Cerebrospinal Fluid

Formation and Circulation of CSF

Cerebrospinal fluid (CSF) is found within the brain in the four ventricles, and also surrounds the brain in the subarachnoid space. CSF is mainly secreted by the choroid plexus that is found in all four ventricles. CSF flows from the lateral ventricles into the third ventricle through the intraventricular foramina of Monro. CSF then leaves the third ventricle via the cerebral aqueduct (of Sylvius) and flows into the fourth ventricle. CSF then exits the fourth ventricle via the midline foramen of Magendie and via the two lateral foramina of Luschka, and enters the subarachnoid space. The CSF then descends into the subarachnoid space overlying the spinal cord into the lumbar cistern, and also ascends in the subarachnoid space overlying the convexities of the hemispheres. It is finally reabsorbed by the arachnoid granulations into the superior sagittal sinus.

CSF is formed at a rate of 0.35 ml/min, which is about 500 ml/d. Thus, the entire volume of CSF is turned over 3-4 times per day.

Composition of CSF

CSF is an ultrafiltrate of plasma, but the exact composition of CSF is altered by active transport. Spinal fluid thus has a much lower concentration of protein, glucose, potassium, calcium and magnesium than does serum. Spinal fluid is also slightly more acidic than serum, and has a pH of 7.33.

Function of CSF

- CSF maintains a constant external environment for neurons and glia. Because of the one-way flow of CSF from the ventricular system, around the spinal cord, into the subarachnoid space around the brain, and into the venous sinuses, potentially harmful brain metabolites are removed from the CNS.

- CSF provides a mechanical cushion for the brain to protect the brain from impact with the bony calvarium when the head moves. By its buoyant action, CSF allows the brain to float, thereby reducing its effective weight to less than 50 grams.

- CSF serves as a lymphatic system for the brain.

- CSF acts as a conduit for peptide hormones secreted by the hypothalamus.
Lumbar Puncture

CSF can be easily sampled by performing a lumbar puncture. In this procedure, a needle is inserted through the skin, between the 4th and 5th lumbar vertebrae, and into the lumbar subarachnoid space. Recall that the spinal cord ends at the L1 vertebral level in the adult, and there is therefore no risk of injuring the cord by performing the puncture at this level. Once the subarachnoid space is entered, the opening pressure is measured by attaching a manometer to the hub of the needle. Normal CSF opening pressure is between 65 and 195 mm H₂O. The spinal fluid is then sampled and various hematologic and chemical determinations are performed as follows:

- **Gross Appearance**: Clear, colorless
- **WBC**: < 5 mm³
- **Differential**: 100% lymphocytes
- **RBC**: 0 mm³
- **Protein**: < 60 mg/dL
- **Glucose**: > 60 mg/dL

The composition of the spinal fluid is known as the "CSF formula". Viral, bacterial and fungal infections of the meninges all have their own characteristic CSF formulae, as noted in the table.

**Blood-Brain Barrier**

Specific permeability barriers exist between blood and CSF, and between blood and brain. The purpose of the blood-brain barrier is to prevent certain substances from entering the brain.

The blood-brain barrier has an anatomic and physiologic component. In general, small, lipophilic molecules enter most easily into the brain from blood. Active transport systems are required for the transport of glucose and amino acids into the brain.

**Anatomical Basis of the Blood-Brain Barrier**

The most important anatomical component of the blood-brain barrier is the capillary endothelial cell tight junction. Ancillary anatomical components include the astrocytic foot processes, as well as the capillary basement membrane.

**Physiological Basis of the Blood-Brain Barrier**

In contrast to peripheral endothelial cells, brain endothelial cells show little, if any, transcellular transport of compounds. Thus, fluid-phase endocytosis, and receptor-mediated endocytosis, two means by which molecules move across endothelial cells in the periphery, are not present in the brain.

**Brain Areas Devoid of the Blood-Brain Barrier**

Certain cerebral blood vessels contain fenestrated capillaries, resulting in a "leaky" blood brain barrier. These areas include the posterior pituitary gland, and circumventricular
organs, such as the area postrema and the subfornical organ. These areas have a permeable blood-brain barrier because they produce neurosecretory products that need to pass into the circulation. As you recall, the posterior pituitary gland secretes oxytocin and vasopressin into the systemic circulation, and the subfornical organ contains a chemoreceptive area required for water balance.

Rationale for the Blood-Brain Barrier

The blood-brain barrier is necessary to protect neurons from extraneous changes in extracellular ion concentrations, which tend to change abruptly in serum. In addition, neurons must be protected from certain neurotransmitters and growth factors that are also present in peripheral blood.

Brain Edema

Breakdown in the blood-brain barrier may result in brain edema. Pathological situations that can result in breakdown of the blood-brain barrier include ischemia, brain tumors and brain abscesses. Three different types of brain edema may be identified.

- **Cytotoxic:** This form of brain edema implies intracellular swelling of neurons, glia and endothelial cells, with a concomitant reduction of brain extracellular space. Cytotoxic edema can be seen with hypoxia from asphyxia or global cerebral ischemia following cardiac arrest.

- **Vasogenic:** This form of brain edema is attributed to increased permeability of brain capillary endothelial cells, which increases the volume of extracellular fluid. Vasogenic edema enhances with contrast administration on CT and MR scans of the brain, and results in the "ring pattern" seen with brain tumors or abscesses. White matter is affected more than gray matter.

- **Interstitial:** This form of brain edema is due to transependymal reabsorption of CSF, and is most commonly seen with obstructive hydrocephalus, in which water content increases in the periventricular white matter.

Hydrocephalus

Hydrocephalus is a general term that is used to describe increased amounts of CSF within the intracranial cavity.

Non-Obstructive Hydrocephalus

- **Oversecretion of CSF:** This is a rare condition seen with tumors of the choroid plexus (papilloma).

- **Hydrocephalus Ex Vacuo:** This term is really a misnomer, and describes the situation in which CSF "fills" intracranial areas left empty following loss of brain tissue from atrophy or infarction. A common example is enlargement of the ventricular system that is seen with advanced cerebral atrophy in Alzheimer's disease.
Obstructive Hydrocephalus

- **Communicating Hydrocephalus:** In this form of hydrocephalus, absorption of CSF by the arachnoid granulations is impaired. This results in an elevation of CSF pressure. The term "communicating" refers to the fact that the obstruction is at the level of the arachnoid granulations, and does not impair flow of CSF from the lateral ventricles into the subarachnoid space through the foramina of Luschka and Magendie.

  Communicating hydrocephalus is an occasional sequela of meningitis or subarachnoid hemorrhage. The meningeal inflammation produced by infection or blood results in scarring of the arachnoid granulations, impairing CSF reabsorption. Communicating hydrocephalus can also be seen with thrombosis of the superior sagittal sinus, an unusual occurrence seen in the post-partum period or with a hypercoagulable state.

- **Non-Communicating Hydrocephalus:** In this form of hydrocephalus, CSF circulation is impaired due to stenosis of the cerebral aqueduct, or due to obstruction at the foramina of Luschka and Magendie. Aqueductal stenosis may be congenital, or can be seen with tumors of the pineal gland. Obstruction of the foramina of Luschka and Magendie can be seen following basilar meningitis.

**Treatment:** Treatment of chronic hydrocephalus includes diverting CSF flow past the block. Placement of a permanent ventriculo-peritoneal shunt is the most popular procedure performed for relieving chronic obstructive hydrocephalus.
### CHARACTERISTIC CSF FORMULAE

<table>
<thead>
<tr>
<th></th>
<th>Color Turbidity</th>
<th>Opening pressure</th>
<th>WBC</th>
<th>Differential</th>
<th>RBC</th>
<th>Protein</th>
<th>Glucose</th>
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<tbody>
<tr>
<td>Normal</td>
<td>Clear colorless</td>
<td>70-180 mm H₂O</td>
<td>0-5</td>
<td>Mononuclear</td>
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<td>&lt;60 mg/dl</td>
<td>&gt;2/3 serum</td>
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<td>↑↑</td>
<td>PMNs</td>
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<td>↑↑</td>
<td>↓</td>
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<tr>
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<td>↑</td>
<td>↑</td>
<td>Lymphs</td>
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<td>↑</td>
<td>NI</td>
</tr>
<tr>
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<td>↑</td>
<td>↑</td>
<td>Lymphs</td>
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</tr>
<tr>
<td>Viral encephalitis</td>
<td>Cloudy Straw-colored</td>
<td>NI - ↑</td>
<td>↑</td>
<td>Lymphs</td>
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<tr>
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<td>↑</td>
<td>Lymphs</td>
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<td>↑</td>
<td>PMNs and Lymphs</td>
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<td>NI</td>
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<td>0-5</td>
<td>Mononuclear</td>
<td>0</td>
<td>↑</td>
<td>NI</td>
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### NORMAL CSF VALUES FOR INFANTS

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<thead>
<tr>
<th>Age</th>
<th>WBC</th>
<th>Differential</th>
<th>RBC</th>
<th>Protein</th>
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<tbody>
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<td>Macrophage</td>
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<td>150</td>
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<td>Monos</td>
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<td>1 - 2 yr</td>
<td>3</td>
<td>Lymphs</td>
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Evaluation and Treatment of Headache
Ralph F. Józefowicz, MD

Pathophysiology of Intracranial Pain

In order for a pathologic process to cause intracranial pain, structures that contain pain fibers must be irritated. Although the brain itself is largely insensitive to pain, the meninges and blood vessels contain numerous pain fibers, and irritation or distention of either of these structures may cause headache.

Headache can be divided into two broad categories, symptomatic headache and essential headache. In symptomatic headache, head pain is a symptom of a primary, oftentimes serious, intracranial or extracranial disease process; the neurologic examination typically reveals focal or generalized abnormalities.

In essential headache, head pain is the primary manifestation of a benign disease process; the neurologic examination is typically normal.

Symptomatic Headache

Numerous intracranial or extracranial pathologic processes may cause headache, as noted below. In addition, headache is a major manifestation of idiopathic intracranial hypertension and temporal arteritis, and these are discussed below as well.

- **Expanding CNS mass lesions**, including brain tumors, cerebral abscesses and intracranial hemorrhages such as subdural hematomas, epidural hematomas and intracerebral hemorrhages.
- **Meningeal inflammation**, such as can be seen with meningitis or subarachnoid hemorrhage.
- **Hydrocephalus** may produce a dull, global headache in many patients.
- **Systemic illnesses**, such as influenza, systemic infections associated with fever and many generalized autoimmune disorders frequently cause headache.
- **Referred pain**: Headache can be due to pain referred from many extracranial sites, as follows:
  - **Eye pain**, as can be seen with corneal abrasions, iritis, or acute, open-angle glaucoma.
  - **Ear pain**, such as that seen with otitis media.
  - **Dental pain**, especially temporomandibular joint (TMJ) dysfunction.
  - **Sinusitis**
  - **Cervical radiculitis** (occipital neuralgia, cervicogenic headache) is a common cause of head pain in the elderly. The head pain is intermittent, is often brought on by neck motion, and typically radiates up the posterior neck to the occiput. The etiology of occipital neuralgia is compression of the C2 and C3 cervical nerve roots by bony spurs, as they exit from the neural foramina.
Idiopathic Intracranial Hypertension  
(Pseudotumor Cerebri)

**Definition:** a disorder of young, obese women that results in a severe, global, constant headache which may last for weeks and which may be associated with visual disturbances.

**Etiology:** The cause of idiopathic intracranial hypertension (IIH) is unknown. As noted, this disorder typically affects young, obese women. Some cases may be associated with previous meningeal inflammatory disorders, such as meningitis or subarachnoid hemorrhage. Thrombosis of the superior sagittal sinus is an increasingly recognized cause of IIH.

In rare cases, IIH has been associated with various other conditions, including hypervitaminosis A, tetracycline ingestion or corticosteroid withdrawal. The vast majority of cases are idiopathic, however.

**Pathophysiology:** Although the exact pathophysiology of IIH is unknown, it is felt that this disorder represents a defect in CSF absorption by the arachnoid granulations. This results in excessive CSF accumulation by brain tissue with resultant brain edema and headache.

Increased intracranial pressure is also transmitted to the optic nerve, resulting in papilledema and visual loss.

**Diagnosis:**

- **History:** Global headache is the most common presenting complaint. Diplopia may occur, due to bilateral abducens nerve palsy. Visual loss is a late and ominous finding.

- **Physical examination:** Papilledema is the cardinal finding in this disorder. Bilateral CN VI nerve paresis may be seen. The earliest visual field defect seen is enlargement of the blind spot; constricted peripheral vision is a late finding, as is loss of visual acuity.

- **Laboratory testing:**
  - **Head MR or CT scan:** These are typically normal, although slit-like ventricles may be present.
  - **Lumbar puncture:** Opening pressure is most often elevated (usually 250-500 mm H₂O). Cell counts and chemistries are normal, although occasionally the total protein may be reduced significantly.
  - **Visual fields:** These may show an enlarged blind spot. Constricted peripheral visual fields are a late finding.

**Complications:** Visual field abnormalities and loss of visual acuity are the two most serious complications of untreated IIH. Diplopia due to bilateral CN VI nerve paresis can also occur.

**Treatment:** Since visual loss is a major complication of IIH, this disorder should be treated aggressively. Although some cases remit spontaneously, the following measures should be tried while waiting for a spontaneous remission.

- **Weight loss**
• **Repeated lumbar punctures**, using a large bore spinal needle, and removing at least 30 ml of CSF to reduce the closing pressure to < 180 mm H₂O. Lumbar punctures may be performed daily at first if necessary.

• **Acetazolamide**, 125 - 250 mg po tid. This medication is the most effective one available for reducing CSF production by the choroid plexus.

• **Corticosteroids**: A short course of prednisone, i.e. 40 - 60 mg po qd, may be helpful in refractory cases.

