Localization-Related  
2. Generalized Epilepsies

These are further subdivided and the full classification may be found in Appendix II. The subdivisions often relate to causation and the following terms:

- **Idiopathic/primary** - the epilepsy is intrinsic to the brain, mostly related to familial factors affecting seizure threshold. Usually not associated with or independent of other expressions of CNS dysfunction.

- **Cryptogenic** - caused by an unidentifiable CNS abnormality, known to be present because other forms of CNS dysfunction are present or will develop.

- **Symptomatic** - the epilepsy is related to a findable cause that may or may not cause other forms of CNS dysfunction.

Examples of common epilepsies include:

**Juvenile Absence Epilepsy:**

Absence seizures usually begin between the ages of 3 and 12 years with a peak of onset between 3 and 6 years of age. Probably a number of children with absence seizures are never diagnosed due to the brevity of the seizures, their minor motor component, and their usual self limited course.
Typically absence seizures consist of staring with slight upturning of the eyes, and slight bobbing of the eyelids and the head. Sometimes there is associated lip smacking or mouthing or even occasionally, a simultaneous minor rhythmic movement of an upper extremity. Usually the patient does not fall but may lean in whichever direction he was tilting at the onset. The onset is interruptive, the offset is also quick, and the seizure lasts from 2 to 30 seconds but typically from 3 to 10 seconds. There is no postictal phase.

The EEG findings during the absence seizure consist of 3 cycle per second spike and wave discharges. This same pattern may be seen during an interictal EEG for up to 2 seconds without clear associated clinical changes. Usually the interictal EEG pattern and an absence seizure are evoked by hyperventilation in an untreated or under-treated patient.

This is an idiopathic form of epilepsy and there are no associated findings on neuroimaging. Treatment is usually ethosuximide in the younger children and valproate in older children.

Absence seizures must be differentiated from the staring that is associated with lapses in attention due to inattention or daydreaming. In the latter, the staring does not interrupt an activity and is not associated with the rhythmic small amplitude blinking of the eyelids or head.

**Benign Rolandoic Epilepsy:**

Benign Rolandoic seizures are simple partial seizures which usually begin at the face or tongue with either a tingling sensation or twitching or both. They may secondarily generalize or spread to involve clonic activity of one side (often with preservation of consciousness at that point) or to full generalization with loss of consciousness. These tend to start in children ages 5 to 12 years. The seizures tend to occur in the first or last hour of sleep. They may also occur during the day when it is more obvious that they are followed by weakness on the side involved or, if generalized, by a post ictal sleep.

This form of epilepsy has a highly characteristic interictal finding on EEG: a spike and slow wave discharge maximal in the Rolandoic area (central and midtemporal electrodes or sometimes a little more posteriorly at the parietal and posterior temporal electrodes) with a positive component in the mid or contralateral frontal area. The epileptiform discharge is brought out by drowsiness and light sleep. The EEG may be completely normal in waking. Therefore, obtaining sleep during the EEG is essential. If sleep is obtained, the discharge is present > 90% of the time. The combination of this EEG finding with the characteristic seizures in an otherwise normal child of the appropriate age makes the diagnosis.

If the episodes are associated with sleep and/or are infrequent, the clinician and family together may opt not to treat them. If the episodes have been with sleep, a suppotime or bedtime dose of carbamazepine, the drug of choice, may be appropriate. With or without treatment, this seizure disorder tends to remit with the onset of puberty in > 90% of children.
Benign Rolandic Epilepsy is an idiopathic form of epilepsy and is not associated with relevant abnormalities on neuroimaging.

**Juvenile Myoclonic Epilepsy:**

This form of Primary Generalized Epilepsy consists of two seizure types: myoclonic jerks of the upper extremities and generalized tonic clonic seizures. Both forms of seizure tend to occur just after awakening in the morning - during the first 45 minutes of wakefulness. These are precipitated by sleep deprivation, alcohol, sudden awakening. They typically begin in the latter teen years or early twenties and the tendency for the seizures continues at least into middle adulthood if not longer.

In this form of epilepsy the EEG may contain 4-6 cps spike and wave discharges in drowsiness and light sleep and up to 30% have a photoparoxysmal response (epileptiform changes on the EEG in response to flashing light) though fewer than that have clinical seizures brought out by flashing lights. Again, since this is an idiopathic form of epilepsy, there are no associated abnormalities on neuroimaging.

In this form of epilepsy, the tip off to diagnosis is the timing of the generalized seizure (which is usually what brings patients to medical attention) and the associated “morning jerks”. It is essential to ask for that history. Teenagers, who are eager to be like all of their peers, usually do not voice a concern about these morning jerks even though they may be enough to spill orange juice or fling something out of their hands. The adolescents seem to assume that everyone has them.

Usually the generalized and myoclonic seizures are well-controlled on low doses of sodium valproate. In my experience, giving the medication just at night has been successful. Lamotrigine is also useful.

**Lennox Gastaut Syndrome:**

This syndrome is a form of cryptogenic or symptomatic secondary generalized epilepsy. The term was originally used to describe children with mental retardation; mixed seizures including atypical absences, tonic, atonic, and secondarily generalized motor seizures; and “slow” (≤2.5 cps) spike and wave discharges on the EEG.

The Lennox Gastaut syndrome is usually a manifestation of congenital or acquired brain pathology and an etiology should be sought if the history does not make it clear. Sometimes this syndrome follows neonatal insults or infantile spasms. Usually the three components of the syndrome are not present until at least 3-4 years of age.

Seizures associated with this syndrome are resistant to therapy. The advent of valproate was a major breakthrough in treatment, lamotrigine looks promising, and felbamate is helpful. Carbamazepine is of little value and may make seizures worse. The children are sensitive to the behavioral and cognitive side effects of any of the medications, probably because they have problems in those areas at baseline. Weighing acceptable seizure control against side effects is a fine line to walk in managing treatment. Long term monitoring may help clarify what is seizure and what is not, and what types of seizures are present. Typically epilepsy surgery is not helpful
unless rarely when there is a clear focal lesion in a resectable place which seems to initiate most of the seizures; if drop attacks are prominent, a corpus callosotomy may be helpful.

Treatment usually consists of a combination of medications, which includes valproate. It is important to avoid multiple drugs simultaneously. It is in this group of children that the ketogenic diet has been tried most often and found to be quite successful in some. Helping these children reach their maximum quality of life may require that the clinician understand and communicate with parents about the relative risks of lamotrigine and felbamate, and be willing to consider therapy with those drugs. Additionally, treatment involves appropriate protection from injuries (helmets, restrictions) and support for the families such as through the local epilepsy foundation.

**Temporal Lobe Epilepsy:**

This is the most common form of Localization Related Epilepsy because the temporal lobe, especially mesially, is so epileptogenic. Children may present with complex partial seizures of temporal lobe origin as neonates, but more commonly, these seizures begin after age 5 years, and sometimes as late as in the teenage years, even if they relate to an insult that occurred in very early life.

Complex partial seizures of temporal lobe origin will usually begin with an aura if they remain confined to one temporal lobe for longer than a few seconds. The aura may consist of a "rising epigastric feeling" (sick feeling in the upper stomach), or deja vu or other head/thought feelings or sometimes with an unusual smell or harsh mechanical sound. Once both temporal lobes are involved, there is alteration of consciousness (hence **complex** partial seizure) and though the child may not look unconscious, he/she is no longer forming memory. During this phase there may be automatisms such as lip smacking, repeated throat sounds, swallowing, hand rubbing or wringing. Usually complex partial seizures of temporal lobe origin do not generalize and they are less likely than other partial seizures to occur in sleep.

These seizures are not idiopathic though the cause may not be found. They are sometimes a sequela of processes that cause brain swelling such as prolonged generalized motor status epilepticus – especially with fever, meningitis, or serious head trauma. It has been proposed (no proof at this point) that they may sometimes be caused by tissue damage from distortion of the artery that supplies the mesial temporal area or of the tissue itself with head molding during delivery. All of these known or proposed causes may lead to mesial temporal sclerosis. Other causes include minor malformations in the mesial temporal area and small indolent tumors. In the milder cases with more easily controlled seizures, no abnormalities may be seen even on careful special protocol MRIs.

Carbamazepine is the drug of first choice for these seizures. If the seizures are resistant to carbamazepine and one other anti-epilepsy drug in appropriate doses with appropriate compliance, a special protocol MRI should be done to look for abnormalities of the temporal lobe, and consideration should be given to the surgical approach to treatment. A seizure-free outcome after surgery occurs in 60-75% of the appropriate candidates, while becoming seizure-free with continued medical management after the child has been resistant to two anticonvulsants occurs in only 10%. If the child is an appropriate candidate for surgery, it should be done early in the course of their epilepsy.
in order to avoid the inevitable secondary social, behavioral, and cognitive sequelae caused by the burden of recurrent complex partial seizures in the formative childhood and adolescent years.

EPIDEMIOLOGY

Seizures are a relatively common disorder, occurring in 10% of individuals at some time in their life. The incidence of epilepsy is 1% in children and 0.5% in adults. The idiopathic epilepsies are most likely to start in childhood or early adulthood. Symptomatic epilepsies may start at any time.

DIFFERENTIAL DIAGNOSIS

Non-epileptiform paroxysmal events in children

- Benign infantile myoclonus
- Breath holding spells
  - cyanotic
  - pallid
- Shuddering attacks
- Benign paroxysmal vertigo
- Paroxysmal torticollis
- Night terrors
- Staring/daydreaming
- Cyclic vomiting
- Confusional migraines
- Tics

Non-epileptiform paroxysmal events in adults and children

- Syncope
- Panic attacks
- Pseudoseizures
- Rage attacks
- Stereotypic behavior
- Cardiac events, including arrhythmias associated with the prolonged QT syndrome
- Narcolepsy/cataplexy
- Parasomnias

Further information will be given about some of the above.

Cyanotic Breath-holding Spells:

Episodes of cyanosis, often with loss of consciousness, occurring during vigorous crying. These are not, in fact, related to “breath-holding” but rather to the child’s inability to relax his musculature at the end of exhalation in vigorous crying. The chest and facial muscles are tightly contracted, all the air is expelled from the lungs, and the infant quickly becomes cyanotic and passes out from lack of oxygen (associated with marked slowing and loss of voltage on the EEG). As soon as consciousness is lost, the
expiratory muscles relax and the lungs inflate back up at least to neutral position, bringing in oxygen which fairly quickly revives the infant. The revived infant then may go on crying or be subdued for a few minutes. Sometimes a few clonic jerks or tonic posturing occur right after loss of consciousness. Contrary to popular thought, it is not willful, and only occurs in those who are prone to it (it sometimes runs in families), but children will learn that if they make themselves cry vigorously it will happen - and they can then get their own way!

**Pallid Breath-holding Spells:**

Episodes of marked pallor, abrupt loss of consciousness, and clonic activity caused by vasoconstriction and bradycardia/asystole with resultant CNS ischemia. The bradycardia/asystole seems to be related to a massive vagal output induced by unexpected injury. The typical story is that of a toddler playing actively and suddenly slipping, or being hit from behind by a thrown object or swing, followed by up to 20 seconds of becoming upset, whimpering or running toward a parent for consolation before the sudden loss of consciousness occurs. The loss of consciousness lasts for 20 to 40 seconds and the child is subdued afterwards but rarely falls asleep. This type of breath-holding spell ("breath-holding" is again a misnomer) is much less common than the cyanotic type but is much more likely to be mistaken as a seizure disorder because clonic activity is usually present. Children with this disorder may be prone to syncope in later life. The diagnosis is made by obtaining a history of the preceding injury, the associated pallor, and the brief or absent postictal phase.