• **Surgery**, particularly optic nerve decompression, if visual loss is present. In refractory cases, a ventriculo-peritoneal shunt may be necessary.

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**Temporal Arteritis**

**Definition:** An inflammatory blood vessel disorder of older individuals affecting primarily large intra and extracranial blood vessels, which can cause headache, systemic symptoms, visual loss, and other neurologic disturbances.

**Etiology:** Temporal arteritis (TA) is a disease of older adults. Individuals younger than 50 years are rarely affected. The cause is unknown.

Temporal arteritis is frequently associated with *polymyalgia rheumatica* (PMR), a rheumatologic disorder of older individuals that causes proximal muscle aching and tenderness. About 50% of individuals with TA have signs and symptoms of PMR. Conversely, about 15% of individuals with PMR have positive temporal artery biopsies demonstrating vasculitis.

**Pathophysiology:** TA is a large-vessel vasculitis that typically involves large intra or extracranial arteries, including the temporal, ophthalmic, posterior ciliary and vertebro-basilar arteries. Temporal artery biopsy demonstrates a necrotizing vasculitis with multinucleated giant cells. The vasculitis, if left untreated, can cause infarction in the involved vascular territory.

**Diagnosis:**

• **History:** Patients most often complain of headache that is often localized over the temporal arteries. Jaw claudication (jaw pain with chewing) is a frequent complaint. Systemic symptoms, including low-grade fever, fatigue, weight loss and weakness, are commonly present. Visual loss is a late finding. As noted above, symptoms of PMR are seen in about half of the patients with TA.

• **Physical examination:** The temporal arteries are frequently enlarged, tortuous, firm and tender. Funduscopic examination may show retinal infarction and optic atrophy. Visual acuity may be reduced in later stages of the disease. Patients with concomitant PMR may have proximal muscle tenderness.

• **Laboratory studies:**
  
  • **Blood work:** The erythrocyte sedimentation rate (ESR) is significantly elevated in the vast majority of patients, and is typically > 60 mm/hr. The CBC may reveal a normochromic, normocytic anemia, as well as a neutrophilic leukocytosis.

  • **Temporal artery biopsy** reveals a necrotizing vasculitis with multinucleated giant cells. A negative temporal artery biopsy does not rule out TA, since skip lesions may be present. For this reason, a large segment of temporal artery
should be removed and sectioned, and in certain situations the opposite temporal artery may need to be biopsied if clinical suspicion remains high.

**Complications:** As noted above, visual loss due to ophthalmic artery infarction is the most significant complication, and may lead to total blindness in 35% of patients if the disease remains untreated. Vasculitic occlusion of other intracranial vessels may lead to cerebral infarction.

**Treatment:** Corticosteroids remain the mainstay of treatment in TA. This disease is exquisitely sensitive to steroids, and early treatment almost always prevents progression with subsequent vascular infarction.

Oral prednisone, at a dosage of 45-60 mg per day, is recommended for several weeks to months, until clinical symptoms have resolved and the ESR has normalized. A slow steroid taper is then begun, watching for signs of disease recurrence or elevation of the ESR. Spontaneous remission is oftentimes seen, and in many patients steroids can ultimately be discontinued.

**Essential Headache**

**Migraine**

**Definition:** A syndrome of recurrent, severe, unilateral and bilateral headaches, frequently associated with transient focal neurologic abnormalities, and due to alterations in cerebral blood flow.

**Incidence:** Migraine is quite common; it is estimated that between 4 and 15% of the general population suffer from migraine headaches. Migraine headaches are more common in women by a factor of 3:2.

About 50% of patients with migraine have a positive family history of the disorder.

About 25% of migraine patients have a childhood onset of the disease ("sick" headaches).

**Classification:**

- **Migraine with aura (Prodromal):** Migraine headaches associated with neurologic symptoms. Several types are worth mentioning:
  - **Classic:** The migraine headache is preceded by neurologic deficits that are typically visual (scintillations, scotomata, hemianopsias, fortification spectra). These visual changes resolve after about 15 minutes, following which a severe unilateral headache develops. About 15% of all migraine patients experience classical migraine headaches.
  - **Hemiplegic:** a "protracted prodromal" migraine that begins with an aura of hemiplegia that then persists into the headache phase.
  - **Ophthalmoplegic:** Intra or extraocular ophthalmoplegia develops during a severe, retro-orbital headache, typically in an older individual. This form of migraine is a diagnosis of exclusion; aneurysmal rupture and ischemic cerebrovascular disease need to be ruled out in individuals presenting with this clinical picture.
• **Vertebral-basilar**: Drowsiness, dizziness and other vertebro-basilar symptoms develop during a severe headache. This migraine variant is usually seen in young girls and women.

• **Complicated**: The neurologic deficit does not resolve, and permanent infarction develops as a result of irreversible ischemia due to vasospasm.

• **Migraine equivalent**: Transient neurologic deficits occur in the absence of headache. This is a diagnosis of exclusion, and other causes of neurologic dysfunction need to be considered before this diagnosis is made.

• **Migraine without aura (Non-prodromal)**: Migraine headaches not associated with neurologic symptoms. Several examples follow:

  • **Common**: Recurrent, severe, unilateral and bilateral headaches, frequently associated with nausea, vomiting and photophobia, and not associated with neurologic deficits. This is the most common form of migraine, seen in up to 80% of patients with migraine.

  • **Perimenstrual**: a common migraine headache occurring perimenstrually.

Many migraine headaches are preceded up to 24 hours by drowsiness, or changes in mood, appetite or thirst, due to alterations in central hypothalamic monoamines. These have been called "premonitory migraines" by some authors.

**Pathophysiology**: Several theories exist concerning the etiology of migraine headaches. The vascular theory and the neurohumoral theory are the two that are most supported in the literature.

• **Vascular theory**: According to this theory, migraine headaches are associated with changes in cerebral blood flow. During the **prodromal phase** of a classic migraine, blood flow is decreased due to vasospasm of the involved artery. This vasospasm typically occurs in the posterior circulation and affects blood flow to the occipital lobes. This accounts for the frequency of visual symptoms in an attack of classic migraine. During the **headache phase**, blood flow is increased as a result of arterial vasodilatation.

The autonomic innervation to the posterior circulation is different from that to the anterior circulation, and this is felt to be the reason why posterior circulation neurologic symptoms are common in migraine.

• **Neurohumoral theory**: Platelet serotonin levels are chronically increased in patients with migraine. During an attack, the platelets aggregate and release serotonin into the circulation. Serotonin then binds to bradykinin adherent to blood vessel walls, causing vasodilatation and subsequent pain. Serum dopamine levels are also believed to be elevated during a migraine attack, resulting in the nausea and vomiting that occur with the headache.

• **Hypothesis**: A unified hypothesis postulates that migraine is a hereditary disorder, occurring in patients with a genetic predisposition to the disease. In response to certain trigger factors which may be neural (glare), vascular (exercise, alcohol), or neurohumoral (stress, relaxation after stress), various neurotransmitters are released into the circulation which then bind to blood vessel walls. This binding results in caliber changes to the blood vessels, with resultant neurologic symptoms and pain.
These trigger factors all may represent a potential threat to the organism, whose brain is the most vulnerable part. The resultant pain is a warning that, like any other pain, alerts the organism to potential danger.

**Treatment:** Numerous forms of treatment exist for migraine headaches. None is completely satisfactory. It should be kept in mind that the response to placebo in patients with migraine is around 30%.

- **Psychotherapeutic measures:** Since many migraine headaches are triggered by stress, relaxation training and stress management is very important in migraine management and should be tried initially.

- **Abortive medications:** The following medications may be helpful in terminating an acute migraine attack.
  - **Aspirin**
  - **Non-steroidal medications**, particularly ibuprofen, 400-800 mg, or naproxen, 500-750 mg.
  - **Triptans (Sumatriptan, Zolmitriptan, Naratriptan, Rizatriptan):** These new agents are potent serotonin agonists and are quite effective in terminating or ameliorating an acute attack of migraine. Sumatriptan is available in oral, intranasal and subcutaneous preparations; the other triptans are only available in an oral preparation. Sumatriptan subcutaneous injection has a more rapid onset of action and is more effective than the oral preparations. All oral triptans are essentially equally effective, however.
  - **Ergotamine:** This is a potent vasoconstrictor that may be helpful in aborting the headache in some patients with classic migraine when taken during the prodrome phase of migraine. The typical dose is 1-2 mg initially, then 1 mg every hour as needed, up to a total of 6 mg per attack, or 10 mg per week.
    
    **Side effects** include significant nausea and vomiting. Ergotamine is contraindicated in patients with significant hypertension, peripheral occlusive vascular disease and pregnancy.

- **Phenothiazines**, including prochloreperazine and metoclopramide, are effective in relieving nausea as well as ameliorating headache pain in some patients.

- **Prophylactic medications:** These medications should be considered in patients with severe migraine headaches that occur more than three or five times per month.
  - **Tricyclic antidepressants**, particularly amitriptyline or nortriptyline, at a dose of 50-75 mg taken once daily at bedtime. These drugs inhibit cellular reuptake of serotonin, which is integrally involved with CNS pain pathways. This anti-migraine effect of these drugs is independent of their anti-depressant effects. Both of these agents have significant anticholinergic side effects, and may cause drowsiness, dry mouth and weight gain, and urinary retention in males with prostatism.

- **Beta blockers**, particularly propranolol, 80-160 mg per day. Beta blockers are peripheral vasoconstrictors, and also may act centrally by reducing anxiety. These agents should be used with extreme caution in patients with asthma, congestive heart failure or occlusive vascular disease.
• **Anti-epileptics:** Both valproate and gabapentin have been found to be helpful in migraine prophylaxis in some patients.

• **Calcium channel blockers,** particularly verapamil at a dose of 80 mg tid. These agents prevent the influx of calcium into blood vessel walls, thereby stabilizing vascular smooth muscle tone.

• **Selective serotonin reuptake inhibitors,** particularly fluoxetine (Prozac), paroxetine (Paxil) and sertraline (Zoloft). These new drugs do not have anticholinergic side effects and are therefore better tolerated than the tricyclic compounds by many patients.

• **Methysergide:** This agent is a serotonin antagonist and may be helpful in migraine prophylaxis. It has significant side effects, including retroperitoneal fibrosis when taken for prolonged periods of time, and therefore should not be taken for more than three to five months continuously.

• **Cyproheptadine (Periactin):** This is an antihistamine with serotonin agonist properties. It is very sedating, but may be effective for childhood migraines.

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**Cluster Headache**

**(Migrainous Neuralgia)**

**(Horton'sHistaminic Cephalgia)**

**Definition:** A severe, retro-orbital headache that is associated with changes in extracranial blood flow, and occurs in clusters which may last for several weeks and may recur every several years.

**Incidence:** Cluster headaches are quite rare, with an incidence of 0.1% in the general population. These headaches typically occur in older individuals, and are more common in men by a factor of 9:1.

**Diagnosis:**

• **History:** The typical cluster headache is described as retro-orbital in location, sharp, and boring ("as if a hot poker were placed behind my eye"). Each headache lasts for minutes to an hour or so, and frequently awakens the patient from sleep. The headaches recur at precise intervals during the day, and some patients can "set their watches" by their headaches.

  The headaches occur in clusters, each lasting several weeks, and each cluster may recur every several years. The same side of the head is involved with each cluster. Some patients have associated autonomic symptoms with their headache, including unilateral nasal stuffiness, rhinorrhea, conjunctival injection, and a partial Horner's syndrome, demonstrating unilateral ptosis and miosis.

• **Physical examination:** Signs of unilateral autonomic dysfunction may be seen, as noted above.

**Pathophysiology:** As with migraine, vascular and neurohumoral theories exist to explain the pathophysiology of cluster.

• **Vascular theory:** The pain of cluster headache is felt to be due to extracranial vasodilation of peri-orbital blood vessels.
• **Neurohumoral theory:** Plasma histamine levels are elevated during a cluster attack. Treatment with antihistamine agents is ineffective in terminating a cluster attack, however.

**Treatment:** As with migraine, numerous medications have been tried for the treatment of cluster, although none has been completely satisfactory.

• **Lidocaine,** instilled locally into the involved nostril, may relieve head pain in some individuals, and should be tried initially.

• **Inhalation of 100% oxygen** may terminate a cluster headache because of its vasoconstrictive properties.

• **Corticosteroids:** A short course of oral prednisone, 40-60 mg per day for two-three weeks, may terminate an attack of cluster in some patients.

• **Sumatriptan** subcutaneous injection is quite effective for terminating an acute cluster headache.

• **Ergotamine,** particularly if taken 30 minutes before the headache starts, has been found to be helpful in some individuals.

• **Lithium carbonate** has also been reported to terminate a cluster in some patients. Blood levels should be monitored, however.

• **Methysergide** has also been found effective in terminating a cluster. Since the cluster usually resolves in several weeks, concerns over long-term side effects of methysergide are not as great as in migraine.

• **Indomethacin** may be of benefit in patients with atypical cluster headache.

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**Tension Headache**  
(Muscle Contraction Headache)

**Definition:** A global, band-like, constant headache, usually located over the frontal, temporal or occipital areas, that is due to contraction of scalp and shoulder musculature as a result of chronic stress and fatigue.

**Incidence:** Tension headaches are quite common, and it is estimated that 80% of the population will experience a tension headache at some point in their lives. Tension headaches are more common in women by a factor of 3:2.

**Pathophysiology:** Stress, vascular, and neurohumoral factors all may play a role in the pathophysiology of tension headaches. In addition, many patients appear to have an overlap syndrome with components of both migraine and tension headache.

• **Stress:** Many patients with chronic tension headaches have significant amounts of depression and anxiety. The associated stress may cause persistent contraction of scalp and shoulder musculature, resulting in a dull headache.