**Staring/Daydreaming:**

Recurrent staring usually occurring when the child is not strongly engaged in an activity or is (mindlessly) watching TV. This must be differentiated from absence seizures in which the observer can usually describe the start of the staring, and the activity that the staring interrupts. Additionally, absence seizures are usually associated with eyelid movement and sometimes small amplitude head bobbing. Staring behaviors are more common in children who have difficulty maintaining attention. The following table helps to differentiate the two behaviors:

**Differentiating Inattentive Staring from Absence Seizures**

<table>
<thead>
<tr>
<th></th>
<th>ABSENCE</th>
<th>DAYDREAMING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency/day</td>
<td>multiple</td>
<td>several</td>
</tr>
<tr>
<td>Situation</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Induced by hyperventilation</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Onset</td>
<td>abrupt, witnessed</td>
<td>variable</td>
</tr>
<tr>
<td>Movements:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eye blinking</td>
<td>often</td>
<td>no</td>
</tr>
<tr>
<td>automatisms</td>
<td>common</td>
<td>no</td>
</tr>
<tr>
<td>Duration</td>
<td>&lt;30 sec.</td>
<td>seconds, minutes</td>
</tr>
<tr>
<td>Recovery</td>
<td>abrupt</td>
<td>abrupt</td>
</tr>
<tr>
<td>EEG findings</td>
<td>3 cps spike &amp; wave</td>
<td>normal</td>
</tr>
</tbody>
</table>
Tics:
Sudden involuntary contraction of muscles, occasionally in semi-purposeful movements, usually within the face, neck, or upper torso. These may be confused with myoclonic seizures. Repetitive eye blinking and throat clearing are among the most common tics. They wax and wane in prominence. Often children with tics have some characteristics of Attention Deficit Disorder and may have some obsessive-compulsive traits.

Syncope:
Loss of consciousness related to inadequate cerebral perfusion because of pooling of blood in the peripheral vasculature that causes a decrease in cardiac return. Syncope is usually precipitated by either a perceived “threat” (blood, needles, anticipating a dental procedure, etc.) which initiates vasodilatation in the peripheral vasculature, or prolonged standing with passive pooling of intravascular blood. If syncope occurs in a situation where the patient does not fall to a horizontal position, or if a well-intending unknowing person tries to keep the patient sitting up or standing, the ischemia is more prolonged and resulting tonic and/or clonic activity is common. Syncope is associated with pallor and is preceded by lightheadedness and a fading-out of vision, and even hearing. Recovery of consciousness is within less than a minute if the patient is prone or supine, especially if the legs are elevated. Postictal sleep is uncommon.

Differentiating Syncope from Seizure

<table>
<thead>
<tr>
<th></th>
<th>SEIZURE</th>
<th>SYNCOPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precipitant</td>
<td>sometimes</td>
<td>usually</td>
</tr>
<tr>
<td>Onset</td>
<td>abrupt or aura</td>
<td>lightheadedness, visual dimming</td>
</tr>
<tr>
<td>Position</td>
<td>variable</td>
<td>upright</td>
</tr>
<tr>
<td>Color change</td>
<td>sometimes pale or cyanotic</td>
<td>pale, ashen</td>
</tr>
<tr>
<td>Injury</td>
<td>sometimes</td>
<td>rare</td>
</tr>
<tr>
<td>Duration</td>
<td>minutes</td>
<td>seconds</td>
</tr>
<tr>
<td>Incontinence</td>
<td>sometimes</td>
<td>rarely</td>
</tr>
<tr>
<td>Postictal phase</td>
<td>usually</td>
<td>rare</td>
</tr>
</tbody>
</table>

Pseudoseizures:
Episodes of seizure-like behavior that are not generated by excessive cortical discharges but are a form of conversion disorder caused by psychological factors. As in all conversion reactions, the patient usually has a template (example) for that particular behavior. Thirty percent of people with pseudoseizures have had epileptic seizures. There is a secondary gain associated with the pseudoseizures. They tend to occur only when there is an observer present. They occur in developmentally disabled children and in children as young as 5 or 6 years of age. The following table helps to differentiate pseudoseizures from seizures.
Comparison of Epileptic Seizures and Pseudoseizures

<table>
<thead>
<tr>
<th></th>
<th>EPILEPTIC SEIZURES</th>
<th>PSEUDOSEIZURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precipitated by stress</td>
<td>sometimes</td>
<td>usually</td>
</tr>
<tr>
<td>Ictal behavior</td>
<td>stereotyped,</td>
<td>variable, strange</td>
</tr>
<tr>
<td></td>
<td>no directed violence</td>
<td>combativeness</td>
</tr>
<tr>
<td>Incontinence</td>
<td>sometimes</td>
<td>rare</td>
</tr>
<tr>
<td>Ictal EEG</td>
<td>paroxysmal with</td>
<td>normal</td>
</tr>
<tr>
<td></td>
<td>postictal slowing</td>
<td></td>
</tr>
<tr>
<td>Postictal phase</td>
<td>usually</td>
<td>rarely</td>
</tr>
<tr>
<td>Responsiveness to meds</td>
<td>usually</td>
<td>rarely</td>
</tr>
</tbody>
</table>

Rage Attacks:

Recurrent episodes of marked anger and aggression, usually triggered by a frustration, but the response is way out of proportion to the trigger and, in autistic children, the trigger may not be identifiable. The activity during the rage usually includes verbal and physical attacks on things and/or people, including favorite objects and well-loved family members, but the exact behavior and movements are not stereotyped. It is often associated with reddening of the face and sweating and followed by fatigue or even sleep.

Comparison of Rage Attacks and Complex Partial Seizures

<table>
<thead>
<tr>
<th></th>
<th>RAGE ATTACKS</th>
<th>COMPLEX PARTIAL SZs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identifiable precipitant</td>
<td>usually</td>
<td>rarely</td>
</tr>
<tr>
<td>Ictal features</td>
<td>variable</td>
<td>stereotyped</td>
</tr>
<tr>
<td></td>
<td>directed rage*</td>
<td>no directed rage</td>
</tr>
<tr>
<td>Amnesia for event</td>
<td>often</td>
<td>usually</td>
</tr>
<tr>
<td>Postictal fatigue</td>
<td>often</td>
<td>usually</td>
</tr>
</tbody>
</table>

*directed rage is almost never an epileptic seizure

Stereotypic Behaviors:

Recurrent stereotyped movements, often rhythmic and associated with emotion or with a soothing effect on the child (self-stimulation). These are particularly frequent in children with developmental disabilities, but may also be seen in normal children.
EVALUATION OF THE PATIENT WITH SEIZURES

The goals of the evaluation of the patient presenting with suspected seizures is to determine:
1. Did the patient have a seizure?
2. If so, what type of seizure?
3. What is the cause of the seizure(s)?

History

The most important aspect of the evaluation is

HISTORY

The value of a careful, accurate and detailed history of the event cannot be overemphasized. The history should be obtained from the patient and from an observer. Help the patient and/or observer to set the scene - what were they doing at the time? What did they see? Hear? Help them to determine how long the event was. Remember that an observer who has not previously witnessed seizures is panicked and usually believes that their loved one is dying as they helplessly watch the seizure. The questions you ask at the time of a first seizure will help both the patient and the observer to "notice" more detail at the time of the next seizure. Most of the pitfalls with respect to diagnosis and treatment of seizures occur because of insufficient history with respect to the seizures themselves.

History should also include a search for predisposing factors - any injuries to the nervous system before birth, at birth, or thereafter? Any abuse of the nervous system by excessive drug or alcohol intake or sleep deprivation? Physical or emotional stressors?

Physical Examination

- signs of neurologic dysfunction - asymmetries
- dermatologic markers that might suggest a neurocutaneous syndrome
- signs of systemic illness or disorders on general exam that might be associated with seizures.

Laboratory testing:

For the most part, blood studies are not very useful if the history or physical examination has not found the cause of a patient's seizure. However, if the patient is being evaluated soon after the seizure, and particularly if the seizures are recurrent or prolonged, it may be appropriate to look for transient metabolic causes such too low amounts of:

- serum glucose
- sodium
- calcium
- magnesium
- blood oxygen
If the patient is febrile consider:

- CBC and differential WBC count
- lumbar puncture, to examine cerebrospinal fluid
  (if one can be sure that the patient does not have increased intracranial pressure)

**Electroencephalograms (EEGs)**

The EEG records the summation of electrical potentials generated by inhibitory post-synaptic potentials in the cortex of the brain. It is a useful tool in helping to diagnose the type of seizure a patient has, because various seizure types are often associated with specific epileptiform discharges – distinct, usually sharp activity followed by a slow wave, having a voltage gradient in the area in which it occurs, such as:

<table>
<thead>
<tr>
<th>EEG FINDING</th>
<th>EPILEPSY</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 cps (cycles per second) spike and wave, symmetric and frontally predominant, augmented by hyperventilation</td>
<td>absence epilepsy</td>
</tr>
<tr>
<td>3-4 cps spike and wave in light sleep or with photic stimulation</td>
<td>primary generalized epilepsy</td>
</tr>
<tr>
<td>centro-mid temporal spikes</td>
<td>Benign Rolandic epilepsy</td>
</tr>
<tr>
<td>anterior temporal spikes or sharp waves</td>
<td>simple or complex partial seizures of mesial temporal origin</td>
</tr>
<tr>
<td>hypsarrhythmia (high voltage chaotic slowing with multifocal spikes)</td>
<td>infantile spasms</td>
</tr>
</tbody>
</table>

However, only 50% of patients with seizures will have epileptiform activity on their first EEG. This percentage may increase to 90% by repeating the EEG with provocative modalities, sleep depriving the patient prior to the EEG, and using special electrodes.

The EEG is not very useful in deciding whether or not a patient has had a seizure unless the EEG is recorded during the actual event. There are a number of paroxysmal EEG patterns that are normal variants but often misread as being "epileptiform". Also, approximately 1% of adults and up to 3.5% of children who are normal and have never had a seizure will have epileptiform activity on their EEG. Only 1.5% to 6% of these will develop seizures on follow-up. Epileptiform patterns particularly likely to be seen in "normals" include 3-4 cps spike and wave, and centro-temporal spikes that are markers of a familial tendency to epilepsy. Up to 50% of children with centro-temporal spikes on their EEG will never develop seizures.

**Remember that the diagnosis of seizures is made primarily by a detailed history, not from an EEG report!**
Neuroimaging Studies

CT or MRI scans may be helpful in finding the cause of partial or secondarily generalized seizures. Adults with new onset of seizures are more likely to have partial seizures and are more likely than children to have a findable reason for their partial seizures and, therefore, neuroimaging is more useful in adults than in children.

However it is rarely necessary and may be inappropriate to obtain an imaging study urgently except when the history or physical examination have indicated the possibility of trauma or intracranial bleeding, or when there are associated signs or symptoms of increased intracranial pressure.