• **Vascular theory:** Extracranial blood vessels appear to be dilated during a tension headache in some patients, although cerebral blood flow is not altered.

• **Neurohumoral theory:** Platelet serotonin has been found to be chronically decreased in some patients with this disorder.
Treatment: As in migraine and cluster headache, many agents are available, but none is completely effective.

- **Aspirin, acetaminophen, and non-steroidal medications** are first-line therapy, but most patients have already tried these medications by the time they see a physician for their headaches.

- **Tricyclic antidepressants.** Amitriptyline and nortriptyline are particularly effective because of their antidepressant effects and their serotonin agonist-like properties. Dosages and side effects are noted above.

- **Selective serotonin reuptake inhibitors,** particularly fluoxetine (Prozac), paroxetine (Paxil) and sertraline (Zoloft). These new drugs do not have anticholinergic side effects and are therefore better tolerated than the tricyclic compounds by many patients.

**Evaluation of Headache**

When a patient presents for evaluation of headache, the physician must quickly determine whether the headache is a symptom of a primary, and sometimes serious disease process, or if it is part of a benign headache syndrome.

**Ominous Signs and Symptoms:** The following signs and symptoms suggest a serious cause of headache that warrants further evaluation.

- New onset of headache in an individual not previously predisposed to headache
- New onset of headache in an old individual
- Relentlessly progressive course
- Unilateral localization
- Headache made worse by head position (Traction headache)
- Fever
- Focal neurologic findings
- Signs of raised intracranial pressure

**Diagnosis:** The following should be considered in all patients presenting with headache:

- **History,** particularly location of the pain, quality, duration, onset, as well as associated symptoms, including nausea, neck stiffness, fever and other systemic symptoms.

- **Physical examination,** with particular emphasis to the following:
  - Vital signs
  - Palpation of carotid and temporal arteries
  - Auscultation for cranial and carotid bruits
  - Cervical range of motion
  - Visual acuity, visual fields
  - Funduscopic examination
  - Cranial nerve examination
  - Screening motor and sensory examination
• **Laboratory studies:** Judicious use of the laboratory is essential in the proper evaluation of the patient with headache. The following tests should therefore be considered:
  
  • **Head CT or MR scan,** particularly if a serious cause of headache is suspected.
  
  • **Lumbar puncture,** especially when evaluating headaches of sudden onset if CT is negative.
  
  • **Sedimentation rate** in individuals older than 50 years if temporal arteritis is suspected.
  
  • **Cervical spine X rays** to evaluate cervical spine disease, particularly if cervical range of motion is reduced.

**Bibliography**


EVALUATION OF THE DIZZY PATIENT
Ralph F. Jozefowicz, MD

Four categories of dizziness

When a patient complains of "dizziness", the physician must determine exactly what type of "dizziness" the patient has in order that appropriate evaluation and therapy can be undertaken. In general, there are four major categories of dizziness as noted below, and most patients can be placed into one of these categories.

1. **Vertigo**: a sense of motion of self or surroundings, usually accompanied by nausea and occasionally vomiting. Most patients with vertigo have nystagmus. Vertigo implies dysfunction of the peripheral vestibular system or its central brain stem connections.

2. **Syncope and presyncope**: actual or impending loss of consciousness of brief duration, usually due to transient reduced cerebral blood flow. There are two major causes: cardiac arrhythmias and orthostatic hypotension.

3. **Dysequilibrium (sensori-neural mismatching)**: a sense of imbalance due to dysfunction of one of the three neurologic systems used to maintain balance: vision, proprioception, or the vestibular apparatus. These patients often complain of being "dizzy in their feet".

4. **Lightheadedness or giddiness (psychogenic dizziness)**: an ill-defined form of dizziness frequently associated with anxiety or depression. Chronic hyperventilation is a major mechanism in many cases. These patients often complain of being dizzy "all day long" for months on end.

**Pathophysiology of Balance**

Three systems are routinely used to maintain balance, namely proprioception, the vestibular apparatus and vision. Only two of these systems are required at any one time. This is the basis of the Romberg test, where one asks the patient to stand with his/her feet together and then close his/her eyes. Eye closure removes visual clues for maintaining balance. If balance is maintained, this implies integrity of both the vestibular apparatus and proprioception. Falling to one side implies dysfunction of one of these balance systems.

Patients with dizziness often will have dysfunction of one of these balance systems.

**The Vestibular System**

The vestibular system senses changes in head and body position in space, and uses this information in numerous ocular and somatic reflex circuits.
Peripheral apparatus:

The peripheral apparatus has two types of receptors: those that sense angular acceleration, and those that sense linear acceleration (see figure).

**Angular acceleration:** The receptors for angular acceleration are the semicircular canals. There are three pairs of canals, and all pairs are mutually orthogonal (all at right angles to each other). Each canal is filled with endolymph and has a dilated portion at one end, called the ampulla. The ampulla contains hair cells that protrude into a gelatinous substance known as the cupula.
The hair cells for each of the semicircular canals have a \textit{tonic rate of electrical firing}, which means that they all fire at a baseline rate when the head is not moving. Rotating the head in a certain direction causes endolymph to deflect the hair cells in a specific direction in one or more of the semicircular canals. This deflection results in a change in the baseline electrical firing rate, which then propagates down the vestibular nerve into the brain stem.

- \textbf{Linear acceleration (gravity):} The receptors for linear acceleration are the \textit{utricle and saccule}. These structures contain hair cells that have calcium carbonate crystals sitting on them. Moving the head in any direction causes gravity to deflect the calcium crystals and the attached hair cells, and this deflection results in an electrical potential that propagates down the vestibular nerve into the brain stem.

\textbf{Central connections:}

The primary sensory cell bodies for the vestibular system are located in the \textit{vestibular (Scarpa's) ganglion}. Axons from these bipolar cells synapse on the \textit{superior, inferior, lateral and medial vestibular nuclei} in the pons. Secondary sensory axons from these nuclei project to five areas of the CNS, as follows:

- \textit{Spinal cord}, via the lateral and medial vestibulospinal tracts.
- \textit{Cerebellum}, particularly the vermis.
- \textit{Reticular formation}, particularly the vomiting center in the medulla.
- \textit{Extraocular muscles} via the medial longitudinal fasciculus (MLF) and CN nuclei III, IV and VI.
- \textit{Medial geniculate body and cortex}, perhaps providing conscious perception of orientation of the body in space.

\section*{Pathologic vertigo}

Pathologic vertigo can be due to diseases affecting the peripheral vestibular apparatus, or due to diseases affecting the central vestibular brain stem connections.

\subsection*{Peripheral Vertigo:}

Vertigo due to pathology involving the peripheral vestibular system typically is severe, positional, fatigable, and of relatively short duration with a lag time of several seconds following change in head position.

1. \textbf{Acute vestibulitis:} A clinical syndrome that results in severe, positional vertigo of acute onset, nausea and vomiting which can persist for days to weeks and resolves spontaneously. Although the cause is unknown, a viral etiology is postulated.
According to this theory, a viral infection of the vestibular apparatus results in a decrease in the rate of firing of the semicircular canals on the involved side. The semicircular canals on the unaffected side continue to fire at the normal baseline rate. The end result is a net imbalance in the firing rate between the involved and uninvolved ears, and a false sense of motion with the fast phase of nystagmus beating towards the uninvolved ear.

On examination, the patient appears acutely ill, anxious and diaphoretic. Any change in position will exacerbate the vertigo. Nystagmus is present that beats towards the unaffected ear, and also worsens when the patient looks towards the unaffected ear. The neurologic examination is non-focal and hearing is usually normal.

Treatment is symptomatic, and the disease process resolves in several weeks. Mild bouts of positional vertigo may persist for months to years after an attack.

2. Benign positional vertigo (BPV): A syndrome affecting older individuals and resulting in brief attacks of severe vertigo lasting several seconds that are brought on by changes in head or body position. Typically, one specific position will bring on an attack. Turning in bed or arising from a supine position are two maneuvers that frequently precipitate attacks of vertigo in predisposed individuals.

The vertigo occurs several seconds after change in body position, and is fatigable. Nystagmus may be seen during an attack. Performing a Nylen-Barany maneuver (see below) will often precipitate an attack.

BPV is felt to be caused by dislodgment of calcium otoliths from the utricle and saccule (cupulolithiasis). These calcium crystals then migrate into the ampulla of one semicircular canal (typically posterior), thereby transforming an organ that normally senses only angular acceleration into one that now senses linear acceleration as well. When a certain head position is achieved such that gravity can influence these dislodged crystals, the patient gets a false sense of motion (vertigo).

BPV is self limited since the vestibular apparatus "resets itself" with time, and most patients improve after several months.

The modified Epley liberatory maneuver is the most effective form of treatment for BPV. This maneuver consists of a single series of rapid head/trunk tilts that forces the dislodged calcium debris from the ampulla of the posterior semicircular canal into the utricular cavity, where it is harmless. The exact sequence of body motions for this maneuver is depicted in the adjacent figure. Following effective liberation, about 50% of patients will have a recurrence of attacks within several weeks to months. Performing the liberatory maneuver again is often effective in this situation.

Positional exercises are also an effective treatment for BPV. These consist of a sequence of rapid lateral head/trunk tilts, repeated serially to promote loosening and, ultimately dispersion of the calcium debris toward the utricular cavity. The patient is instructed to sit; to then move rapidly into the challenging position to induce vertigo; to remain in this position until the vertigo subsides; to then sit up for 30 seconds; and finally to assume the opposite head-down position for an additional 30 seconds.
Figure 2. Schematic drawing of modified Epley liberatory maneuver. Patient characteristics and abbreviations are as in figure 1. (1) In the sitting position, the head is turned horizontally 45° to the affected (left) ear. (2) The patient is tilted approximately 105° backward into a slight head-hanging position, causing the clot to move in the canal, deflecting the cupula downward, and inducing the BPPV attack. The patient remains in this position for 3 minutes. (3a) The head is turned 90° to the unaffected ear, now untermost, and (3b) the head and trunk continue turning another 90° to the right, causing the clot to move toward the exit of the canal. The patient remains in this position for 3 minutes. The positioning nystagmus pointing toward the affected (uppermost) ear in positions 3a and 3b indicates effective therapy. (4) The patient is moved to the sitting position.
Pharmacologic treatment of vertigo is ineffective, due to the brief nature of the attacks.

3. **Meniere's syndrome:** A rare, paroxysmal disorder producing a **clinical triad of recurrent vertigo, tinnitus and hearing loss.** Each episode lasts from a minimum of 30 minutes to several hours, and all three components of the triad need not be present during each episode. Onset is usually during the third and fourth decade.

After years of repeated attacks, many patients develop permanent hearing loss and chronic tinnitus and vestibular dysfunction. Meniere's disease is usually unilateral, but can be bilateral in up to 30% of patients.

**Physical examination** during an attack can reveal hearing loss and nystagmus that beats towards the unaffected ear, and also worsens when the patient looks towards the unaffected ear.

The cause of Meniere's disease is uncertain, although an increase in the amount of endolymph is one postulated mechanism (**endolymphatic hydrops**). **Neurosyphilis** is an important differential diagnosis.

Treatment is symptomatic, and includes anti-vertigo medications (see below). Diuretics, such as acetazolamide and furosemide have been tried with varying success. Surgical shunting of endolymph, and destructive labyrinthectomy in advanced cases with little or no usable hearing, are other therapeutic alternatives.

4. **Post-traumatic vertigo:** Vertigo is a sequela of blunt head trauma in over 20% of cases, as part of the post-concussive syndrome (a collection of symptoms including headache, dizziness and vertigo, sleep disorders, depression, and lassitude). There are three main types of post-traumatic vertigo:

   - **Acute post-traumatic vertigo:** Vertigo, nausea, vomiting and nystagmus that begin acutely after head injury, due to unilateral labyrinthine concussion causing vestibular paresis. The natural history and treatment of acute post-traumatic vertigo are similar to that for acute vestibulitis.

   - **Post-traumatic positional vertigo:** Positional vertigo that begins several days or weeks after the injury. The clinical features and treatment of post-traumatic positional vertigo are identical to that for benign positional vertigo.

   - **Perilymphatic fistula:** Intermittent or positional vertigo accompanied by fluctuating conductive hearing loss, and due to a fistula developing in the region of the oval or round windows. Most of these fistulae heal spontaneously, although surgical exploration and repair of the fistula is occasionally necessary in refractory patients.

**Central Vertigo:**

Vertigo due to pathology involving the central vestibular brain stem connections is typically less severe than vertigo due to peripheral vestibular pathology. It is also less related to change in head position, and tends to be non-fatigable and of longer duration than peripheral vertigo.
1. **Acoustic Schwannoma**: A rare tumor of the Schwann cells lining the VIIIth cranial nerve that results in a clinical triad of hearing loss, tinnitus and ill-defined dizziness. As the tumor grows larger, other cranial nerves may become involved, particularly V and VII, with resultant facial numbness and weakness. Ataxia may also develop, due to compression of the middle cerebellar peduncle.

Bilateral acoustic neuromas can be seen with neurofibromatosis.

CT scanning or MR imaging visualize the tumor in most cases. Audiograms confirm sensorineural hearing loss, and brain stem auditory evoked response (BAER) testing demonstrates a prolongation in the latency between waves I and II on the involved side.

Treatment is surgical.

2. **Vertebro-basilar insufficiency (VBI)**: A syndrome of episodic brain stem dysfunction due to vascular insufficiency of the vertebro-basilar arterial system. Elderly individuals with diffuse atherosclerosis are at the highest risk for this disorder.

Each episode typically lasts several minutes, and may consist of dizziness, diplopia, dysarthria, ataxia, and facial and limb weakness and numbness. Neurological examination between attacks is frequently normal. Subclavian bruits may be present in a certain number of individuals with this disorder.