Remember that seizures by themselves are not a sign of increased intracranial pressure. In situations other than those with the possibility of intracranial bleeding or increased intracranial pressure, obtaining an urgent imaging study is often inappropriate because the patient may not yet be back to an alert state and able to cooperate for the study, and may therefore require sedation which is not desirable when one is evaluating a new neurologic symptom. Also, usually only a CT scan can be obtained urgently. A CT scan is appropriate for diagnosing intracranial bleeding and a mass lesion that may be causing increased intracranial pressure, but the MRI is the appropriate study in other situations because it gives much better detail of brain parenchyma and can therefore find small scars or other lesions.

In a patient with intractable partial complex seizures, a special protocol MRI scan should be done to look for lesions in the mesial temporal regions.

If the history, physical examination and EEG establish a diagnosis of primary generalized seizures, neuroimaging is not useful and should not be done.

TREATMENT

The reasons for the treatment of seizures are:
1. To prevent injuries
2. To prevent embarrassment and social stigmatization
3. To prevent potential brain damage from repeated seizures.

The goals of treatment are:
1. The fewest possible seizures
2. The fewest possible side effects
3. The fewest possible restrictions

Anti-epileptic drugs (AEDs) are the mainstays of the treatment of seizures. However, before initiating an AED in a patient, it is important to (re) consider:

- Are you sure the patient has had a seizure?
- How likely is it that the patient will have another seizure?

To answer the latter question, you must have excluded transient causes of seizures that have corrected themselves or that you can correct (such as metabolic abnormalities),
and you must have some knowledge of the likelihood of recurrence of various seizure types or epilepsy types.

Only 50% of all patients who are evaluated after a first seizure will have another. Therefore, a first seizure is often not treated, especially in children and especially if there was some kind of provocation such as sleep deprivation that may have temporarily lowered the patient’s seizure threshold.

The principles of treatment of seizures with AED’s are similar to that of many medical situations.

- Initiate a first choice AED for the patient’s seizure type. Use low doses, working up as needed to keep seizures under control.
- Use the lowest dose necessary to keep the seizures under control.
- Use the most practical dosing schedule that fits the pharmacokinetics of the drug. If breakthrough seizures are occurring at times of trough serum levels, or toxicity is occurring at times of peak serum levels, increase the frequency of dosing.
- Monitor side effects as well as efficacy.
- Educate the patient about side effects and potential drug interactions.
- Second Drug: If the seizures do not come under control with the first drug at levels that are tolerable without significant side effects, either switch to (if there was no benefit) or add (if there was some benefit) a second drug. Choose a second drug that has a different mechanism of action from the first.
- Try to avoid more than two drugs. Usually the side effects are additive but the beneficial effects are not.

Treatment of seizures with AEDs is helped by the judicious use of serum anticonvulsant levels. Anticonvulsant levels should be obtained in the following situations:

- At baseline, when the patient has been regulated on the appropriate dosage.
- When breakthrough seizures or toxicity occur.
- To judge appropriate increments in dosing when pushing up levels to obtain control.
- To monitor for drug interactions – i.e., when other drugs have been added or removed from the patient’s regimen.
- To check on compliance.
- To check on a fall in levels due to growth in a child.
- At occasional intervals, especially for patients on polytherapy or high dose monotherapy.

Drugs of choice are listed in Appendix III. The order of drugs of choice depends on their efficacy and especially on their relative side effects. Such a listing will change at times with the advent of new drugs, or new information about drugs or their side effects. This
listing is intended to be a reference for you as you encounter patients with epilepsy during your clinical training. A few hints about choosing from among these drugs:

- Drugs with the widest spectrum of efficacy include valproate, the benzodiazepines, lamotrigine and phenobarbital.
- Sometimes the drugs that are the best for partial seizures, especially carbamazepine, will make generalized seizures worse.
- The AEDS which are most likely to be sedating and/or interfere with concentration are the benzodiazepines (clonazepam, lorazepam, diazepam, clobazepate), primidone and phenobarbital.
- Consider how the side effects of any drug will fit with that particular patient (i.e., avoid a drug with a risk for bone marrow suppression in a patient on chemotherapy, etc.).
- Consider how the pharmacokinetics of the AED will fit with any other drugs the patient must take.

Other important aspects of the treatment of seizures include:

- Education about seizure types, risks and the AEDs.
- Restrictions to promote the patient's safety (driving, open machinery, heights, hot surfaces, baths alone) but no more restrictions than necessary.
- Help with educating family, friends, schools and employers so that undue fears or restrictions are not applied.
- Support to the patient and his family with respect to the burden of the diagnosis.
- Many larger communities have branches of the national Epilepsy Foundation that can provide additional education and support to persons with epilepsy and their families.

**OUTCOME OF SEIZURES**

Eighty percent of patients with epilepsy will have full control of their seizures on AEDs. Additionally, many children will grow out of their tendency for seizures. This is particularly likely in absence seizures of early onset, and in Benign Rolandoic epilepsy.

Usually if a child has been seizure-free for two years on anticonvulsant therapy, it is appropriate to taper him off the drug to see if he still needs it. Usually some restrictions must be reinstated during the tapering and initial period off the medication because of the chance of seizures. Approximately 75% of those who will have another seizure will do so in the first year off therapy. Sometimes adults do not want to risk the recurrence of seizures and/or give up driving. Trials off anticonvulsants should be instituted individually and as a joint decision between the patient and the physician.
INTRACTABLE SEIZURES

When a patient continues to have seizures despite treatment with AEDs, the following reasons for continuing seizures should be considered:

1. Non-electrical "seizures" or paroxysmal events such as:
   - pseudoseizures
   - rage attacks
   - staring spells related to inattention
   - other stereotyped behavior

2. Wrong drug for seizure type
   - especially generalized seizures being treated with drugs that are good for partial seizures

3. Right drug but insufficient dose
   - non-compliance
   - dose interval too long
   - dose too low
   - drug interactions

If none of the above situations apply, the patient is having intractable seizures. Up to 50% of such patients may be candidates for epilepsy surgery.

Resective surgery removes the epileptogenic tissue. Patients are appropriate candidates for resective surgery if 1) the epileptogenic focus is localizable (by ictal EEG recordings and/or detailed MRIs or other functional neuroimaging) and 2) that tissue is expendable without significant morbidity. The most common form of resective surgery is temporal lobectomy. Approximately 65% of patients with intractable complex partial seizures who undergo temporal lobectomy will become seizure free.

Disconnection surgery disconnects the epileptogenic tissue from the rest of the brain or from the other side of the brain. Corpus callosotomies are palliative and may prevent recurrent drop attacks and subsequent seizures in persons with mixed seizure disorders.

Intractable seizures carry a heavy toll for the patient. They usually interfere with employment and driving. They lead to over protection of children and social isolation with resultant loss in self-esteem. Recurrent seizures and side effects from the AEDs add to learning and behavior problems. The recurrent seizures may cause repeated injuries with resultant CNS damage, and they may cause dysfunction and eventually damage to tissue surrounding the epileptogenic zone. For all these reasons, persons with intractable seizures should be referred to an epilepsy center as soon as it is determined that the seizures are intractable, not only for reassessment of their medical treatment, but if they are candidates for epilepsy surgery, so that an opportunity may be provided early, before they are taken out of the mainstream of life.
REFERENCES


APPENDIX I

TABLE 1. THE INTERNATIONAL CLASSIFICATION OF EPILEPTIC SEIZURES

I. Partial (focal, local) seizures

A. Simple partial seizures (consciousness not impaired)
   1. With motor symptoms
   2. With somatosensory or special sensory symptoms
   3. With autonomic symptoms
   4. With psychic symptom

B. Complex partial seizures (with impairment of consciousness)
   1. Beginning as simple partial seizures and progressing to impairment of consciousness
      a. With no other features
      b. With features as in I.A.1 – I.A.4
      c. With automatisms
   2. With impairment of consciousness at onset
      a. With no other features
      b. With features as in I.A.1 – I.A.4
      c. With automatisms

C. Partial seizures evolving to secondarily generalized seizures
   1. Simple partial seizures evolving to generalized seizures
   2. Complex partial seizures evolving to generalized seizures
   3. Simple partial seizures evolving to complex partial seizures to generalized seizures

II. Generalized seizures (convulsive or nonconvulsive)

A. Absence seizures
   1. Absence seizures
   2. Atypical absence seizures

B. Myoclonic seizures

C. Clonic seizures

D. Tonic seizures

E. Tonic-clonic seizures

F. Atonic seizures (astatic seizures)

III. Unclassified epileptic seizures

Includes all seizures that cannot be classified because of inadequate or incomplete data and some that defy classification in hitherto described categories. This includes some neonatal seizures, e.g. rhythmic eye movements, chewing, and swimming movements

* from "Commission on Classification and terminology of the International League Against Epilepsy (1981); Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 22:489-501, with permission.
TABLE 2. INTERNATIONAL CLASSIFICATION OF EPILEPSIES AND EPILEPTIC SYNDROMES

1. Localization–related (focal, local, partial) epilepsies and syndromes

1.1 Idiopathic (with age related onset): At present, two syndromes are established:
   - Benign childhood epilepsy with centrotemporal spike
   - Childhood epilepsy with occipital paroxysms

1.2 Symptomatic: This category comprises syndromes of great individual variability
   - Chronic progressive epilepsy partialis continua of childhood
   - Temporal lobe epilepsies (hippocampal, amygdala, lateral posterior temporal, opercular, insular)
   - Frontal lobe epilepsies (supplementary motor, cingulate, anteror polar, orbitofrontal, dorsolateral, motor)
   - Parietal lobe epilepsies
   - Occipital lobe epilepsies

1.3 Cryptogenic: presumed symptomatic but etiology is unknown

2. Generalized epilepsies and syndromes

2.1 Idiopathic (with age-related onset, in order of age appearance)
   - Benign neonatal familial convulsions
   - Benign neonatal convulsions
   - Benign myoclonic epilepsy in infancy
   - Childhood absence epilepsy (pyknolepsy, petit mal)
   - Juvenile absence epilepsy
   - Juvenile myoclonic epilepsy (impulsive petit mal)
   - Epilepsy with grand mal seizures (GTCS) on awakening
   - Other generalized idiopathic epilepsies not defined above
   - Epilepsies with seizures precipitated by specific modes of activation

2.2 Cryptogenic or symptomatic (in order of appearance)
   - West's syndrome (infantile spasms, Blitz-Nick-Salaam Krampfe.)
   - Lennox-Gastaut syndrome
   - Epilepsy with myoclonic-astatic seizures
   - Epilepsy with myoclonic absences

2.3 Symptomatic
   2.3.1 Nonspecific etiology
      - Early myoclonic encephalopathy
      - Early infantile epileptic encephalopathy with suppression burst
      - Other symptomatic generalized epilepsies not defined above

2.3.2 Specific syndromes: Epileptic seizures may complicate many disease states. Under this heading are included those diseases in which seizures are presenting or predominant feature
   - Metabolic errors (amino acidurias, gangliosidosis etc)
   - Progressive myoclonic epilepsies with specific pathology (ceroid-lipofuscinosis, Lafora disease, Kufs disease, etc)
### TABLE 2. INTERNATIONAL CLASSIFICATION OF EPILEPSIES AND EPILEPTIC SYNDROMES (Cont.)

#### 3. Epilepsies and syndromes undetermined as to whether they are focal or generalized
3.1 With both generalized and focal features
- Neonatal seizures
- Severe myoclonic epilepsy in infancy
- Epilepsy with continuous spikes and waves during slow-wave sleep
- Acquired epileptic aphasia (Landau-Kleffner syndrome)

3.2 Without unequivocal generalized or focal features

(3.3) Symptomatic mixed epilepsies
- Presumed or known focal brain disorder with mostly generalized seizures
- Multifocal brain disorder with mostly generalized seizures
- Unifocal or multifocal brain disorder with both partial and generalized seizures)

#### 4. Special syndromes
4.1 Situation-related seizures (Gelegenheitsanfälle)
- Febrile convulsions
- Seizures related to other identifiable situations, such as stress, hormones, drugs, alcohol, or sleep deprivation

4.2 Isolated, apparently unprovoked epileptic events

4.3 Epilepsies characterized by specific modes of seizures precipitated

4.4 Chronic progressive epilepsia partialis continua of childhood


#### Examples:

1. **Juvenile Myoclonic Epilepsy**
   - Onset in teens
   - Myoclonic jerks – predominantly in the arms, without loss of consciousness soon after awakening
   - Often associated with generalized tonic-clonic seizures shortly after awakening
   - Sometimes associated with absences
   - EEG findings: rapid generalized spike and wave, polyspike and wave, often photosensitive
   - Good response to Valproate
   - Seizure tendency persists well into adulthood

2. **Benign childhood epilepsy with centrotemporal spikes**
   - Onset 3-13 years
   - Brief simple partial hemifacial motor/sensory seizures
   - Tend to evolve into secondarily generalized clonic seizures
   - Most seizures occur at sleep onset of offset
   - EEG: unilateral or shifting bilateral frequent high voltage centro-temporal spikes often with positive end of dipole in mid frontal region
   - Tendency to seizures and EEG findings disappear around puberty
APPENDIX II

DRUGS OF CHOICE FOR SEIZURES

Partial Seizures: (simple, complex, or secondarily generalized)

- carbamazepine
- phenytoin, gabapentin
- valproate
- primidone, phenobarbital
- lamotrigine, tiagabine, topiramate, felbamate

Primary Generalized Seizures

**Absence**
- ethosuximide
- valproate
- acetazolamide
- lamotrigine, clonazepam

**Myoclonic and Akinetic**
- valproate
- ethosuximide
- lamotrigine
- clorazepate, clonazepam, topiramate?

**Tonic, Clonic, and Tonic-clonic**
- valproate
- phenytoin (esp. for tonic seizures)
- phenobarbital, lamotrigine,
- the benzodiazepines

**Infantile spasms**
- ACTH
- valproate, clorazepate, (vigabatrin)
APPENDIX III

CARBAMAZEPINE (CBZ) (Tegretol)

Mechanism of Action: limits sustained repetitive firing
Efficacy: partial or secondary generalized seizures
Half-life: 26 hours post induction (20-30 days), 18-55 hours at first
Dose: 10 mg/kg when starting CBZ monotherapy
(work up over 5-10 days to avoid initial sedation)
Serum level: 12 μg/ml – often well tolerated to 12-14 μg/ml
(hard to get high levels in polytherapy)
Peak level: 8 hours post oral dose

Side effects:
• Sedation at high levels
• Elevated mood, positive behavioral effects
• Blurry vision, diplopia (higher levels)
• Nausea
• Cholestatic jaundice
• Dry mouth
• Tremor, chorea, dystonia, asterixis
• Water retention (especially in severely handicapped patients)
• Leukopenia – common in first few weeks of therapy – rarely requires cessation of therapy
• Aplastic anemia (very rare)
• Allergic skin rash with eosinophilia (8%) – may be severe
• Increased seizures – especially in Lennox-Gastaut syndrome or in primary generalized epilepsy

Rarely:
• Behavioral disturbances – hyperactivity irritability
• Bone marrow suppression
• relatively little effect on attention or learning

Laboratory monitoring:
• CBC and differential. Initially and 2 X in the next 2 months, then q 6-12 months. WBC may be lower than usual in viral illness.

Medications or conditions which increase carbamazepine levels:
- Acetazolamide
- Isoniazid (INH)
- Triacetyloleandomycin (TAO)
- Cimetidine
- Nicotinic acid
- ? Valproate slightly
- Erythromycin
- Propoxyphene
- Verapamil
- Isonicotinic acid
- Tetracycline

Decreased levels or effect:
• Drugs which include hepatic enzymes such as phenobarbital, phenytoin, primidone, clonazepam
• Pregnancy

Medications which are affected by carbamazepine administration:
Decreased levels or effect on:
• Anticonvulsants affected by increased hepatic degradation – phenobarbital (variable effect), phenytoin, valproate, clonazepam, warfarin, oral contraceptives, haloperidol, doxyyadine, theophyllines
PHENOBARBITAL (PB)

Mechanism of action: enhances GABA-ergic inhibition
Efficacy: partial and secondary generalized seizures, febrile seizures
Half-life: 2 ½ - 6 days, 1 ½ - 3 days in children
Dose: 3-5 mg/kg up to 25 kg, 2 – 2.5 mg/kg at 25-50 kg,
1-2 mg/kg in adults
Therapeutic serum level: 10-40 μg/ml

Side effects:
- Sedation – especially initially and at higher levels
- Hyperactivity in most children, irritability in older children and adults
- Attention deficit (all ages)
- Decreased short term memory
- Decreased adaptive skills
- Ataxia
- Megaloblastic anemia (rare)
- Skin reactions, including Stevens-Johnson Syndrome (rare)
- Chemical, and rarely clinical rickets especially in polytherapy
- Marked toxicity – respiratory depression – in overdose

Medications that increase phenobarbital levels:
Acetazolamide  Dextropropxyphene  Phenytoin (sometimes)
Chloramphenicol  Isonicotinic acid  *Valproate

Medications that decrease phenobarbital levels:
- Any drug that induces hepatic degradative enzymes, including phenobarbital itself, phenytoin, carbamazepine

Medications whose levels are decreased by phenobarbital administration:
Aminopyrine  Coumadin  Phenytoin
Betadine  Dexamethasone  Testosterone
Beta blockers  Doxycycline  Theophyllines
Carbamazepine  Digitoxin  Valproate
Chloramphenicol  Griseofulvin  Vitamin D3
Chlorpromazine  Quinine  
Corticosteroids  Oral contraceptive
PHENYTOIN (PHT) (Dilantin)

**Mechanism of Action:** on voltage dependent sodium channels, reduces repetitive firing

**Efficacy:** partial (all forms), generalized tonic-clinic, tonic

**Half-life:** 7-42 hours (average 22 hours), varies with dose (zero order kinetics)

**Dose:** 5-8 mg/kg/day up to 500 mg in large adults

**Therapeutic serum level:** 5-20 μg/ml, levels vary dramatically in therapeutic range with small changes in dosage

**Peak oral levels:** 4-7 hours with secondary peak at 8-15 hours

**Side effects:**
- Gingival hypertrophy
- Hirsutism, thickened facial features
- Depression, lethargy, slowed mentation and motor responses
- Nystagmus, ataxia
- Nausea
- Allergic dermatitis, fever, and eosinophilia (in 10%)
- Lupus-like reaction with antinuclear antibodies
- Megaloblastic anemia, bone marrow suppression
- Chemical and clinical (rare) rickets
- Cerebellar degeneration & dementia with chronic high doses
- Hypersensitivity reactions with hepatitis, nephritis, etc.

**Medications which affect phenytoin levels or effect:**

**Increased levels:**
- Aminosalicylic acid
- Chloramphenicol
- Chlor Diazepoxide
- Chlopromazine
- Cimetidine
- Co-trimoxazole (Septra)
- Coumadin
- Cycloserine
- Dexamethasone
- Disulfiram
- Doxycycline
- Halothane
- Isoniazid (INH)
- Isonicotinic acid
- Methylphenidate
- Phenobarbital (variable)
- Phenylbutazone
- Prochlorperazine
- Sulfonides
- Trimethoprim

**Decreased levels or effects:**
- Alcohol (chronic use)
- Antacids
- Antineoplastics
- Carbamazepine
- Diazoxide
- Folic acid
- Phenobarbital (variable)

**Decreased levels without decreased effect:**
- Salicylate (displaces from binding)
- Tolbutamide
- Valproate

**Medications affected by phenytoin administration:**

**Increased levels or effect of:**
- Cardiac depressive effect of lidocaine
- Diazoxide
- Warfarin

**Decreased levels or effect of:**
- Coumadin
- Dexamethasone
- Disopyramide
- Furosemide
- Hypoglycemics
- Levodopa
- Methadone
- Oral contraceptives
- Phenobarbital
- Primidone
- Quinidine
VALPROIC ACID (VPA) (Depakene)
SODIUM VALPROATE (Depakote)

Mechanism of action:
- Effect on sodium channel, blocks sustained repetitive firing, reduces T-type currents in primary afferent neurons

Efficacy:
- Primary generalized (all types), febrile, partial and secondarily generalized

Dose:
- 10-30 mg/kg/day
  (sometimes 40-50 mg/kg/day, especially in infants on polytherapy)

Half-life:
- 6-18 hours, average 9 hours if on other anticonvulsants

Therapeutic serum level:
- 50-100 µg/ml
  (sometimes up to 150 µg/ml is well tolerated and helpful)

Peak oral level:
- 1-3 hours after regular capsule
- 3-6 hours after the enteric coated tablet

Side effects:
- Sedation at high levels
- Nausea and vomiting
- Increased appetite and weight gain (may be prominent in 30-40%)
- Tremor at higher levels
- Mild to moderate reversible hair loss
- Pancreatitis
- Thrombocytopenia – especially at high doses
- Hyperammonemia
- *hepatitis – rare idiosyncratic reaction which may be fatal – seen most in age < 2 years in neurologically handicapped children on multiple drugs – very rare after 6 months of therapy
  - avoid by taking 50 to 100 mg/kg/day of Carnitine

Laboratory monitoring:
- ALT (SGPT) before beginning therapy and 10-14 days after onset, then at 1 month and 3 months, then 6 to 12 months
- CBC and platelet count before starting therapy and then q 6-12 months with high levels of valproate

Medications which affect valproate levels:

Decreased levels:
- Drugs which induce hepatic enzymes such as carbamazepine, phenobarbital, and phenytoin
- Salicylic acid and free fatty acids displace valproate from albumin and decrease the level but may not decrease the effect – may increase the effect

Medications which are affected by the administration of valproate:

Increased levels or effect:
- * Carbamazepine
- * Ethosuximide
- Phenobarbital (levels go up 30-60%, sometimes 200%)

Decreased levels but not effect:
- Phenytoin (displaced from albumin) but free level, and therefore the effect remains unchanged
ETHOSUXIMIDE (ETX) (Zarontin)

Mechanism of action: reduces T-type calcium currents in thalamic neurons
Efficacy: primary generalized: absence, myoclonic, akinetic (not tonic-clonic)
Dose: 15-30 mg/kg, up to 40 mg/kg in children
Half-life: 15-68 hours (mean 36-39), shorter in children than adults
Therapeutic serum level: 40-100 µg/ml, peak levels in 3 hours