Characteristic symptoms, advanced age, the presence of risk factors for atherosclerosis, and a high index of suspicion are sufficient to make the diagnosis.

Treatment consists of risk factor modification and aspirin.

Acute vestibulitis and vertebro-basilar insufficiency can at times be confused with each other, due to similar presenting symptoms. In general, age and the presence of risk factors help one to make the proper diagnosis: acute vestibulitis usually affects young individuals, while VBI affects older individuals.

3. **Multiple sclerosis (MS)**: Demyelinating plaques involving the vestibular nuclei in the brain stem frequently cause dizziness and imbalance. In young individuals with signs and symptoms suggestive of MS, new-onset dizziness implies a brain stem demyelinating lesion until proven otherwise.

4. **Basilar migraine**: Basilar artery migraines are sometimes accompanied by acute vertigo, nausea, vomiting and dizziness. A severe, unilateral headache typically follows the vertiginous attack.

**Drug-induced Vertigo**:

Numerous medication have both cochlear and vestibular toxicity, as shown in the following table:
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Vestibular toxicity</th>
<th>Cochlear toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Aminoglycoside antibiotics</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Salicylates</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Quinine</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cis platinum</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Evaluation of the Dizzy Patient**

A careful history and physical examination will identify the cause of dizziness in the majority of patients. A few specialized bedside tests can aid in the diagnosis. Laboratory testing is seldom necessary in the evaluation of dizziness.

**History:**

The patient should be specifically asked to describe the sensation without using the word "dizzy". Specifically ask for precipitating factors, duration, direction, Fatigability, severity, relationship to head position, associated hearing loss, tinnitus, diplopia, oscilop sia, and nausea.

**General physical examination:**

In addition to a careful screening examination looking for associated diseases, the following areas should be carefully examined:

- **Cardiac examination**, specifically evaluating for arrhythmias.
- **Orthostatic blood pressure measurements**
- **Tympanic membranes**, particularly evidence for otitis
- **Bedside audiological testing**, including Rinne and Weber testing
- **Neurologic examination**, particularly balance assessment, including Romberg testing, gait, turns, proprioception, and evidence for nystagmus.

**Specialized testing:**

The following three tests help define the etiology of dizziness in many patients:

1. **Head shake test:** Having the patient shake his/her head rapidly for several seconds can sometimes precipitate an attack of vertigo and nystagmus.

2. **Nylen-Barany (Dix-Hallpike) positioning maneuver:** In this test, the patient is quickly moved from the sitting position to a supine position with the head positioned 45° below the plane of the table and to one side. This position is maintained for about one minute, during which time the patient is observed for nystagmus. The test is then repeated with the head turned to the other side. If the patient reports typical "dizziness" during the maneuver, or if nystagmus develops, vestibular dysfunction may be the cause of dizziness. (See figure).
The Nylen-Barany maneuver for positional vertigo and nystagmus. The patient is moved abruptly from a seated [A] to a prone [B] position, with his head hanging 45° below the horizontal and rotated 45° to one side. He is observed for the development of nystagmus and vertigo.

The pattern of vertigo and nystagmus evoked by the Nylen-Barany maneuver may help determine whether a central or peripheral vestibular disorder is the cause of the patient's dizziness. The following table illustrates this point:

**NYLEN-BARANY (DIX-HALLPIKE) MANEUVER**

<table>
<thead>
<tr>
<th>Vertigo and Nystagmus</th>
<th>Peripheral Disorders</th>
<th>Central Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latent period</td>
<td>Seconds</td>
<td>None</td>
</tr>
<tr>
<td>Duration</td>
<td>Minutes</td>
<td>Minutes</td>
</tr>
<tr>
<td>Fatigability</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Direction</td>
<td>One</td>
<td>May change</td>
</tr>
<tr>
<td>Head position</td>
<td>Single</td>
<td>More than one</td>
</tr>
<tr>
<td>Intensity</td>
<td>Severe</td>
<td>Mild</td>
</tr>
</tbody>
</table>

1. **Hyperventilation for two minutes**: If a typical attack of "dizziness" is provoked by two minutes of hyperventilation, chronic, low-grade hyperventilation is the likely cause of dizziness. These patients frequently have panic disorders or other neuroses that underlie their "dizziness".
Laboratory testing:

Judicious use of the laboratory may help define the etiology of dizziness in the occasional patient, as follows:

- **Electronystagmogram (ENG):** This is a test that accurately records eye movements and nystagmus with respect to certain provocative maneuvers. Disc electrodes are placed over the bridge of the nose and lateral to each outer canthus, and the leads are connected to an oscilloscope. Since the cornea is electro-positive and the retina is electro-negative, these electrodes will accurately record lateral eye movements. The patient is then observed for spontaneous nystagmus with the eyes open and closed, for nystagmus evoked with lateral gaze, for nystagmus induced by hot and cold air instilled in the outer ears (caloric-induced), and for positional nystagmus. The latter is performed by rotating the patient in a specialized chair. Spontaneous nystagmus, or an imbalance in the nystagmus evoked by these maneuvers for the right and left ears suggest vestibular pathology.

- **Audiograms (Pure tone audiometry):** air and bone conduction are recorded for both ears to determine whether a conductive or sensorineural hearing loss is present. In addition, specialized tests of retro-cochlear auditory processing can be performed to further define the cause of sensorineural hearing loss, if present.

- **Speech discrimination testing** is the most useful test of retro-cochlear auditory processing. In this test, monosyllabic words are presented individually to each ear at supra-threshold intensity levels, and the percentage of words that the listener repeats correctly is recorded. Cochlear lesions typically have preserved speech discrimination, while in retro-cochlear lesions, speech discrimination is markedly impaired.

A useful rule of thumb is that if the sum of the discrimination score (in percent) plus the speech reception threshold (in decibels) is less than 100, an eighth nerve lesion should be considered (acoustic schwannoma). If the sum is greater than 100, a cochlear lesion is more likely.

- **Brain stem auditory evoked responses (BAER):** This test measures conduction velocities for central auditory pathways in the brain stem by means of computer averaging techniques. EEG electrodes are placed over the posterior scalp and a series of clicks at a frequency of 2 Hz are delivered to each ear separately for 1 1/2 minutes. The scalp potentials elicited by the clicks are then recorded and signal averaged by a computer. This signal averaging cancels the random EEG noise, thereby amplifying the evoked potential. A series of five waves are recorded for each ear, and each wave corresponds to a different point in the central auditory pathway as noted in the following table and figure:

<table>
<thead>
<tr>
<th>Wave</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Auditory nerve</td>
</tr>
<tr>
<td>II</td>
<td>Cochlear nucleus</td>
</tr>
<tr>
<td>III</td>
<td>Superior olivary nucleus</td>
</tr>
<tr>
<td>IV</td>
<td>Lateral lemniscus</td>
</tr>
<tr>
<td>V</td>
<td>Inferior colliculus</td>
</tr>
</tbody>
</table>

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The wave latencies for the right and left ears are compared, and a delay in any of the latencies suggests a lesion at that point in the central brain stem auditory pathway.
Drug Therapy of Vertigo

The following classes of drugs provide symptomatic relief of vertigo in some individuals. All have considerable side effects, particularly drowsiness. Response rates vary from patient to patient.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drug(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines</td>
<td>Meclizine, Dimenhydrinate</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Scopolamine</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Promethazine</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Tricyclic Antidepressants</td>
<td>Amitriptyline, Nortriptyline</td>
</tr>
</tbody>
</table>

References


THE EVALUATION OF NECK AND LOW BACK PAIN
RALPH F. JOZEFOWICZ, MD

LOW BACK PAIN

Incidence:

Low back pain is an extremely common complaint that accounts for a significant amount of work-related injury and disability. It is estimated that one in five adults will develop back pain at some time or another.

Causes of low back pain:

Back pain can have many causes. The four most common sources are discussed below:

1. **Referred pain**: pain that originates in diseased abdominal organs and is "referred to" or felt in the back. The mechanism for this referral of pain is based on the fact that pain fibers from abdominal viscera intermingle with pain fibers supplying dermatomes. Stimulation of these intra-abdominal pain fibers by disease processes will cause pain to be felt in dermatomes that are roughly adjacent to the involved organs.

   Abdominal organs that typically are the source of referred low back pain include the lower bowel, kidneys, ureters, bladder, uterus, fallopian tubes and ovaries.

2. **Musculoskeletal**: Numerous derangements in the bones, joints, muscles, ligaments or tendons frequently cause low back pain. It is important to note that these derangements do not produce neurologic abnormalities, such as limb weakness, sensory loss or reflex changes.

   - **Muscle sprains and strains** are perhaps the most common cause of low back pain, and are due to shearing injury to muscles, tendons and ligaments that stabilize the spine. Poor posture and improper lifting techniques are the cause of most low back sprains and strains.

   - **Arthritis**, either degenerative (osteoarthritis) or inflammatory, are another major cause of low back pain. **Degenerative arthritis** usually occurs in older individuals and produces back pain with motion.

   - **Ankylosing spondylitis** is a major cause of inflammatory arthritis involving the low back in young males. The diagnosis is confirmed with spine radiographs that reveal destruction of the sacro-iliac joints and bony bridging of the vertebral bodies producing a "bamboo spine".

   - **Intrinsic bone diseases**, including Paget's disease of bone, metabolic bone diseases such as osteomalacia and osteoporosis, primary and metastatic bone malignancies, and osteomyelitis all can produce low back pain as a cardinal symptom. Bone radiographs often establish the diagnosis.
• **Spinal epidural abscess** is another rare cause of low back pain, and should be considered when acute, localized low back pain develops in a febrile individual with sepsis.

3. **Radiculopathy**: Radiculopathy refers to the neurologic signs and symptoms produced by compression or inflammation of a particular nerve root (nerve "radical"). Lumbar radiculopathy has various causes, as noted below:

   • **Herniated nucleus pulposus**: Compression of a nerve root by a herniated intervertebral disc (nucleus pulposus) is the most common cause of a lumbar radiculopathy. Middle-aged adults are most commonly affected. Although most ruptured discs occur in the setting of significant back trauma, many cases do not and may follow a trivial activity, such as bending or lifting a light object.

     The **most common location** for a ruptured lumbar intervertebral disc is L5-S1; L4-5 is the next most common location, followed by L3-4. Since the lateral portion of the disc is the most likely segment to rupture, the nerve root exiting below the disc is the one most likely to be compressed, (e.g. a ruptured L5-S1 disc will most likely compress the S1 nerve root).

   • **Lumbar spinal stenosis (LSS)**: A condition in which the lumbar spinal canal becomes critically narrowed due to a combination of factors, the most important being the superimposition of bony spurs from degenerative arthritis and bulging degenerating discs on a congenitally narrowed spinal canal. This narrowing then compresses the cauda equina, producing a lumbo-sacral radiculopathy.

     LSS is a disease of older individuals, and affects predominantly the mid lumbar segments of the spinal canal, namely at L2-3 and L3-4.

     The signs and symptoms of LSS are those of a lumbar polyradiculopathy. Symptoms are often made worse with prolonged standing, and the patient may gain some relief by bending forward at the waist. In addition, prolonged walking frequently results in leg fatigue requiring the patient to sit and rest for a moment before resuming this activity, a syndrome known as **neurogenic claudication**.

   • **Compressive radiculopathy**: Metastatic tumors, abscesses and hematomas all can cause nerve root compression with resultant radiculopathic signs and symptoms.

   • **Inflammatory (diabetic) radiculopathy**: Patients with diabetes mellitus may develop a painful, inflammatory lumbar radiculopathy that is indistinguishable clinically from a compressive radiculopathy.

4. **Psychogenic**: Chronic, diffuse, unremitting low back pain with a paucity of neurologic findings is seen in quite a few individuals, particularly in those awaiting the settlement of disability or compensation claims. Depression and anxiety may play a key role in the etiology of their illness. These patients tend to "doctor shop" and may become addicted to narcotics and anxiolytics. It is important to minimize
invasive testing and addictive medications in these patients. Antidepressants may be of particular benefit in a subgroup of these patients.

**Diagnosis**

**History**: A careful description of the patient's pain is key to arriving at the correct diagnosis. The location of the pain, severity, pattern of radiation, exacerbating and relieving factors, and patterns of motor and sensory loss are most important. The physicians should also inquire about associated bowel and bladder symptoms, suggesting sacral nerve root compression.

Compressive radiculopathies are often exacerbated by maneuvers such as coughing, sneezing, or **Valsalva**, since these maneuvers all raise intra-abdominal pressure.

**Sciatica** refers to pain that radiates down the leg intermittently in the distribution of the sciatic nerve. A compressive neuropathy of the nerve roots that comprise the sciatic nerve (L4,5,S1,2) is the most common cause of this syndrome.

**Physical examination**: The following areas should be carefully evaluated in all patients with low back pain:

- **Abdominal and rectal examination**, looking for evidence of intra-abdominal pathology that could cause referred pain.

- **Pelvic examination** in women, if indicated.

- **Musculoskeletal examination** of the back and lower limbs, including palpating and percussing the spine and paraspinal regions for tenderness, back and hip range of motion assessment, and sciatic and femoral nerve stretch tests.

- The **sciatic stretch test** (straight leg raising test, LeSeque sign) is performed by placing the patient supine and flexing the leg at the hip, keeping the knee extended. This procedure stretches the sciatic nerve (L4,5,S1,2). If this maneuver produces pain that radiates down the posterior thigh and into the leg, the L4, L5, S1 or S2 nerve roots may be compressed by a disc or other process. The examiner usually notes the number of degrees that the leg can be raised before the onset of pain. Dorsiflexing the ankle places further stretch on the sciatic nerve and will worsen the pain, thus confirming that the pain is due to a lumbo-sacral radiculopathy.

Many patients, particularly those who are "out of shape", may develop **pain behind the knee** with this maneuver. This pain is indicative of tight hamstrings, and does not imply lumbo-sacral nerve root pathology.