Side effects:
- Nausea, abdominal discomfort
- Drowsiness
- Rare idiosyncratic behavioral disturbances, hallucinations
- Ataxia
- Acute dystonias that respond to diphenhydramine
- Pancytopenia, some suggest monthly CBC's
- Elevated liver function tests
- Rashes, erythema multiforme, Stevens-Johnson syndrome
- Lupus-like reactions
- ? may induce grand mal seizure
- No significant interactions with other medications

PRIMIDONE (PMD) (Mysoline)

Mechanism of action: enhances GABA-ergic inhibition
Efficacy: partial (including secondarily generalized) seizures
Dose: 5-20 mg/kg/day (start slowly to avoid initial sedation)
Half-life: primidone 3-20 hours, phenobarbital 4 days
(1/3 of drug is converted to phenobarbital)
Therapeutic serum level: primidone 6-12 µg/ml, phenobarbital 10-40 µg/ml
Phenobarbital/primidone ratio usually 1 – 1.5
Peak oral level: 1-2 hours

Side effects:
- Initial drowsiness, weakness, dizziness
- Sedation
- Slowed mentation and motor responses
- Behavioral changes as in phenobarbital
- Ataxia, vertigo, nystagmus
- Visual disturbances
- Allergic skin rash, systemic lupus
- Megaloblastic anemia (rare)
- Chemical rickets

Medications which affect primidone levels or effect:
Increased level or effect:
Isoniazid  Isonicotinic acid  ? Methylphenidate  Valproate

Decreased levels or effect:
Acetazolamide (interferes with absorption)  Carbamazepine

Other:
- Phenytoin increases the phenobarbital/primidone ratio to 4:1
LAMOTRIGINE (Lamictal)

Mechanism of action: ? inhibits release of glutamate, blocks MES
Efficacy: symptomatic generalized, primary generalized, partial seizures
Dose: 200-400 mg, more if on a hepatic enzyme inducer, less if on valproate
Half-life: 24 hours, 15 hours if on a hepatic enzyme inducer,
72 hours if on valproate
Serum levels: not yet determined

Side effects:
• Rash in 10% to 15%
  Starting dosage slowly (over several weeks) helps minimize chance of rash
• Dizziness, ataxia
• Headache
• Diplopia, blurred vision
• Nausea, vomiting

Medications which decrease its level:
• Hepatic enzyme inducers (phenytoin, carbamazepine, phenobarbital, and non AEDs)

Medications which increase its level:
• Valproate (if taken with valproate and no hepatic enzyme inducers, require 1/3 the usual dose)

Medications affected by lamotrigine:
• None

GABAPENTIN (Neurontin)

Mechanism of action: binds to a specific receptor but no effect on GABA system, anti MES and anti PTZ activity
Efficacy: partial and secondarily generalized seizures
Pharmacokinetics: Dose dependent decrease in absorption, because it saturates an active transport system
< 3% is protein bound
Dose: 900 to 4200 mg/day, divided qid
Half-life: 5-7 hours,
water soluble, excreted unchanged in urine

Side effects:
• Fatigue
• Dizziness
• Headache
• Nystagmus
• Irritability

Drug interactions: None
SECONDARY ANTICONVULSANTS

CLONAZEPAM (CZP) (Klonopin)

Efficacy: primary generalized including absence, myoclonic infantile spasms, and tonic-clonic, rarely in partial or secondarily generalized
Dose: starting with 0.01 – 0.02 mg/kg working up to 0.1 – 0.2 mg/kg
Half-life: 24-36 hours
Therapeutic serum level: 0.01 – 0.05 µg/ml
Peak oral level: 2-4 hours

Side effects:
• Sedation
• Behavioral changes including hyperactivity, inattention, restlessness, disruptive behavior, aggressiveness – frequent. These are sensitive to small changes in dosage
• Skin changes/rashes
• Increased secretions (wheezing)
• Blurred vision, diplopia
• Habituation of efficacy
• Prominent withdrawal symptoms or irritability, myoclonus and increased seizures in combination with valproate may produce absence status, though may also be effective
• Increased seizures

Clonazepam induces hepatic enzymes and therefore may lower other drug levels. Drugs that induce hepatic enzymes may also reduce its level. CZP levels increase with cimetidine, disulfiram. Sedative effect of CZP increased by theophyllines. CZP increases digoxin toxicity, lithium neurotoxicity, increases or decreases muscle relaxants.

ACETAZOLAMIDE (Diamox)

Efficacy: absence, myoclonic, akinetic, (especially with valproate), partial (with carbamazepine)
Dose: 10-20 mg/kg/day (tid) up to 1 gram
Half-life: 10-12 hours
Therapeutic serum level: 10-14 µg/ml, (not easily available)

Side effects:
• Diuresis
• Sedation in higher doses
• Paresthesias
• Skin rashes
• Dizziness
• Nausea
• Hyperpnea
• Not significantly affected by other drugs.

Medications that are affected by administration of acetazolamide:

Increased levels or effect:
• Increased concentrations of weak acids (most anticonvulsants) in tissues
• Increased carbamazepine levels - ? other anticonvulsants
• Salicylic acid (increased absorption)
FELBAMATE (Felbatol)

**Mechanism of action:** Glycine antagonist on NMDA complex

**Efficacy:** Mixed symptomatic seizures (Lennox-Gastaut)

**Pharmacokinetics:** 90% absorbed, peak at 1-3 hours
25% protein bound

**Dose:** Initiate with 15 mg/kg/day, top dose of 45 mg/kg/day or 3600 mg in monotherapy

**Half-life:** 20 hours (shorter with hepatic enzyme inducers)
50% excreted unchanged in urine, 40% metabolized in liver

**Side effects:**
- Appetite suppression
- Insomnia
- Increased alertness and attentiveness
- *Fatal bone marrow suppression in 1/2 - 5000

**Drug interactions:**
- Serum levels decreased by hepatic enzyme induces
- It increases valproate, phenytoin, and carbamazepine-epoxide levels
SLEEP DISORDERS
Ralph F. Jozefowicz, MD

Polysomnography

**Definition:** The continuous recording of the electroencephalogram (EEG), the electro-oculogram (EOG-a measure of eye movement activity), and the electromyogram (EMG) to define sleep and wakefulness.

1. **Electroencephalogram (EEG)**

   **Definition:** The recording and measurement of electrical brain potentials by means of scalp electrodes.

   **EEG frequencies:**
   - Delta  < 4Hz
   - Theta  4-7Hz
   - Alpha  8-13Hz
   - Beta   > 13Hz

2. **Electro-oculogram (EOG)**

   **Definition:** The recording and measurement of eye movements. The EOG is recorded from electrodes placed on the outer canthus of each eye. The cornea is weakly electropositive, and the retina is weakly electronegative. Eye movements thus produce an electrical potential that can be recorded by the EOG electrodes.

3. **Electromyogram (EMG)**

   **Definition:** The recording and measurement of electrical activity of muscle. For purposes of polysomnography, the EMG is recorded from the submentalis muscle of the chin.

Normal Sleep Physiology

**Stages of Sleep:** Sleep is staged by means of polysomnography. Two states of sleep are identified: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep.

1. **Non-rapid Eye Movement (NREM) Sleep**

   This state of sleep is sub-divided into four stages, based on findings on polysomnography:
Stage I  low-amplitude theta  
Stage II  K-complexes and sleep spindles  
Stage III  20-50% high-amplitude delta  
Stage IV  >50% high-amplitude delta  

Eye movements are absent during NREM sleep, except during Stage I sleep when slow, rolling eye movements may be present. EMG activity is reduced in the submentalis muscle in NREM sleep.

2. Rapid Eye Movement (REM) Sleep

This state of sleep has an EEG pattern similar to NREM Stage I sleep, with low-amplitude, mixed frequency waves. In addition, rapid, conjugate ocular movements are present, and EMG activity from the submentalis muscle is absent.

Organization of Human Sleep

In normal adults, after sleep onset, sleep usually progresses through NREM Stages I to IV within 45-60 minutes. Slow-wave sleep (NREM Stages III and IV) predominates in the first third of the night and comprises 15-25% of total nocturnal sleep time in young adults. After the first slow-wave sleep episode, the progression of NREM stages reverses. The first episode of REM sleep then occurs, usually within one hour after sleep begins. NREM and REM alternate throughout the night with an average cycle of 90-110 minutes. Four to six such cycles are present each night. After the first REM, the intervals between successive REM periods decrease throughout the night, while the length of each REM episode tends to increase. Overall, REM sleep occupies approximately 20-25% of sleep; Stage II sleep occupies about 1/2 of total sleep; and Stage III and IV sleep occupy about 15%.

Dreams can occur during all stages of sleep. In general, vivid dreams with well-developed story lines occur during REM sleep, whereas dreams associated with NREM sleep are less vivid and visual, and more conceptual.

The Effect of Age on Sleep Patterns:

Daily sleep requirements decline steadily throughout childhood and adolescence, leveling off during middle years, and often declining further with old age.

REM sleep occupies 1/2 of the normal sleep time in newborns, and then declines to about 25% by 10 years of age. This percentage remains steady until the seventh or eighth decade, when it once again decreases. Stage IV sleep declines exponentially throughout the developing and middle years, often disappearing after 60 years of age.

Neuroanatomy of Sleep:

- The reticular activating system (RAS) is integrally involved in inducing sleep and wakefulness. The rostral RAS may contain a population of neurons whose activity is required for wakefulness. Conversely, the caudal RAS may contain neurons that are
required to induce sleep. Two groups of neurons in the caudal brain stem have been implicated in promoting sleep, namely the raphe nuclei and the nucleus of the solitary tract in the medulla.

- The suprachiasmatic nucleus of the hypothalamus is also important in inducing sleep. This nucleus is also felt to be the "biologic clock" for circadian rhythms, and is involved in regulating the diurnal secretion of various hormones. This hypothalamic nucleus also receives direct input from the retina via the retinohypothalamic fibers. This retinal input helps reset the intrinsic rhythmicity of the suprachiasmatic nucleus to coincide with the external light-dark cycle.

**Neurochemistry of Sleep:**

- Many substances have been identified as promoting sleep. One of the first "sleep factors" identified was serotonin, which is secreted by the raphe nuclei in the brain stem. Intracerebral injection of serotonin induced sleep, and destruction of the raphe cells induced complete insomnia for several days in cats in one study. Slow-wave sleep gradually returned, however, following several days.

- Other sleep promoting factors that have been identified include delta sleep-inducing peptide and muramyl peptide, the latter substance being involved with the serotonergic system.

**Disorders of Sleep**

**Insomnia:** This is defined as the chronic inability to obtain the amount or quality of sleep necessary to maintain adequate day time behavior.

- **Sleep Misperception Syndrome:** A syndrome in which individuals underestimate actual sleep and complain of poor quality, unrefreshing sleep, despite the fact that polysomnograms demonstrate normal physiologic sleep.

- **Psychophysiological Insomnia:** A behavioral disorder in which patients are preoccupied with a perceived inability to sleep at night. The sleep disturbance is often triggered by an emotionally stressful event, and the poor sleep habits acquired during the stressful period persist long after the initial incident.

- **Psychopathological Insomnia:** Insomnia associated with emotional disturbances. Anxiety and depression are two common causes. Anxiety tends to be correlated with difficulty falling asleep, while depression is correlated with early awakenings. Of note, patients with chronic schizophrenia sleep well.