- The **femoral stretch test** (reverse straight leg raising test) is performed by placing the patient prone and hyperextending the leg at the hip. This procedure stretches the femoral nerve (L2,3,4). If this maneuver produces pain that radiates into the anterior thigh, the L2, L3 or L4 nerve roots may be compressed by a disc or other process.

- **Neurologic examination**, particularly the assessment of patterns of weakness and sensory loss and reflex changes. As one would expect, the neurologic signs and
symptoms depend upon which nerve root is compressed, and include various combinations of radiating pain, weakness, sensory abnormalities, and reflex changes, as noted in the following table:

<table>
<thead>
<tr>
<th>Disc</th>
<th>Root</th>
<th>Pain</th>
<th>Sensory loss</th>
<th>Motor loss</th>
<th>Reflex loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>L3-4</td>
<td>L4</td>
<td>Anterior thigh, Medial calf</td>
<td>Anterior thigh, Medial calf</td>
<td>Quadriceps</td>
<td>Knee jerk</td>
</tr>
<tr>
<td>L4-5</td>
<td>L5</td>
<td>Posterior thigh, Lateral calf, Dorsum of foot</td>
<td>Lateral calf, Great toe</td>
<td>Dorsiflexors and evertors, EHL</td>
<td>None</td>
</tr>
<tr>
<td>L5-S1</td>
<td>S1</td>
<td>Posterior thigh and calf, Sole of foot</td>
<td>Posterior calf, Lateral foot</td>
<td>Plantar flexors and invertors</td>
<td>Ankle jerk</td>
</tr>
</tbody>
</table>

Laboratory testing: Judicious use of the laboratory can help identify the nerve root that is compressed or inflamed, as well as the cause.

- **Blood work**, including a screening chemistry and hematology profile and an erythrocyte sedimentation rate. These tests are obtained to screen for metabolic, malignant or infectious etiologies of lumbar radiculopathy.

- **Plain films of the lumbar spine** are usually normal or demonstrate only inconsequential findings in the majority of patients with low back pain. They may reveal congenital anomalies or bone pathology, however, and should be obtained in certain circumstances if clinically warranted.

- **MR scanning** visualizes intervertebral discs as well as nerves, and is superior to CT scanning for visualizing lumbar pathology. It does not visualize bone, however, and is more expensive and time consuming than CT scanning. For this reason, CT scanning remains a valuable procedure for evaluating patients with low back pain.

- **CT scanning** of the lumbar spine is an excellent test to confirm disc herniation, narrowing of the intervertebral foramen by bony spurs, or lumbar spinal stenosis. It can also demonstrate metabolic or malignant bony pathology.

- **Myelography** remains the "gold standard" for evaluating nerve root compression, but has largely been supplanted by CT and MR scanning. It may require hospital admission and carries significant risks, and hence should only be obtained if other less invasive procedures have failed to establish the diagnosis.

- **Bone scanning** remains useful in the evaluation of patients with suspected malignancy of bone. This test is also useful in evaluating and following the course of osteomyelitis.

- **Electromyography** can help determine whether there is evidence for acute or chronic denervation involving a particular nerve root. Acute denervation, in particular, signifies ongoing nerve root compression which may warrant more aggressive management. An abnormal EMG does not determine etiology, however.
A negative screening EMG can be helpful, particularly in ruling out nerve root compression in patients with suspected psychogenic causes for low back pain.

**Treatment:**

Most back pain remits spontaneously within two weeks regardless of the treatment options followed. Hence, a conservative approach is warranted initially.

- **Conservative measures**, including bed rest for several days for patients with severe pain, will result in a resolution or amelioration of symptoms in the majority of individuals. Weight loss and back-strengthening exercises may help minimize further back injury in overweight, "out of shape" individuals.

- **Analgesics**, including aspirin and non-steroidal anti-inflammatory agents, help relieve pain in the majority of individuals. Narcotics may be necessary for patients with severe back pain.

- **Muscle relaxants**, including carisoprodol (Soma), diazepam, Flexeril or Robaxin, can help ameliorate pain that is due to reflex muscle spasm.

- **Surgery**, most commonly a decompressive laminectomy, is performed if conservative measures are ineffective. The most common indications for surgery include persistent, severe, incapacitating pain, motor weakness or sensory loss, or bowel or bladder dysfunction.

- It should be kept in mind that most herniated discs heal with time, and non-operative treatment is preferred in most circumstances. Also, repeat myelography and repeat spinal surgery, procedures that have been performed all too often in the past in some patients with chronic, recurrent back pain, have a high incidence of delayed complications, including arachnoiditis and the "failed back syndrome" of recurrent, persistent back pain.

**NECK PAIN**

**Neck pain**, like back pain, is a common cause of disability in the general public. The etiology, evaluation and treatment of neck pain are similar to that for back pain, and the discussion above will apply in most circumstances. Exceptions will be noted below.

**Causes of neck pain:**

Muscle sprains and strains, degenerative arthritis and herniated cervical discs are the most common causes of neck pain. In addition, rheumatoid arthritis and cervical spondylosis can cause cervical dysfunction, and these will be discussed below.

- **Rheumatoid arthritis** may involve the cervical apophysial joints, producing neck pain, stiffness, and limitation of neck range of motion. In addition, synovitis of the atlanto-axial joint may cause forward displacement of the atlas on the axis with resultant spinal cord compression (atlanto-axial subluxation).
• **Cervical spondylosis** is a condition, similar to lumbar spinal stenosis, in which the cervical spinal canal becomes critically narrowed due to a combination of factors, the most important being the superimposition of bony spurs from degenerative arthritis and bulging degenerating discs on a congenitally narrowed cervical spinal canal. This narrowing then compresses the spinal cord and cervical nerve roots producing a myelopathy and cervical radiculopathy.

Patients with cervical spondylosis have a combination of central and peripheral motor and sensory findings. Neurologic findings in the upper extremity are due to cervical nerve root compression, and include weakness in a LMN pattern and a dermatomal sensory loss. Neurologic findings in the lower extremity are due to cervical spinal cord compression, and include weakness in an UMN pattern and a dorsal column sensory loss.

• **Herniated nucleus pulposus**: Ruptured cervical discs have the potential for compressing the spinal cord as well as cervical nerve roots, and the signs and symptoms produced by a ruptured cervical disc are dependent upon this fact.

The most common location of a herniated cervical disc is C6-7, with compression of the C7 nerve root. The next most common location is C5-6, with compression of the C6 nerve root. Compression of the C5 and C8 nerve roots is the least common situation.

**Diagnosis:**

Evaluation of patients with neck pain is similar to that for patients with low back pain. Since there is potential for spinal cord compression with cervical lesions, the patient should also be carefully evaluated for signs and symptoms of a myelopathy.

**History**: In addition to noting the character of the pain, including the pattern of radiation, one must inquire about bowel or bladder symptoms as well as weakness or numbness in the lower extremities suggestive of a myelopathy.

**Physical examination**: Neck range of motion must be carefully evaluated and any limitations noted

**Neurologic examination**, particularly the assessment of patterns of weakness and sensory loss and reflex changes. As one would expect, the neurologic signs and symptoms depend upon which nerve root is compressed, and include various combinations of radiating pain, weakness, sensory abnormalities, and reflex changes, as noted in the following table:
<table>
<thead>
<tr>
<th>Disc</th>
<th>Root</th>
<th>Pain</th>
<th>Sensory loss</th>
<th>Motor loss</th>
<th>Reflex loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4-5</td>
<td>C5</td>
<td>Neck, shoulder, Upper arm</td>
<td>Shoulder</td>
<td>Deltoid, biceps</td>
<td>Biceps</td>
</tr>
<tr>
<td>C5-6</td>
<td>C6</td>
<td>Neck, shoulder, Lateral arm and forearm, Digits 1,2</td>
<td>Lateral arm and forearm, Digits 1,2</td>
<td>Deltoid, biceps</td>
<td>Biceps</td>
</tr>
<tr>
<td>C6-7</td>
<td>C7</td>
<td>Neck, lateral arm and forearm, Digits 2,3</td>
<td>Digit 3</td>
<td>Triceps, radial flexors and extensors</td>
<td>Triceps</td>
</tr>
<tr>
<td>C7-T1</td>
<td>C8</td>
<td>Neck, medial arm and forearm, Digits 4,5</td>
<td>Medial forearm, Digits 4,5</td>
<td>Intrinsic hand muscles</td>
<td>Triceps</td>
</tr>
</tbody>
</table>

Laboratory testing for patients with neck pain is similar to that for back pain, with the following exceptions:

- **Plain films of the cervical spine** are quite useful for evaluating the diameter of the cervical canal, which is normally greater than 14 mm. A canal diameter less than 14 mm is highly suggestive of spinal stenosis. Evidence for subluxation, disc space narrowing, and narrowing of the neural foramina by bony spurs should also be noted.

- **MR scanning** of the cervical spine is perhaps the best imaging study available to evaluate the spinal canal, spinal cord and nerve roots. T₂-weighted images in the sagittal plane are particularly useful, in that the white spinal fluid clearly outlines the subarachnoid space, resulting in an image of the spinal cord not unlike that produced by conventional myelography. Cervical spondylosis, syringomyelia, spinal cord tumors and herniated cervical discs can all be diagnosed with reasonable certainty by means of cervical MR scanning.

- **CT scanning** of the cervical spine is only helpful if performed after intrathecal injection of a water-soluble contrast agent, and if performed in this fashion, the spinal cord and subarachnoid space can be visualized with precision. CT scanning performed without intrathecal contrast enhancement is quite useless, since the densities of spinal fluid and of the spinal cord are too similar to allow any differentiation between these two structures.

- **Myelography** remains the "gold standard" for diagnosing cervical nerve root pathology, although it has largely been supplanted by MR scanning of this region. This procedure has potential adverse effects, as noted above.

**Treatment:**

- **Conservative measures** remain the mainstay of treatment of neck pain. A hard cervical collar (Philadelphia collar) and cervical traction are particularly useful in relieving neck pain. Analgesics and muscle relaxants should be prescribed as needed.
• Surgery (decompressive laminectomy) is primarily indicated for patients with evidence for cervical spinal cord compression, including those with bowel or bladder symptoms, leg weakness and spasticity. In addition, patients with intractable neck pain, and those with evidence for a progressive cervical radiculopathy despite an adequate trial of conservative therapy should be considered for a decompressive cervical laminectomy.
Pain is the most common symptom of that brings patients to medical attention. Pain is also a perception in addition to being a symptom. The underlying psychological state of the patient has a profound effect on how the pain is experienced. Effective evaluation and treatment strategies for pain must include evaluating both the symptomatic aspects as well as the psychological aspects of the pain.

Anatomy of Pain

There are three major ascending systems that carry pain information into the central nervous system:

1. **Spinothalamic pathway:** This pathway carries "fast pain" sensation, which is a brief and localized pain stimulus that is described as sharp, pricking or pinching in quality. This sensation arises from activation of mechanical nociceptors via small diameter, thinly myelinated Aδ fibers. Glutamate is the primary neurotransmitter for these axons. These axons then synapse in the dorsal horn of the spinal cord in Rexed lamina I and V. Secondary neurons from these lamina then cross in the anterior white commissure of the spinal cord and ascend in the contralateral ventrolateral funiculus of the spinal cord to nucleus VPL of the thalamus as the spinothalamic tract. Tertiary neurons then ascend to the primary sensory cortex located in the post-central gyrus of the parietal lobe, and provide information about location and intensity of the painful stimulus.

2. **Spinoreticulothalamic pathway:** This pathway carries "slow pain" sensation, which is a prolonged and poorly localized pain stimulus that is described as burning, itching and aching in quality. This sensation arises from activation of polymodal nociceptors via small-diameter unmyelinated C fibers. Glutamate and substance P are the primary neurotransmitters for these axons. These axons then synapse in the dorsal horn of the spinal cord in Rexed lamina II (substantia gelatinosa). Signals then make their way via diffuse polysynaptic connections to Rexed lamina V, VII and VIII of the dorsal horn. Projection axons from these lamina then ascend ipsilaterally and contralaterally to the reticular formation of the brain stem and to intralaminar nuclei of the thalamus (primarily nucleus CM). "Tertiary" projections from these thalamic nuclei then ascend to diffuse non-specific areas of cortex, including parietal, frontal and limbic regions, and provide information about the quality of the painful stimuli. These projections also arouse the cortex and hypothalamus and are thought to be responsible for the affective components of pain, including anguish, depression, fear and anger.

3. **Spinomesencephalic pathway:** This pathway carries pain information from Rexed lamina I and V in the spinal cord to midbrain sites, including the mesencephalic reticular formation and the periaqueductal gray (PAG). The PAG has reciprocal connections with the limbic system via the hypothalamus and is involved in the
central modulation of pain. The PAG also sends descending projections to the dorsal horn of the spinal cord to modulate pain impulses at a spinal cord level.

**Classification of Pain**

1. **Somatic pain:** pain caused by damage to skin, muscles, joints, bones or viscera. The pain is usually localized and typically responds well to analgesic drugs. Somatic pain can be divided into three major types:
   - **Cutaneous pain:** pain due to irritation to the skin and subcutaneous tissues. This pain is well localized and is perceived as superficial in location by the patient.
   - **Musculoskeletal pain:** pain due to damage to muscles, joints, tendons or ligaments. This pain is also well localized but is perceived as deep in location by the patient. Moving limbs across joints frequently worsens musculoskeletal pain.
   - **Visceral pain:** pain due to disease involving viscera. Examples include cardiac pain, stomach pain, or intestinal pain. Pain of visceral origin is poorly localized and is often perceived by the patient as originating in a dermatome, so called “referred pain”. An example of referred pain is cardiac ischemia, which typically is perceived by the patient as localized to the left shoulder and arm. “Referred pain” occurs because of convergence of visceral and dermatomal pain fibers onto the same dorsal horn sensory neurons.

2. **Neuropathic pain:** pain caused by damage to peripheral nerves and central nervous system pain pathways. Neuropathic pain is poorly localized and does not respond well to conventional analgesic drugs. There are three major types of neuropathic pain:
   - **Neuralgia:** pain due to injury to a single nerve. Several different types of painful sensations may be experienced by patients with neuralgia, as follows:
     - **Hyperesthesia:** an exaggerated response to touch
     - **Hyperalgesia:** an exaggerated response to a noxious stimulus
     - **Dysesthesia:** a spontaneous background burning sensation
     - **Allodynia:** perceiving a non-painful stimulus as exquisitely painful
   - **Peripheral neuropathy:** a degeneration of distal nerves seen in a variety of conditions and causing a painful distal burning sensation, usually in the toes and feet. Diabetes mellitus is the most common cause of painful peripheral neuropathy in the Western world.
   - **Central pain syndromes:** pain due to injury to central pain pathways, including the sensory pathways in the spinal cord and the thalamus. Central pain is usually dysesthetic in quality and is generally diffuse in location.

3. **Psychogenic pain:** Chronic, unrelenting pain without an organic cause. Many patients with the psychogenic pain syndrome (chronic pain syndrome) had an initial organic cause of pain that then evolved into a persistent pain syndrome despite resolution of the organic cause. Psychogenic pain is seen primarily in two settings:
• Axis I disorders: Patients with chronic pain syndromes are frequently depressed and anxious. The relationship between the pain and the affective symptoms is complex and one may enhance (or even cause) the other.

• Axis II disorders:
  • Somatoform disorders: These include Briquet’s somatization disorder, hypochondriasis, and the psychogenic pain syndrome. In all of these disorders, subconscious mechanisms produce physical symptoms without an organic cause. The patient usually lacks insight into his condition. Some patients with the chronic pain syndrome become so preoccupied with their pain and its cause that they develop full-blown hypochondriasis, resulting in “doctor shopping” and medication abuse.
  • Personality disorders: Patients with psychogenic pain syndromes have a higher incidence of certain personality disorders, including borderline, histrionic, and dependent personality disorders.

Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) is a disorder characterized by severe, unremitting pain affecting a distal extremity, usually the entire hand or foot. There are two forms of CRPS:

• CRPS type 1 (Reflex sympathetic dystrophy; shoulder-hand syndrome; Sudeck’s atrophy, posttraumatic pain syndrome): a chronic pain syndrome that usually develops following an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and is apparently disproportional to the inciting event. Inciting events may include blunt trauma, inflammation after infection, laceration, surgery, myocardial or cerebral infarction, degenerative joint disease, frostbite and burn.

• CRPS type 2 (Causalgia): the same disorder as above, but occurring in patients with demonstrable peripheral nerve injury. Causalgia was first described by S. Weir Mitchell during the American Civil War in soldiers with traumatic peripheral nerve injuries.

Clinical Features:

These disorders typically have three stages with the following clinical features:

Stage 1 – acute stage (3-6 months):
• Severe pain, usually burning, aching and throbbing
• Hyperpathia and allodynia
• Diffuse tenderness
• Swelling, both pitting or non-pitting
• Vasomotor changes (changes in temperature – usually cold, or color – usually dusky purple)
• Sudomotor changes (changes in sweat and hair apparatus, usually hyperhidrosis and hypertrichosis)
Stage 2 – dystrophic stage (3-6 months):
- Persisting aching and burning pain
- Swelling with induration
- Dystrophic skin and nails (shiny skin with loss of normal wrinkling)

Stage 3 – atrophic stage (chronic):
- Atrophy of skin and subcutaneous tissues
- Contractures

Laboratory investigation:

Radiographs may show diffuse osteopenia, and bone scans frequently show an increase in blood flow and pooling in the affected limb.

Etiology:

The etiology of CRPS is poorly understood and may have a peripheral or central cause. Disruption of peripheral nerve pathways due to trauma may promote formation of synapses between efferent and afferent nerves, known as ephapses. These neuronal “short circuits” may then cause pain in response to normal cutaneous stimuli. Allodynia and hyperalgesia may be explained by sensitization of peripheral mechanoreceptors due to trauma.

Central causes of pain in CRPS include sensitization of neurons in the dorsal horn of the spinal cord as a result of persistent aberrant peripheral sensory stimuli.

Another theory is that CRPS is sympathetically mediated, since anesthetic blocks to regional sympathetic ganglia may relieve symptoms in some patients.

Treatment:

The treatment for CRPS remains controversial and largely ineffective. Anesthetic blocks to sympathetic ganglia have had variable success. A conservative and multi-disciplinary approach to treatment is favored, including judicious use of pharmacologic approaches including corticosteroids and adjuvant analgesics, physical therapy, anesthesiologic therapies and psychological therapies.

Evaluation of the Patient with Pain

1. Rule out organic causes of pain. Laboratory investigations should be focussed and dictated by the location of pain and knowledge of pathophysiology. If the initial evaluation is negative, a repeat evaluation in several weeks or months may be warranted if the pain persists or worsens.

   EMG and nerve conduction studies may be particularly helpful in diagnosing mononeuropathies and peripheral neuropathies. Small fiber sensory neuropathies are not routinely detected with nerve conduction studies, however, and may require cutaneous nerve biopsies to confirm the diagnosis.
2. Explore psychosocial stressors with the patient and his/her family. Psychosocial factors frequently contribute to the severity of the pain. On occasion, such factors may be the entire cause of the pain.

**Treatment of Pain**

**Drug Therapy**

1. **Non-narcotic analgesics:** These are excellent for mild to moderate somatic pain, such as musculoskeletal pain and some post-operative pain.
   - Acetaminophen
   - Aspirin
   - Non-steroidal anti-inflammatory drugs (NSAID’s), including ibuprofen, naproxen, indomethacin, Trisalicylate, and the new COX-2 selective NSAID’s.

   Aspirin and the NSAID’s frequently cause gastro-intestinal discomfort and may also inhibit platelet aggregation. Acetaminophen is generally well tolerated but does not suppress inflammation. Trisalicylate is a non-acetylated salicylate that is thought to have minimal effects on inhibition of platelet aggregation, and thus should pose less of a risk to patients with a tendency towards bleeding.

2. **Narcotic analgesics:** These drugs are excellent for more severe pain, such as cancer pain and post-operative pain.
   - Codeine
   - Hydrocodone (Vicodin, Lortab)
   - Oxycodone
   - Hydromorphone (Dilaudid)
   - Morphine
   - Methadone
   - Fentanyl (IV or transdermal patch)

   The narcotic analgesics all have significant side effects, in particular constipation, nausea, and somnolence. Prolonged use usually leads to tolerance and occasionally addiction. Narcotics should be avoided in patients with chronic pain syndromes for these reasons.

   Propoxyphene is generally not recommended, since it is relatively ineffective. Meperidime (Demerol) is not recommended for standard analgesia because toxic metabolites, including normeperidine, accumulate with repeated use and may lead to seizures and mental status changes.

3. **Adjuvant analgesics:** These drugs are especially useful for neuropathic pains.
   - **Tricyclic antidepressants:** Drugs in this category include amitriptyline, nortriptyline, desipramine, and imipramine. These drugs inhibit the re-uptake of the catecholamine neurotransmitters epinephrine and norepinephrine as well as serotonin, and thus may enhance central pathways that suppress pain transmission. The tricyclic compounds are quite useful for treatment of the burning, dysesthetic pains seen with peripheral neuropathies. Most of these drugs are sedating and, when given at bedtime, promote sleep.

   Effective dosages of these drugs for treating chronic neuropathic pain are typically lower than the dosages used for treating depression. We recommend
starting with a low single dose at bedtime and slowly increasing the dose over several weeks. Patients should be informed that it may take several weeks before full therapeutic effects are realized.

- **Anticonvulsants**: Drugs in this category include carbamazepine, phenytoin, gabapentin and lamotrigine. These drugs stabilize neuronal membranes and may thus prevent neuronal "short-circuits" that lead to neuropathic pain. The anticonvulsant drugs are quite useful in treating the lancinating pains frequently seen with trigeminal neuralgia and in some other peripheral neuropathies.

Effective dosages for treating neuropathic pain are similar to the dosages used for treating seizures. Blood levels of these drugs may be monitored and dosages adjusted as needed.

- **Lamotrigine**: a new anti-seizure drug effective for primary generalized seizures, can cause a severe and fatal cutaneous hypersensitivity reaction if the starting dosage is high, and therefore must be started at a very low dose with a very gradual dosage escalation.

- **Alpha-2 adrenergic agonists**: Clonidine and tizanidine may be effective in some patients with chronic neuropathic pains. Hypotension and somnolence, respectively, limit their usefulness.

- **Corticosteroids**: Both prednisone and dexamethasone have been tried in patients with CRPS and with certain refractory neuropathic pains. Efficacy is limited and adverse effects limit the usefulness of these drugs.

- **Oral local anesthetic agents**: Mexiletine has been tried in some patients with refractory neuropathic pain. Electrocardiograms should be monitored in these patients. GI and CNS adverse effects limit its usefulness.

- **Miscellaneous drugs**: Both baclofen, a GABA agonist, and pimozide, a neuroleptic, have been tried in patients with refractory trigeminal neuralgia.

- **Topical agents**: Capsaicin, a drug that impedes pain transmission by depleting substance P from sensory nerve fibers, has been found effective in treating refractory neuralgia in several studies. The cream must be applied several times daily to be effective, and patients frequently experience severe burning following each application for one or two weeks following initiation of treatment.

  Transdermal lidocaine (Lidoderm), a local anesthetic, also appears to be effective for some patients with neuropathic pain syndromes. This drug is available as an adhesive patch that may be cut to size and replaced every 12 hours.

**Anesthesiologic Therapies**

- **Intraspinal drug administration**: Both epidural and subarachnoid administration of opioids has been found to be effective in treating chronic pain in some patients. Although opioids are effective by any route, intraspinal administration allows the use of lower doses of the opioid to achieve equivalent pain control with fewer adverse effects. Technical and infectious complications can occur with intraspinal opioid administration, and this form of anesthesia must be carefully monitored.

- **Neural block**: Neural blockade with a local anesthetic may be of benefit in selected patients with CRPS. Chemical neurolysis of the trigeminal nerve with
phenol or alcohol may be considered for patients with trigeminal neuralgia refractory to all other therapies. Permanent facial anesthesia may result from this procedure, however.

Surgical Approaches to Pain Management

In selected patients, an anterolateral cordotomy (sectioning the spinothalamic tract) or a dorsal rhizotomy (sectioning the dorsal root) may offer substantial relief for incapacitating localized pain. In most cases, pain relief is only temporary, since pain afferents rapidly form new synapses that reach brain stem and thalamic pain centers.

Physical Therapy

Physical therapy plays a very important role in treating patients with many forms of musculoskeletal and neuropathic, as well as psychogenic pain. Many different treatment modalities are utilized, including manipulation, massage and mobilization.

Specific pain-directed treatments such as TENS (transcutaneous electrical nerve stimulation), and acupuncture may also have a role in the treatment of neuropathic pain. Although both TENS and acupuncture are widely used, there is no established efficacy in controlled studies for these treatments, and a likelihood for a strong placebo effect with these interventions must be acknowledged.

Psychotherapy

Psychotherapy, including cognitive-behavioral therapy, may be effective in treating patients with pain and coexistent depression and anxiety. Psychotherapy may also benefit a small subset of patients with personality disorders and psychogenic pain syndromes, by helping them attain insight into the cause of their pain. Most patients with personality disorders and somatoform disorders do not respond well to psychotherapy, however, because they lack insight into the underlying psychopathological mechanism of their disorder.

Pain Treatment Center

Patients with chronic pain often benefit substantially from the specialized evaluation and treatment provided by a comprehensive pain treatment center. A multi-specialty approach to diagnosis is utilized, including medical, neurologic, and psychological evaluations. Treatment likewise is multi-modal, and includes drug therapy, nerve blocks and psychotherapy.

References


MULTIPLE SCLEROSIS

Andrew Goodman, MD

Multiple sclerosis (MS) is a CNS-specific immune-mediated disorder that results in demyelination and scarring of white matter pathways and occurs in more than one location over time.

Pathology

Gross: Characterized by multiple graying, hardened lesions (often called “plaques”) distributed throughout the CNS white matter. There is a predilection for peri-ventricular regions for unknown reasons.

Microscopic: Individual lesions are characteristically centered around venules within white matter. Peri-venular cuffing by lymphocytes and edema are commonly seen in acute lesions but give way to astrocytic proliferation (scar) and axonal degeneration in chronic lesions. Most cases show a variety of activity between these extremes in different lesions. Over the years, neuropathologists have noted the commonality of these findings among patients who are biopsied or who come to autopsy despite the marked heterogeneity of their clinical courses.

Epidemiology

The reported prevalence of MS in the United States, Northern Europe, and Australia, where the most complete data have been collected, ranges between 50-150 per 100,000. In the Rochester area, we estimate the prevalence to be about 100-125/100,000. Most studies have found a North-South gradient with latitudes farthest from the equator showing the highest incidence and prevalence rates. This observation remains unexplained though it has been taken to implicate environmental factors in the etiology of this disease (see below).

Etiology

Genetic Factors: Several immunogenetic markers are more prevalent in MS patients than in the general population. These are tabulated below. Taken together they imply that inherited immunogenetic background contributes to susceptibility to MS. We do not have a specific picture as to how these inherited traits are linked to the pathogenesis other than the general notion that they may affect susceptibility to certain viral infections or the intensity or quality of immune responses to viral or auto-antigens.