- **Limb Movement Insomnia:** These patients are kept awake by physiological events of which they are unaware.

- **Nocturnal Myoclonus:** These patients experience periodic stereotyped leg twitches which occur every 20-40 seconds during NREM Stage I and II sleep.
• **Restless Leg Syndrome:** These patients have an irresistible urge to keep the limbs in motion while falling asleep, and this delays sleep onset.

• **Circadian Rhythm Insomnia:**

  • **Jet Lag Syndrome:** In this syndrome, travel across meridians causes a phase shift of the circadian cycle, resulting in a disturbance of sleep. Spending more time outdoors results in more rapid adaptation to the phase shift.

**Treatment of Insomnia:**

• **Barbiturates:** These medications were formerly prescribed to treat insomnia. Tolerance develops rapidly, usually within two weeks, and rebound insomnia is present upon withdrawal of these drugs. Barbiturates severely suppress REM sleep, and drug withdrawal is associated with profound REM rebound. As a result, these drugs are no longer prescribed as hypnotics.

• **Benzodiazepines:** These medications are potent suppressors of deep slow-wave sleep. Nonetheless, they enhance the subjective quality of sleep. They are felt to sharply reduce the number of microwakes that, lasting but a few seconds each, severely diminish the restorative dimensions of sleep. Benzodiazepines are now the medications most commonly prescribed for insomnia.

**Parasomnia:** A normally undesirable behavior that occurs either exclusively during sleep, or is exacerbated by sleep.

• **Nocturnal Enuresis:** Bed wetting is common in children, especially boys and young adults, and has an incidence of 3-6%. Most episodes occur during Stage IV slow-wave sleep. Idiopathic enuresis is felt to be related to a maturational lag in neurological control.

• **Somnambulism:** Sleep walking also occurs most commonly in children and adolescents and typically occurs during Stage III or IV slow-wave sleep. During episodes of sleep walking, the patients carry out automatic motor activities such as walking, urinating inappropriately, or exiting the house. They remain unconsciousness during the episode.

• **Night Terrors:** This disorder occurs primarily in young children during the first several hours of sleep, in Stages III and IV slow-wave sleep. The child abruptly sits up in bed, screams, and appears to be staring wide-eyed at some imaginary object. Autonomic activity is present. After the attack the child resumes sleeping and has no recollection for the attack by the next morning.

• **REM Behavior Disorder:** In this disorder, which is most common in older men, the patients experience violent behavior during sleep. This behavior occurs during REM sleep and the patients describe vivid, violent moving nightmares. Some patients injure themselves or their bed partners during episodes. In REM behavior disorder the normal paralysis of REM sleep is lost, and the person literally jumps out of bed and enacts the dream he experiences. Treatment with anti-convulsant medications may help.
**Hypersomnia**: A group of disorders in which day time somnolence occurs as a result of altered sleep patterns. Sleep apnea and narcolepsy are the two most common hypersomnias, and each of these will be discussed below:

### Sleep Apnea

**Definition**: A syndrome in which abnormal respiratory patterns during sleep result in a combination of hypercapnea and alveolar hypoxemia.

**Classification of Sleep Apneas**:

- **Obstructive Sleep Apnea**: A cessation of air flow due to upper airway obstruction despite persistent respiratory movements. Micrognathia, enlarged tonsils and adenoids, enlarged uvula and posterior pharyngeal tissue, obesity, and other conditions causing increased airway resistance all predispose toward this form of sleep apnea.

- **Central Sleep Apnea**: A cessation of both air flow and respiratory movements, which can occur due to damaged brain stem centers, as seen in brain stem infarction, bulbar poliomyelitis, or bilateral cervical cordotomy. This form of sleep apnea may also occur independent of brain stem pathology, as in the primary alveolar hypoventilation syndrome (Ondine's Curse).

- **Mixed Sleep Apnea**: In this disorder, a central respiratory pause is followed by obstructive ventilatory efforts.

**Clinical Features**: The most common clinical features include loud pharyngeal snoring, nighttime apnea, day time hypersomnolence and morning headaches. Abnormal motor movements are frequently seen during sleep. Cardiac arrhythmias may be present as well.

**Complications**: Long-standing sleep apnea can lead to pulmonary hypertension, cor pulmonale and polycythemia. These complications, when present in an obese individual, are known as the "Pickwickian Syndrome".

**Epidemiology**: Although sleep apnea can occur in all ages and in both sexes, it is most common in older men, particularly those who are obese.

**Treatment**: **Weight loss** is effective in many individuals and is the first treatment employed. **Continued positive airway pressure (CPAP)** is a new treatment similar to a pneumatic splint of the airway. A tight-fitting mask delivers high pressure air that keeps the throat expanded between breaths. At times, surgery to enlarge the upper airway by cutting away the uvula may be successful.

Pharmacologic therapy of sleep apnea is of limited benefit. The respiratory stimulants aminophylline, progesterone and tricyclic compounds have all been tried with varying degrees of success. Acetazolamide, a carbonic anhydride inhibitor, may also be
effective by producing a mild metabolic acidosis that increases the sensitivity of peripheral chemoreceptors to hypercapnea.

**Narcolepsy**

**Definition:** A syndrome of excessive sleepiness and abnormalities of REM sleep.

**Epidemiology:** The prevalence of narcolepsy is between 1:1000 and 1:10,000. Most patients have the onset of symptoms between ages 15-35 years. The disorder tends to be autosomal dominant in inheritance with variable penetrance, and the abnormal gene is felt to be located on the short arm of chromosome 6. Narcolepsy is associated with certain haplotypes, including HLA-DR2 and HLA-DQw1.

**Symptoms:** There are four cardinal symptoms of the narcolepsy syndrome.

1. **Excessive day time somnolence** that usually occurs in boring, sedentary situations and is partially alleviated by motor activity and mental stimulation. It cannot be fully relieved by any amount of sleep, however. The episodes of day time sleepiness are usually brief, lasting less than 15 minutes, following which the patient awakes refreshed. Vivid dreaming typically occurs during these episodes.

2. **Cataplexy,** which is muscular weakness or paralysis brought on by excitement or emotion, such as laughter. Severe attacks cause complete paralysis except for the respiratory and eye muscles. Most attacks last less than one minute.

3. **Sleep paralysis,** defined as brief episodes of inability to move during the onset of sleep or on awakening.

4. **Hypnagogic hallucinations,** which are hallucinatory experiences that accompany the onset of sleep or awakening.

Narcolepsy and cataplexy are present in most individuals with this disorder. Sleep paralysis and hypnagogic hallucinations are present in only about 60% of patients.

**Pathophysiology:** Narcolepsy is felt to be an abnormality of REM sleep in which REM sleep occurs at the onset of sleep or within 10 minutes thereafter. This is due to impaired sleep-wake regulation, rather than an excessive need for REM sleep. Day time somnolence is due to intrusion of REM sleep into wakefulness. Hypragogic hallucinations, sleep paralysis and cataplexy are also felt to be dissociated manifestations of REM sleep that intrude into wakefulness. The atonia that accompanies cataplexy and sleep paralysis is physiologically similar to the atonia of REM sleep.

**Diagnosis:** Narcolepsy is most often diagnosed clinically with the tetrad of symptoms. A positive family history is often helpful.

Laboratory confirmation of narcolepsy includes polysomnography. A multiple sleep latency test is often times performed, which involves repeated measurement of sleep latency (time to onset of sleep) at two hour intervals under standardized conditions.
during a day following quantified nocturnal sleep. The patient is observed for excessive 
day time somnolence, described as the ability to fall asleep within ten minutes of laying 
down. In addition, one looks for direct transitions from wakefulness to REM sleep.

**Treatment:** Modafinil (Provigil), a novel drug that promotes wakefulness, has recently 
been approved for the treatment of hypersomnolence in narcolepsy; it is quite effective 
and well tolerated. Hypersomnolence may also be treated with stimulants, including 
methylphenidate or dextroamphetamine.

Cataplexy, sleep paralysis and hypnagogic hallucinations are treated with tricyclic 
antidepressants, including pemoline or protriptyline.
The somatoform disorders are a group of psychiatric conditions that mimic physical illness. Patients with a somatoform disorder are preoccupied with physical symptoms that suggest physical disease, but which remain unexplained despite exhaustive physical and laboratory evaluations. Although these patients tend to seek medical care relentlessly, they remain dissatisfied with the care received. They also remain convinced that their symptoms have a physical basis and resist psychiatric referral. The end result in many cases is a strained doctor-patient relationship.

The somatoform disorders may be divided into two broad groups: (1) those in which the physical symptoms are not intentional (involuntary), and (2) those in which the physical symptoms are intentionally produced (voluntary). The specific somatoform disorders include the following:

- **Involuntary**
  - Conversion disorder
  - Somatization disorder (Briquet’s syndrome)
  - Pain disorder
  - Hypochondriasis

- **Voluntary**
  - Malingering
  - Factitious disorder (Munchausen’s syndrome)

**Conversion Disorder**

A conversion disorder is a loss or alteration of physical functioning that cannot be explained by physical findings.

Conversion disorder usually has its onset during the second and third decade of life. The incidence has been reported as ranging from 11-300/100,000 in the general population.

The symptoms of conversion disorder are neurological, and include motor symptoms, sensory symptoms, or seizures. Specific symptoms include the following:

- **Motor symptoms**: paralysis, astasia/abasia, globus hystericus, aphonia, impaired coordination or balance, and urinary retention.
- **Sensory symptoms**: numbness, blindness, diplopia, deafness, and hallucinations.
- **Seizures** or convulsions (pseudoseizures).

Conversion symptoms typically do not conform to known anatomical pathways and physiological mechanisms, but instead follow the individual’s conceptualization of a condition. The more medically naive the person, the more implausible are the
presenting symptoms. Findings on neurological examination that suggest a conversion disorder include the following:

- A discrepancy between functional strength testing and formal strength testing.
- Sensory abnormalities that do not follow a dermatomal or peripheral nerve distribution, or which “split the midline” exactly.
- A hysterical gait (“astasia/abasia”) that requires an extraordinary amount of strength and coordination to execute.
- “Psychogenic” seizures characterized by pelvic thrusting, or preserved consciousness despite convulsive movements in all four limbs.

It is important to note that most patients with a conversion disorder are not anxious while they are manifesting conversion symptoms. The physical symptoms that they develop represent a symbolic resolution of an unconscious psychological conflict, thereby eliminating anxiety and keeping the conflict out of awareness (“primary gain”). The individual might also derive “secondary gain” from the conversion symptoms, by obtaining external benefits or avoiding duties or responsibilities. The patient with conversion disorder has little or no insight into his/her condition, and may manifest “la belle indifference” (a relative lack of concern about the nature or implications of the symptom). The onset of symptoms is usually abrupt.

A diagnosis of conversion disorder should only be made after a thorough medical investigation has been performed to rule out neurological or general medical conditions. It is also important to note that conversion symptoms may coexist with somatic pathology. Hence, patients with this disorder need to be evaluated carefully at initial presentation, and re-evaluated at regular intervals.

**Somatization Disorder**

**Briquet’s Syndrome**

Somatization disorder (Briquet's syndrome) is a chronic, relapsing somatoform disorder manifested by recurrent, excessive multi-system complaints.

The onset of somatization disorder occurs before the age of 30, and is much more common in women, with an incidence of approximately 2%.

Patients with somatization disorder consider themselves “sickly” and, by definition, must have eight of the following symptoms at various times during the course of their disease:

- Pain symptoms: head, chest, back, joints, extremities.
- Gastrointestinal symptoms: nausea, vomiting, diarrhea, abdominal pain, bloating, and food intolerance.
- Sexual symptoms: menstrual irregularity, excessive menstrual bleeding, dysparunia, vomiting throughout pregnancy, erectile or ejaculatory dysfunction, and sexual indifference.
- Cardiopulmonary symptoms: dyspnea, palpitations, chest pain, dizziness.
• Neurological conversion symptoms: impaired coordination or balance, paralysis or localized weakness, difficulty swallowing, globus hystericus, aphony, urinary retention, loss of touch or pain sensation, double vision, blindness, deafness, seizures.

Patients with somatization disorder typically have voluminous hospital records, undergo myriads of medical tests, and have an excess number of surgeries. Despite this, they maintain a relatively stable clinical course. They are frequently anxious and depressed, and may threaten suicide.

**Pain Disorder**

Pain disorder is a syndrome of persistent pain without adequate physical findings. The pain causes significant distress, or impairment in social functioning or job performance.

Pain disorder is more common in women.

Psychological factors play a significant role in the onset, severity, exacerbation and maintenance of the pain.

Patients with pain disorder may develop drug dependence or abuse.

**Hypochondriasis**

Hypochondriasis is a state of hyper-alertness to physical symptoms without demonstrable physical findings. Patients with this disorder misinterpret normal physiologic sensations as indicators of serious disease.

Although hypochondriasis can begin at any age, this disorder is most common in middle and older age. Men and women are equally affected.

Patients with hypochondriasis are concerned that they may have a specific disease (cancer, cerebral aneurysm, brain tumor, multiple sclerosis and amyotrophic lateral sclerosis), and visit numerous specialists (doctor shopping).

Patients with this disorder are typically demanding. Anxiety and depression frequently coexist with this condition.

**Malingering**

Malingering is the intentional production of false or grossly exaggerated physical symptoms for obviously secondary gain, such as obtaining drugs, avoiding the law, or obtaining disability. Malingering is not a somatoform disorder in a strict sense, in that it is under the voluntary control of the individual.

Antisocial personality disorder is common in malingers, as is drug abuse. Patients with malingering usually sign out against medical advice when exposed.
Factitious Disorder
Munchausen’s Syndrome

Factitious disorder is the intentional production or feigning of physical or psychological signs or symptoms for unconscious psychological reasons. The motivation for the behavior is to assume the sick role. External incentives for the behavior are absent, as compared with malingering.

Patients with factitious disorder typically follow through with surgical procedures and have numerous abdominal surgical scars (the abdomen is like a "railroad yard").

Examples of mechanisms to produce abnormal physical signs and laboratory data include the following:

- Rubbing a mercury thermometer on the bed sheets.
- Contaminating a urine sample with a drop of blood from a finger stick.
- Taking anticoagulants.
- Taking thyroid medicine.
- Injecting oneself with insulin.
- Applying a mydriatic to one eye.
- Self injecting feces to produce fever.

Patients with factitious disorder are typically loners, and engage in pathological lying, in a manner that is intriguing to the listener (pseudologia fantastica). They often have extensive knowledge of medical terminology and hospital routines. They travel from city to city, and from hospital to hospital, frequently within the same city. When confronted with evidence that their symptoms are factitious, they deny the allegations and rapidly discharge themselves against medical advice.

Personality disorders are common in patients with factitious disorder.

Clinical Formulation

Patients with the various somatoform disorders all tend to have a unifying clinical formulation that may help explain their behavior. These patients all have dependent personalities and a low self-esteem. They frequently consider themselves “worthless”. Thus, they develop “symptoms” to obtain compassion and care (misinterpreted as “love”) from others, especially physicians, the “ultimate care takers”.

Patients with somatoform disorders are difficult to care for and, all too often, receive fragmented care from a large number of physicians. They will receive conflicting diagnoses and may be told that their symptoms “are all in my head”. Anxiety and depression frequently coexist in these patients.
Treatment

Effective treatment of patients with somatoform disorders is difficult, time consuming, and requires much patience and understanding by the physician. Organic medical conditions must first be ruled out in these patients. Psychiatric conditions should be looked for next, including depression, anxiety disorders, substance abuse or dependence. Finally, a positive diagnosis of a somatoform disorder needs to be confirmed.

The following eight points represent one approach to treatment of patients with somatoform disorders:

1. Establish a long-term relationship with the patient.

2. Realize that the patient's symptoms are an emotional communication rather than a sign of illness. Respect the adaptive value of the symptoms. The patient wants palliation (continued care) and not cure (termination of care).

3. Perform a complete physical examination initially to rule out organic illness, and periodically thereafter. The physical examination represents a “laying on of hands”, which indicates concern to the patient.

4. “Don't just do something, stand there!” Avoid unnecessary laboratory testing. Time is an extremely effective test for patients with somatoform disorders, and merely following symptoms over the course of several weeks may result in resolution of the symptoms.

5. See the patient at regular intervals, and as often as necessary to reassure the patient. Setting limits may be necessary for patients who may abuse the physician’s time.

6. Avoid psychotropic medications and prescription analgesics.

7. Don't confront the patient with the psychological basis of their symptoms. These patients almost uniformly resist psychiatric referrals. The patient's awareness of the emotional cause for their illness is not necessary for improvement in symptoms.

8. Be aware of countertransference, that is the emotional reactions to the patient that are determined by the physician's own unconscious conflict.
BIBLIOGRAPHY


NEURO-ONCOLOGY
Joohee Sul, MD

The practice of neuro-oncology involves the diagnosis and treatment of central nervous system (CNS) tumors as well as the neurological complications of cancer. The incidence of both primary and metastatic brain tumors has been increasing, and neuro-oncology is a growing subspecialty. The purpose of this chapter is to present an overview of neuro-oncology. We will discuss 3 fundamental topics:

- Primary brain tumors of the central nervous system (CNS)
- Metastases to the CNS
- Neurological complications of cancer

PRIMARY BRAIN TUMORS

Primary brain tumors are a rare disease and account for only 1-2% of all cancers. Approximately 40,000 primary CNS tumors are diagnosed each year. Tumors may occur in the parenchyma, meninges or skull base. The most common tumors in adults are gliomas which account for roughly 40% of all tumors, and nearly 80% of all malignant tumors. Meningiomas are the second most common and account for 20-30% of all tumors; however, the majority of these are histologically benign. The most common histologies of adult brain tumors are described in Figure 1.

Most primary brain tumors arise from glial cells (astrocytes, oligodendroglia and ependymal cells). Neuronal tumors and mixed neuronal tumors are much less common. Rarely, brain tumors may arise from cells not typically found in the brain such as lymphocytes (lymphoma), germ cells (germinoma) and embryonic tissue (choriocarcinoma).

The World Health Organization (WHO) classifies CNS tumors based on cell of origin, site and differentiation. A summary of the major categories and tumor types adapted from the WHO classification system is listed in Table 1. Glioblastoma or glioblastoma multiforme (GBM) is the most common of the gliomas, and account for the majority of malignant tumors in adults. The focus of this section will be on diagnosis and treatment of malignant gliomas.

ETIOLOGY:

In the majority of primary brain tumors, there is no identifiable cause. In a small number of patients there may be a clear risk factor identified, such as radiation exposure, genetic susceptibility, or immunosuppression.

1. Radiation Therapy: Radiation exposure is a known risk factor for malignancy. In the past low dose radiation to the scalp was used as treatment for various diseases such as
tinea capitis, and is associated with an increase risk of meningiomas and gliomas. In addition, children who received radiation for primary tumors such as medulloblastoma are at increased risk for developing secondary intracranial gliomas and sarcomas.

2. **Genetic causes:** Hereditary syndromes associated with brain tumors include: Li-Fraumeni, Tuberous sclerosis, Neurofibromatosis type I and type II (NF I and II), Multiple endocrine neoplasia type I (MEN I), Turcot’s syndrome, von Hippel-Lindau, and Cowden’s syndrome. These account for a very small percentage of brain tumors, but are important to identify in order to provide counseling for the patient and family.

3. **Immunosuppression:** HIV infection or post-transplant immunosuppression can increase the risk of CNS lymphoma. In addition, patients with HIV infection have a higher incidence of gliomas.

Other postulated risk factors include cellular telephone exposure, aspartame, N-nitrosourea compounds, head trauma, hair dyes, pesticides, and exposure to electromagnetic waves from power lines. There is no definitive data to support these as causes of tumors, although there are anecdotal accounts.

**DIAGNOSIS:**

The presentation of brain tumors is quite variable. Symptoms may progress slowly over time, or may occur abruptly and can even be mistaken for an acute stroke. They can range from clearly localizing symptoms and signs such as hemiparesis and aphasia, or may be non-specific such as headaches and personality changes. Common signs and symptoms of brain tumors include:

- Headache
- Cognitive changes
- Memory loss and confusion
- Seizures
- Cranial Neuropathy
- Focal weakness
- Aphasia

It is important to keep in mind that brain lesions can also cause raised intracranial pressure, leading to false localizing signs.

1. **Imaging:** The mainstay of brain tumor evaluation continues to be magnetic resonance imaging (MRI) with gadolinium. MRI is clearly superior to computed tomography (CT) in defining anatomical location and tumor characteristics. Adjunct studies such as MR spectroscopy, MR perfusion, and positron emission tomography (PET) scans may be able to provide additional information about histology or grade of tumors. The ready availability of MR imaging has no doubt also improved the ascertainment of both primary brain tumors as well as metastases. CT does have its uses, and is helpful in identifying calcifications or hemorrhage.

2. **Pathology:** Tissue diagnosis is critical in guiding therapy and determining prognosis. Generally, every attempt is made to safely obtain tissue through biopsy or resection.
One exception is with brainstem gliomas which have a characteristic appearance on imaging. In this case the risks of surgery are increased, and biopsy may not be an option. If so, most neuro-oncologists will treat these tumors empirically. Although classic histologies may be well described, there are cases where the biopsy tissue does not adhere to a normative pattern. Even amongst well trained and experienced pathologist, there is often discordance about diagnosis. In addition as we learn more about the gene profiles and molecular characteristics of these tumors, new classification systems will likely emerge. For example, it was recently determined that oligodendroglomas with 1p and 19q gene deletion correspond with a “classic” oligodendrogial histological pattern. More importantly, these tumors tend to be associated with better prognosis and survival. Methyl guanine methyl transferase (MGMT) is a repair enzyme found in astrocytomas. Methylation of this enzyme has been postulated to lead to better chemotherapy responses and survival outcomes.