Environmental factors: These are tabulated below. The most recent viral candidate agent, based on circumstantial evidence, is human herpesvirus 6 (HHV6); some studies have found evidence of HHV6 genome in or around MS brain lesions. Other investigators have reported the presence of IgM antibodies in relapsing-remitting patients.
FACTORS ASSOCIATED WITH MS SUSCEPTIBILITY

Genetic:

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>low-MS groups:</th>
<th>Japanese, Chinese, African-Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MS-free groups:</td>
<td>Bantu, Eskimo, Yakut</td>
</tr>
</tbody>
</table>

HLA type in Northern Europeans: HLA A3, B7, DR2, DQ1 (chromosome 6)

Other immunogenetic markers:

- Chromosome 14: antibody Gm allotype, alpha-1 anti-trypsin, T cell receptor alpha chain
- Chromosome 7: T cell receptor beta chain
- Chromosome 6: vasoactive amine (e.g. histamine) sensitivity

Environmental:

Triggering the disease:

- latitude effect
- epidemics of MS (Faeroe Islands)
- ? infection in childhood
  - (measles, mumps, rubella, EBV, HHV6, others)

Exacerbation

- viral infections
- seasonal variation
- ? emotional and physical stress

Pathogenesis

A widely held working hypothesis is that a viral infection occurring during childhood or adolescence in a genetically susceptible individual triggers an ongoing (but fluctuating) autoimmune process within the CNS white matter. The table below lists several immunologic abnormalities typical of MS which implicate the immune system in the pathogenesis.
EVIDENCE FOR "AUTOIMMUNITY" IN MULTIPLE SCLEROSIS

1. Similarity to experimental allergic encephalomyelitis (EAE)

2. Peripheral blood immune abnormalities:
   - HLA association: A3, B7, DR2
   - T cell subset and functional abnormalities
   - Decreased autologous mixed lymphocyte response
   - T cell receptor Vbeta 8 phenotype association

3. Central nervous system immune abnormalities
   - Pathology: CD4 > CD8 lymphocytic infiltrate
   - CSF:
     - "Oligoclonal" IgG
     - "Oligoclonal" T cells

Diagnosis

*There is no single diagnostic test that is specific for MS.* Rather, the diagnosis is based on the constellation of:

1. History indicative of multiple episodes or chronic progression of neurologic symptomatology

2. Clinical examination findings indicative of neurologic dysfunction in more than one CNS location

3. Electrophysiologic or neuroimaging data indicative of multiple CNS white matter lesions

4. Abnormalities of CSF immunoglobulin indicative of an ongoing immunologic process within the CNS
**COMMONEST MS SYMPTOMS**

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>CNS WHITE MATTER</th>
<th>AT ONSET</th>
<th>LATER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness of limbs</td>
<td>Corticospinal</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>Visual:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central scotoma</td>
<td>Optic nerve</td>
<td>36%</td>
<td>66%</td>
</tr>
<tr>
<td>Diplopia</td>
<td>Brain stem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired sensation</td>
<td>Lemniscal system</td>
<td>21%</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>Spinocerebellar</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spinothalamic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incoordination</td>
<td>Cerebellum</td>
<td>10%</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>Brain stem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder, bowel, sexual dysfunction</td>
<td>Autonomic</td>
<td>9%</td>
<td>56%</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Cerebral</td>
<td>3%</td>
<td>60%</td>
</tr>
</tbody>
</table>

**Electrophysiologic studies:**

Electronic signal averaging permits the recording of low amplitude potentials from scalp electrodes evoked by visual (checkerboard pattern reversal), auditory (multiple clicks), or somatic sensory stimulation (electric shocks). The objective is to demonstrate abnormalities in latency of conduction through myelinated sensory pathways that are not detectable from the clinical manifestations of the patient.

**Example:** A patient has progressive paraparesis with no signs or symptoms of disease beyond the spinal cord. An abnormal visual evoked response implies that the optic nerve has been affected by either sub-clinical or forgotten demyelinating episode(s). Thus, a second commonly affected region of the CNS has been identified.

**Neuroimaging:**

Magnetic resonance scanning (MRI) is the imaging technology of choice in the diagnosis of MS. Its principal diagnostic utility is to identify one or more lesions in the brain or spinal cord that are not apparent on clinical grounds alone. The abnormalities detected on MRI are due to prolongation of T1 and T2 relaxation times that depend upon the tissue-specific content of hydrogen nuclei (protons). Prolongation of the T1 results in decreased signal intensity (darker area) in a T1-weighted technique such as inversion-recovery; prolongation of the T2 causes increased signal intensity (whiter area) in a T-2 weighted technique such as spin-echo. These changes in relaxation times may relate to increased free water content because of instability of the blood-brain barrier in an inflamed area, an increase in neutral lipids due to myelin breakdown products, or to decreased myelin lipid content itself. Certain paramagnetic compounds such as gadolinium-DPTA are used to enhance imaging of acute lesions with blood-
brain barrier breakdown. This is possible because this compound reduces the T1 relaxation time, resulting in an increased signal on a T1-weighted scan.

**Cerebrospinal Fluid (CSF):**

Abnormalities of CSF immunoglobulin content have been recognized for many years and are commonly used adjuncts in making the diagnosis. The first abnormality described was an elevation in the quantity of IgG. Since the amount of IgG in the CSF is small in comparison to blood, it is imperative that a quantitative assessment of blood-brain barrier integrity be included with any evaluation of CSF immunoglobulin in order to determine if an increase is caused by leakage of proteins from blood into the CNS or from a traumatic lumbar puncture. Two widely used indicators of intrathecal IgG synthesis are IgG index (Link) which is a dimensionless quotient that is abnormal in up to 93% of definite MS patients when above 0.7 and IgG synthetic rate (Tourtelotte) which is abnormal in up to 96% of definite patients when greater than 3 mg per day.

**Oligoclonal banding (OCB):**

Oligoclonal banding describes a pathologic pattern of discrete bands rather than a homogeneous smear found in the characteristic region for IgG on an electrophoresis gel of concentrated CSF stained for protein. The standard interpretation of this phenomenon in MS has been that the IgG present in each band in MS CSF is the homogeneous product of a single active plasma cell clone present in the CNS. This technique is now commonly used and is done in the Strong Memorial Hospital clinical labs. OCB are not specific for MS and have been described in a variety of other inflammatory (SLE, lues, SSPE, HIV infection) and non-inflammatory (CVA) conditions of the nervous system.

**Natural History**

The course of MS is highly variable. The disease usually has its onset in the third or fourth decade and is almost two to three times more common in women compared to men. In approximately two-thirds of patients, the disease manifests as well-delineated clinical exacerbations and remissions. Early on, remissions are accompanied by complete or nearly complete recovery of function. In time (months to years) the degree of improvement becomes less after each exacerbation. Often, this heralds a chronic phase of slowly progressive worsening over a period of many years. The average time from diagnosis to requiring support of ambulation (such as a cane) is 15 years. About 10% of patients will have slowly progressive disease (usually myelopathy) from the outset. A small number of patients have a severe, rapidly progressive form that may be terminal within one year of onset.

**Treatment**

There is no definitive cure for this illness. Typically, pulses of corticosteroids are given to early patients with acute exacerbations to shorten the time to clinical remission. If their neurologic signs and symptoms become progressive, cytotoxic agents may be added in an attempt to halt this process, though none have been completely successful.
In 1993, a preventative maintenance drug treatment, interferon β-1b (IFN) (Betaseron), was first introduced. A placebo-controlled multi-center study done in relapsing but still ambulatory MS patients reported a reduction in the number of attacks. Longitudinal MRI studies also showed a reduction in the activity of lesions in the IFN-treated patients. Based on these findings, the Food and Drug Administration (FDA) has approved IFN as prophylactic maintenance therapy only for relapsing cases. A large European placebo-controlled clinical trial IFN was reported to show similar effects in more progressive cases.

This treatment consists of self-administered subcutaneous injections of IFN (8 million IU) given every other day. Common side effects include headache, shaking chills, and other "flu-like" symptoms. These symptoms are generally responsive to treatment with acetaminophen or non-steroidal anti-inflammatory drugs. They usually abate within 3 months after the initiation of therapy.

In 1996, the FDA approved two additional treatments for relapsing MS. Interferon β-1a (Avonex) is a recombinant interferon with the precise amino acid sequence found in humans. It has side effects that are similar to the other IFN (Betase'ron) but is administered as a once weekly IM injection. The other is glatiramer acetate (Copaxone) (formerly known as Copolymer 1) which is a once daily subcutaneous injection that does not have "flu-like" side effects.

The three available therapies for relapsing MS have not been compared directly with one another in any clinical trials.

**TREATMENT DIRECTED AT UNDERLYING IMMUNOPATHOLOGY**

- **Anti-inflammatory**: pulse corticosteroids (prednisone, methylprednisolone, ACTH)
- **Immunomodulatory**: interferon beta-1a and 1b, cytotoxic drugs (azathioprine, cyclophosphamide), glatiramer (copolymer 1)

**SYMPTOMATIC MANAGEMENT**

- **Spasticity**: GABA-ergic drugs (baclofen, diazepam), tizanidine
- **Tremor**: clonazepam, primidone, beta-blockers, gabapentin
- **Seizures**: phenytoin, carbamazepine, valproate
- **Pain**: carbamazepine, phenytoin, antidepressants, gabapentin
- **Fatigue**: amantadine, pemoline, fluoxetine
- **Depression**: tricyclics, fluoxetine, sertraline
- **Emotional incontinence**: amitriptyline
- **Bladder dysfunction**: oxybutinin, imipramine, prazosin, self- catheterization
OTHER MANAGEMENT

- Mechanical devices
- Physiotherapy
- Occupational therapy
- Psychiatric and social rehabilitation
- Job therapy
AGING AND DEMENTIA
Curtis G. Benesch, M.D.

AGING

Epidemiology
Approximately 10% of the U.S. population was > 65 years old in 1978 (22 million). By the year 2000, the number will reach 35 million and by 2050, 67 million. Today, 50% of the population reaches age 75, and 25% reaches the age of 85.

The Aging Nervous System
Age is a complex biological variable and age-related changes in the nervous system have been difficult to characterize. Many studies of the aging process are confounded by comparisons between an elderly cohort and younger controls and fail to account for other differences in socioeconomic status or educational level. Further, identification of clinical features unique to aging is hindered by the presence of one or many chronic diseases.

Listed below are several clinical consequences of the effects of aging on the nervous system:

1. Autonomic nervous system
   - Syncope
   - Orthostatic hypotension
   - Hypertension (amyloid angiopathy, intracerebral hemorrhage, dementia)
   - Reflex sympathetic dystrophy

2. Cognitive function
   - Overestimate of cognitive decline in elderly
   - Forgetfulness vs. dementia
   - Presence of cortical disinhibition signs (snout, suck, rooting, grasp, palmomental)

3. Affect and behavior
   - Depression (uncomplicated, Parkinson's disease, post-stroke)
   - Behavioral disturbances, especially in demented patients

4. Cranial nerves
   - Impaired saccades and smooth pursuit (cogwheel tracking)
   - Impairments in vision, hearing and vestibular system
   - Ageusia and anosmia

5. Sensorimotor function
   - Motor slowing with increased tone (paratonia)
   - Atrophy and decreased strength
   - Postural tremor
Restless legs and periodic movements of sleep
Loss of vibration and proprioception distally

6. Gait
   - Broad-based, decreased arm swing, short steps uncertainty on turning and higher risk of falling

DEMENTIA

Dementia is a global impairment of cognitive function which interferes with normal social and occupational activities.
   - Acquired, usually progressive
   - No disturbance of consciousness
   - Differential includes degenerative disorders, intoxicants, metabolic disorders, nutritional deficiencies, vascular disease, space-occupying lesions, normal pressure hydrocephalus, affective disorders; some of these are either reversible or arrestable

Alzheimer’s Disease

A progressive, acquired neurodegenerative disorder affecting adults which characteristically results in the gradual deterioration of cognitive and social skills over several years.

Epidemiology

   - Most common form of dementia, accounting for approximately 50% of cases
   - Up to 15% of the population over 65 may have mild dementia
   - The prevalence of Alzheimer’s disease over the age of 80 is 20%
   - Fourth leading cause of death in the U.S.
   - Accounts for 50% of nursing home beds
   - Estimated to cost U.S. health care system $80 billion annually

Clinical features

Early stages
   - Usually insidious in onset, beginning in 50s and 60s; age of onset is variable
   - Mild forgetfulness, often repetitious in conversation
   - Restlessness or apathy
   - Small inconsistencies in ADLs with tendency to misplace things
   - Occasionally, subtle personality changes are the first signs
   - Social skills and sensorimotor function are generally preserved

Later stages
   - Increasing disorientation and disorganization with poor judgement
   - Failure at work
   - Altered sleep cycles
   - Worsening memory and language skills
• More severe personality changes with paranoia, delusions, hallucinations
• Behavioral disturbances (irritability, agitation, abusiveness)
• Depression

**End stage**
• Severe cognitive impairment, often mute or incomprehensible
• Markedly impaired ADLs with high risk for aspiration
• Incontinence
• Severe motor involvement with extrapyramidal signs, functional quadriplegia
• Seizures, myoclonus, dyskinesias

**Pathology**
• Brain atrophy (large, cortical neurons; especially in younger patients)
• Neurofibrillary tangles (paired helical filaments, intraneuronal, eventually widespread)
• Senile plaques (dystrophic neurites, gliosis, amyloid core)
• Cerebrovascular amyloid
• All can be seen in varying degrees in normal, aged individuals

**Neurochemistry**
• Decreased choline acetyltransferase (biosynthetic enzyme for acetylcholine)
• Decreased norepinephrine from locus coeruleus
• Decreased serotonin from raphe nuclei
• Decreased neurotransmitters in the cortex (glutamate, GABA, neuropeptides)

**Pathogenesis**
• Mechanism for Alzheimer’s disease is unknown
• Role of genetics in unclear (10% of cases are familial)
• Similar pathology seen in patients with Down’s Syndrome

**Diagnosis**
• Diagnosis of exclusion
• Clinical features and lack of other causes by laboratory studies
• Imaging studies generally not conclusive
• Pathologic confirmation on post-mortem examination

**Treatment**
• Multiple experimental therapies have not been successful
• Tacrine hydrochloride (Cognex) – marginally effective and limited by hepatotoxicity
• Donepezil hydrochloride (Aricept) – safer than tacrine but also marginally effective
• Social services
DEMENTIA AND DELIRIUM

Daniel Giang, MD
Ralph F. Józefowicz, MD

Dementia and delirium represent diffuse dysfunction of the central nervous system. The major feature of delirium is altered attention which tends to be relatively short in duration, follow a fluctuating course, and be fully reversible once injured neurons recover. On the other hand, dementia results from destruction of neurons that leads to a chronic and oftentimes progressive course and is characterized by a clear sensorium. These two conditions of diffuse CNS dysfunctions must be distinguished from focal cognitive disorders. Amnesia represents loss of memory with preserved attention. Wernicke's aphasia is a loss of comprehension of language with the preservation of other components of cognition which are difficult to assess. Various psychiatric disorders may also present with the patient in a confused state. Depressed patients in particular often complain of memory and attentional problems, but cognitive abilities are preserved.