TREATMENT:

1. Surgery: Patients with maximum gross total resection of a primary brain tumor have improved survival and functioning. Surgical resection is also essential in providing a tissue diagnosis and may also help alleviate clinical symptoms. Therefore, surgery is usually the first mode of therapy employed. The extent of resection may vary based on multiple factors. First, the location of the tumor may influence whether or not biopsy or resection is optimal. As mentioned earlier, most brainstem lesions are not biopsied if they have the typical appearance of glioma. Lesions located in so called “eloquent” cortex involving language function may also be avoided. However, even these lesions may be amenable to debulking with careful planning. Brain mapping during awake surgery as well as pre-operative functional MRI (fMRI) are tools which may guide the neurosurgeon in reducing the risk of neurological impairment from surgery. Patient factors may also influence extent of resection. Performance status, age, and existing medical co-morbidities may favor biopsy over a more extensive surgery. For some tumors such as histologically benign meningiomas or dysembryoplastic neuroepithelial tumors (DNET), surgical resection may be all that is required for treatment. More aggressive tumors will likely be targeted with radiation and chemotherapy.

2. Radiotherapy (RT): The role and timing of radiation therapy for low grade tumors is controversial. However, for malignant gliomas, radiation is the single most effective treatment available. Radiation works by damaging DNA in rapidly dividing tumor cells. The tumor bed plus a margin around it are the targets for radiation. However, the surrounding brain tissue is at risk for radiation toxicity, and attempts are made to spare as much of the normal brain as possible.

3. Chemotherapy: The role of chemotherapy in treating brain tumors is evolving. There are numerous obstacles to treating primary brain tumors with systemic chemotherapies. Gliomas are generally quite heterogeneous, and are adept at developing resistance to medical treatments. Also, the blood-brain barrier (BBB) can act to effectively prevent delivery of chemotherapy to brain tumors, although some chemotherapeutic agents are more easily able to cross the BBB than others. In addition, there is a low therapeutic/toxic ratio, so that higher doses of chemotherapy can potentially harm normal brain. Temozolomide (Temozol) is a relatively new oral chemotherapeutic agent that has demonstrated good penetration into the CNS.
In 2005, a large study with more than 500 patients defined the standard of care for glioblastomas. Patients were randomized to receive RT with or without concurrent temozolomide, after surgical resection. This was then followed by adjuvant temozolomide given once every 4 weeks. The patients who received concurrent temozolomide during RT had better overall survival (14.6 vs. 12.1 months) and better 2 year survival (26.5 vs. 10.4%). The standard regimen for initial treatment of GBM is outlined in Figure 2. This regimen has generally been extended to include treatment of all malignant gliomas.

Recently, we have seen improved progression free survival (PFS) in patients with recurrent malignant gliomas using bevacizumab (Avastin). This is a monoclonal antibody that inhibits angiogenesis in tumors. Angiogenesis as a target for cancer therapy is a strategy that has been used in other solid tumors. Other areas of research include small molecule inhibitors of tumor growth factors, and vaccine therapies. These treatments are often available via clinical trials once patients progress despite standard treatment.

PROGNOSIS:

The general prognosis for malignant gliomas is poor. There is no cure for this disease, and our goal is to control tumor growth for as long as possible, while also preserving and improving quality of life. The median overall survival for GBM is 12 months; less without treatment. Oligodendrogliomas generally have better overall survivals than astrocytomas. Low grade gliomas have longer survival times, but unfortunately, most progress to become malignant high grade tumors. It is important to discuss prognosis with patients and their families, and to address issues such as goals of care, palliation of symptoms and advanced directives as appropriate.

BRAIN METASTASES

Brain metastases far outnumber primary brain tumors. Roughly 40,000 primary brain tumors are diagnosed in the US each year, while brain metastases are estimated at 170,000 each year. Brain metastases are one of the most feared complications of cancer. They tend to occur late in the course of disease, and can have a devastating impact on functioning and quality of life. The incidence appears to be increasing over the last few years, in part due to availability of MRI as well as improved survival times of cancer. Overall, prognosis is poor and without treatment median survival time is 2-4 months. The most common solid tumors to metastasize to the brain include:

- Lung
- Breast
- GI
- Melanoma
- Renal
Lung cancer is the most common solid tumor and therefore accounts for the largest proportion of brain metastases. However melanoma, a relatively rare malignancy, seems to have the highest propensity to travel to the brain. This argues there may be a molecular signaling at play between host tissues and cancer cells that influences spread to particular organs. The risk of brain metastases by tumor type is described in Table 2. Hematologic malignancies can also spread to the nervous system, and account for about 10% of CNS metastases, usually to the leptomeninges. However, they differ from solid tumor metastases in clinical presentation, treatment and prognosis and will not be included in this discussion.

**DIAGNOSIS:**

For patients with a known history of cancer, new neurological symptoms should be assumed to be metastatic disease until proven otherwise. The presenting symptoms of brain tumors are similar to those of primary tumors. Brain metastases are distributed throughout the neuraxis, and common sites of spread include the parenchyma, leptomeninges and dural meninges. In contrast, most primary tumors do not tend to involve the leptomeninges or dura. Presenting symptoms of leptomeningeal metastases include discreet cranial neuropathies, hydrocephalus, back pain, and radicular symptoms.

1. **Imaging:** There are certain typical imaging characteristics of metastases. Compared with primary tumors, metastases tend to be smaller, and are more likely to be multiple. They have a predilection for the grey-white junction, often at distal capillaries where tumor cells may settle after hematogenous spread. They are also frequently associated with significant edema.

2. **Pathology:** Tissue diagnosis is not as essential in determining brain metastases. As stated earlier, new enhancing lesions in the brain are considered to be metastases in a patient with a known history of cancer. There are exceptions to this, and there have been cases where lesions thought to be metastases were found to be a primary tumor or abscess upon biopsy. The predilection of certain cancers to travel to the brain should also be considered. For example, prostate cancer almost never causes parenchymal brain metastases and favors the dura instead. Therefore in a patient with prostate cancer and intraparenchymal lesion, biopsy or surgery should be strongly considered. For the most part the history, exam and imaging are enough to justify diagnosis and treatment.

**TREATMENT:**

The mainstay of therapy is whole brain radiation therapy (WBRT). Some tumors are more radiosensitive than others. For example, melanoma is typically not very radiosensitive, and has poor response to treatment. For patients with a single metastasis, good functioning and minimal to no systemic disease; surgery or radiosurgery with WBRT may be considered. Surgical resection may also provide significant symptomatic relief and improve peritumoral edema. Treating brain metastases with chemotherapy presents many of the same challenges faced when treating primary brain tumors. The BBB may be difficult to penetrate. Also, since brain
metastases typically occur late in the course of cancer, these patients are usually heavily pre-treated with other chemotherapy regimens used against their primary disease. Therefore, they are often resistant to the very same treatments that initially worked in the primary tumor, and also have a higher risk of toxic side effects.

PROGNOSIS:

As stated, prognosis is generally poor, especially since most patients have advanced systemic disease as well. With supportive care only, survival is 2-4 months. With radiation, the median survival is extended to 4-6 months. However, there are some patients with prolonged survival, especially those with breast cancer, who may live with stable disease in the CNS for years.

NEUROLOGICAL COMPLICATIONS OF CANCER

Neurological complications of cancer and cancer treatments are common, and have been increasing as more effective therapies are developed and survival times have increased. They are important to recognize as they can cause significant impairment and suffering. Complications can be thought of as either directly involving the nervous system, or indirectly affecting the nervous system. Some of the more commonly encountered complications are described in Table 3.

A full discussion of all these entities is beyond the scope of this chapter. When approaching the diagnosis of neurological disease in a patient with cancer, it is important to include a thorough differential, including entities that may not be related to cancer. After all, patients with malignancy can have concurrent neurological illnesses such as strokes, motor neuron disease, and demyelinating disease.
Table 1

WHO CLASSIFICATION OF CENTRAL NERVOUS SYSTEM TUMORS

I: NEUROEPITHELIAL TUMORS

A. GLIAL TUMORS
   1. Astrocytic Tumors
      Pilocytic (WHO grade I)
      Diffuse (WHO grade II)
      Anaplastic (WHO grade III)
      Subependymal giant cell astrocytoma (WHO grade I)
   2. Oligodendrogial Tumors
      Oligodendroglioma (WHO grade II)
      Anaplastic Oligodendroglioma (WHO grade III)
   3. Ependymal Tumors
      Ependymoma (WHO grade II)
      Anaplastic ependymoma (WHO grade III)
      Myxopapillary ependymoma
      Subependymoma (WHO grade I)
   4. Mixed Gliomas
      Oligoastrocytoma
      Anaplastic Oligoastrocytoma

B. NEURONAL AND MIXED NEURONAL-GLIAL TUMORS
   1. Gangliocytoma
   2. Ganglioglioma
   3. Desmoplastic infantile astrocytoma/ganglioglioma
   4. Dysembryoplastic neuroepithelial tumor
   5. Central neurocytoma
   6. Cerebellar liponeurocytoma
   7. Paraganglioma
   8. Olfactory neuroblastoma

C. NON-GLIAL TUMORS
   1. Embryonal Tumors
      Ependymoblastoma
      Medulloblastoma
      Supratentorial primitive neuroectodermal tumor (PNET)
      Atypical teratoid/rhabdoid tumor
   2. Choroid Plexus Tumors
      Choroid plexus papilloma
      Choroid plexus carcinoma
   3. Pineal Parenchymal Tumors
      Pineoblastoma
      Pineocytoma
      Mixed pineocytoma/pineoblastoma

II: MENINGEAL TUMORS

A. Meningioma
B. Atypical meningioma
C. Anaplastic meningioma
D. Hemangiopericytoma
E. Melanocytic lesion

III: GERM CELL TUMORS

A. Germinoma
B. Embryonal carcinoma
C. Yolk sac tumor
D. Choriocarcinoma
E. Teratoma
F. Mixed germ cell tumors

IV: TUMORS OF THE SELlar REGION

A. Pituitary adenoma
B. Pituitary carcinoma
C. Craniopharyngioma

V: TUMORS OF THE CRANIAL AND SPINAL NERVES

A. Schwannoma
B. Neurofibroma
C. Malignant peripheral nerve sheath tumors

VI: PRIMARY CNS LYMPHOMA
Table 2

**RISK OF BRAIN METASTASES BY TUMOR TYPE**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell lung cancer</td>
<td>80%</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>25-30%</td>
</tr>
<tr>
<td>Breast</td>
<td>10-20%</td>
</tr>
<tr>
<td>Renal</td>
<td>5-10%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>50%</td>
</tr>
</tbody>
</table>

Table 3

**EXAMPLES OF NEUROLOGIC COMPLICATIONS OF CANCER**

**Direct Effects (Disease along the neuraxis)**
- Seizures
- Raised intracranial pressure
- Pain
- Cord compression

**Indirect Effects**
- Hypercoagulable states leading to strokes and venous thrombosis
- Paraneoplastic syndromes
- SIADH
- Infections related to neutropenia
- Encephalopathy from nutritional deficits or metabolic conditions

**Complications of Treatment**
- Radiation necrosis
- Neuropathy related to chemotherapy
- Illness related to surgery and other procedures
Distribution of Primary CNS Tumors by Histology

- Meningioma: 30%
- Glioblastoma: 20%
- Astrocytoma: 10%
- Oligodendroglioma: 4%
- Ependymoma: 2%
- Pituitary: 6%
- Nerve Sheath: 8%
- All others: 20%
TREATMENT PROTOCOL FOR NEWLY DIAGNOSED MALIGNANT GLIOMAS

- Maximal safe surgical resection or biopsy
- 6 weeks of daily RT with temozolomide
- Temozolomide in 4 week cycles until progression of disease (POD)