DELIRIUM

Definition

Delirium comes from a Latin word meaning "to leave the furrow". Acute confusional state is a synonym that has come into recent use. The hallmark of celirium is altered alertness of relatively acute onset and fluctuating course. Delirium can be divided into two types. The more common variety is associated with lethargy, decreased psychomotor activity, and indecisiveness. The second type is exemplified by delirium tremens and is associated with restlessness, irritability, hallucinations, and evidence of autonomic over-activity. Patients may alternate from one type of delirium to the other. The severity may range from very mild cases, where only detailed mental status examinations can reveal the deficits, to severe cases where the patient becomes unresponsive.

Pathophysiology

The basic deficit in delirium is fluctuating alteration in alertness. Abnormally decreased or increased alertness leads to inattention. This in turn causes disrupted memory, disorientation, and confusion. Other symptoms of diffuse neuronal dysfunction include language disorders (anomia, aphasia, misnaming, agraphia, and diminished comprehension), visual/spatial disorientation, impulsiveness, incoherence, concreteness, hallucinations, delusions, mood changes, and sleep disturbances.

The opposite type of delirium, agitated delirium, is most often caused by withdrawal of sedatives after chronic use. The most common agent at fault is ethanol. The patient is hyperalert, and thus distracted by trivial environmental stimuli. This in turn results in decreased attention. In addition, the patient also experiences vivid tactile and visual
hallucinations that precipitate tremendous anxiety and increase autonomic outflow. Delirium tremens is fatal in 10% of cases. Other causes of this type of agitated delirium include hallucinogens and rarely steroids.

All causes of delirium act through widespread injury to the central nervous system. The reticular activating system and its thalamic and cortical extensions appear particularly susceptible to injury. Nuclei in the brainstem provide ascending cholinergic and monoaminergic innervation to the thalamus and neocortex. These neurotransmitters modulate the responsiveness of cortical neurons. Thus, the effects of dysfunction in the brainstem nuclei affect the overall information processing capacity of the central nervous system.

**Etiology**

The causes for delirium can be divided into the following groups: 1) toxic-metabolic encephalopathies, 2) multifocal brain lesions, 3) diffuse primary central nervous system problems, and 4) focal brain lesions which mimic delirium.

The most common cause of delirium are toxic-metabolic encephalopathies. These can be caused by a wide variety of metabolic and environmental substances. These include hypotension, hypo or hyperglycemia, hepatic failure (high ammonia), Reye's syndrome, porphyria, renal failure (elevated BUN), pulmonary failure (hypoxia, hypercapnea), endocrine problems including hyper or hypothyroidism, disturbances in calcium or phosphate metabolism, electrolyte or acid-base alterations, vitamin deficiencies, and anemia. Delirium is a common complication of systemic infections especially in the very young and the very old. Many drugs and environmental toxins may cause delirium especially when taken in overdoses. These include anticholinergics, antiepileptic drugs, antihistamines, antihypertensives, barbiturates, benzodiazepines, bromides, cocaine, dopamine, digoxin, ethanol, hallucinogens, heterocyclic antidepressants, neuroleptics, steroids, and general anesthetic agents.

Multifocal brain lesions as found in vasculitis, endocarditis and various CNS infections (meningitis, encephalitis, PML, and AIDS) may cause delirium. Diffuse primary central nervous system problems include closed head trauma, seizures, migraines, subarachnoid hemorrhage, and increased intracranial pressure from any cause. Finally, certain focal lesions produce syndromes indistinguishable from delirium. These include the "top of the basilar" syndrome, the paramedian thalamic syndrome, and right parietal strokes.

**Clinical Aspects**

Certain factors place a patient at higher risk for developing delirium. The very young and the very old appear more susceptible. Patients with dementia from any source are very prone to getting an overlying delirium. Unfamiliar surroundings and severe medical illnesses also predispose to delirium. Delirium may be produced in otherwise normal individuals by sleep deprivation or by sensory deprivation or sensory overload.

Delirium may be recognized clinically and quantified by assessing the patient's attention span by means of such tests as the digit span and the various GO-NO-GO paradigms.
An electroencephalogram will often show slowing of the background rhythms which correlates with the degree of delirium present. The EEG also excludes status epilepticus as a cause for delirium. Neuroimaging is helpful in excluding structural lesions. A careful investigation of exposure to potential toxins (including medications) and appropriate laboratory studies to evaluate the above-mentioned metabolic conditions are needed.

**Therapy**

The primary therapy for delirium is directed against the underlying cause. Particularly, any metabolic derangements need to be corrected. In dealing with the patient in delirium, the major principle to follow is that of safety. The safety of caregivers and of the patient must be considered. Approaching the patient with a calm demeanor, providing a quiet, well-lit room, and familiar people all help in reassuring the patient. If the patient is agitated, sedation with benzodiazepines or neuroleptics should be considered. In cases of withdrawal syndromes such as delirium tremens, sedation with benzodiazepines and suppression of autonomic outflow with the use of beta-blockers is indicated.

**DEMENTIA**

**Definition**

DSM-III-R defines dementia according to 5 criteria: 1) impaired short and long term memory; 2) at least one other area of cognitive dysfunction such as poor abstraction, poor judgement, personality changes, or cortical dysfunction; 3) the above-mentioned deficits must interfere with work or social functions; 4) there is clear sensorium; 5) there is either a known organic cause or depression has been excluded. Dementia can range from very mild impairment where the patient remains independent and the impairment may not be identifiable except on mental status testing, to severe cases where the patient is completely dependent on others for all aspects of his or her maintenance.

Almost by definition, dementias are relatively irreversible. In most cases, there is actually structural damage to the central nervous system that cannot be fully repaired. In this way, dementia differs from delirium where the structure of the central nervous system remains intact but function is transiently compromised.

Dementia needs to be distinguished not only from delirium but also from normal aging and related conditions. Benign senile forgetfulness is the tendency to intermittently forget minor pieces of information, usually names. Although socially embarrassing, this type of forgetfulness does not progress and does not result in further problems. Older persons with decreased visual or auditory acuity may also appear demented to the casual observer.

**Epidemiology**

Given the wide range of severity of dementing illnesses, epidemiological studies are difficult. Perhaps 1% of the population is notably demented by age 70. This increases to 10-20% by age 80 and 40-50% by age 90. Caring for demented patients represents a major social problem in industrialized societies. Many different disorders result in
dementia. Alzheimer's Disease and multi-infarct dementia or combinations of the two represent almost 2/3 of all demented patients.

**Varieties of Dementia**

Various schemes have been proposed to categorize dementing illnesses. Dementia can be divided into cortical, subcortical, axial and other varieties.

- **Cortical dementias** include Alzheimer's Disease and Pick's Disease and involve degeneration of the association cortex. Aphasias and visual/spatial deficits are common presentations.

- **Subcortical dementias** are seen in patients with Huntington's disease, Parkinson's disease, and multiple sclerosis. These diseases tend to present with slowness in processing information, memory loss, mood and personality changes, and often involve motor and sensory dysfunction. Other dementing illnesses such as multi-infarct dementia and post-traumatic dementia tend to have mixtures of cortical and subcortical problems.

- The prototypic axial dementia is Korsakoff's psychosis, in which impairment of recent memory with confabulation is the most prominent feature. Degeneration of the mammillary bodies and peri-aqueductal structures due to thiamine deficiency is felt to be the pathologic mechanism responsible for the loss of memory seen in this disorder.

- **Alzheimer's disease** (AD) is a progressive degeneration of the association cortex and certain subcortical nuclei. AD is diagnosed pathologically on the basis of excessive amounts of plaques and tangles which are found in the association cortex, hippocampus, and the nucleus basalis of Meynert. AD is familial in 20-50% of cases. It also occurs in Down's Syndrome in virtually 100% of patients above age 40. A number of theories as to the pathogenesis of AD have been proposed including prions, aluminum, and hereditary factors.

- **Dementia with Lewy Bodies** (DLB) is another common degenerative disorder that differs clinically from Alzheimer's disease in that patients experience fluctuations in memory impairment, visual hallucinations, attention deficits and features of Parkinsonism. These patients are also very susceptible to the adverse effects of neuroleptics. The main pathologic finding in patients with DLB is the widespread distribution of Lewy Bodies throughout the cerebral hemispheres and brain stem.

- **Pick's Disease** is an order of magnitude less common than AD. Pathologically, it is characterized by Pick bodies that are found mostly in the frontal and temporal lobes.

- **Huntington's Chorea** is the prototypic subcortical dementia. It is an autosomal dominant degeneration of the caudate nucleus that results in dementia, personality changes, and chorea.
• Parkinson's Disease, and related conditions such as progressive supranuclear palsy, are degenerations of the basal ganglia associated with rigidity, bradykinesia and often dementia.

• Creutzfeldt-Jakob Disease is caused by prions and causes a rapidly progressive dementia associated with myoclonus. This disease can be transmitted by transplantation of infected tissue.

• Normal pressure hydrocephalus results from failure of the arachnoid granulations to reabsorb cerebrospinal fluid. This in turn causes the CSF to recross the ependyma of the lateral ventricles. Clinical symptoms include urinary incontinence, gait apraxia, and dementia. This syndrome is partially reversible with placement of a ventriculo-peritoneal shunt.

• Dementia can result from chronic alcohol abuse. Profound impairment in recent memory is the cardinal feature of Korsakoff's psychosis, and thiamine deficiency is felt to be the underlying mechanism responsible for this form of alcoholic dementia. Various other cognitive deficits may also be seen with chronic alcohol use, and these deficits are felt to be the result of the direct neurotoxic effects of ethanol.

• Prolonged effects of various systemic illnesses can result in dementia. These include hepatic failure, pernicious anemia, hypothyroidism, syphilis, Cushing's Syndrome, and uremia. Primary central nervous system conditions which result in destruction of cerebral tissue such as multiple sclerosis, head trauma, tumors, or multiple strokes may all produce dementia.

Diagnosis

Before dementia is diagnosed, certain characteristics must be established. Premorbid cognitive function must be considered and a decline from the previous level of function must be documented. Metabolic derangements and diminished visual and auditory acuity should be noted and corrected as much as possible. Depression must also be considered and differentiated from dementia.

Various bedside examinations of mental status such as the Mini-Mental Status Examination are useful in detecting dementia. Potentially treatable forms of dementia can be identified by appropriate laboratory studies. Neuroimaging tests may help differentiate multi-infarct dementia, normal pressure hydrocephalus, etc. from primary degenerative processes such as AD. The EEG remains normal early in the course of dementing illnesses but gradually becomes slow and disorganized as dementia progresses.

Treatment

Some dementias have specific treatments associated with them that may prevent further degeneration or at times produce improvement in cognitive function. Even when no specific treatment is available, attention to symptomatic treatment can go a long way towards alleviating patient and caregiver suffering. Some of the symptoms that may
benefit from treatment include wandering, incontinence, superimposed depression, aggression, hallucinations, paranoid ideation, and eventual physical debilitation. Management of concurrent medical problems must be undertaken bearing in mind the fact that the patient may not recognize the benefits of potential treatment. The physician must bear in mind the social and psychological strain that caring for a demented patient places on caregivers. Community resources are often of great benefit in alleviating these stresses.

**Acetylcholinesterase Inhibitors**: Donepezil (Aricept), Rivastigmine (Exelon) and Tacrine (Cognex) are three centrally active Ach inhibitors that have been shown to slightly improve memory and cognitive function in a small percentage of patients with Alzheimer's disease. Tacrine requires frequent monitoring of blood counts and liver chemistries due to its potential to cause bone marrow suppression and hepatotoxicity; it is therefore infrequently prescribed. Donepezil and rivastigmine are tolerated quite well, although their beneficial effects are modest at best.
MOVEMENT DISORDERS

Curtis G. Benesch, MD

The term *movement disorder* describes a wide spectrum of abnormalities in motor control, ranging from excessive, involuntary movements (chorea, dyskinesia) to a relative poverty of movement (akinesia). Although damage to numerous structures in the central and peripheral nervous systems may disrupt normal motor function, movement disorders are typically associated with dysfunction of the basal ganglia.

The basal ganglia are cerebral nuclei that lie deep within the brain and include the following structures: caudate nucleus, putamen, globus pallidus, substantia nigra and subthalamus. These nuclei are richly interconnected and communicate using a multitude of neurotransmitters.

The following sections will describe two degenerative disorders of basal ganglia structures with prominent motor abnormalities as well as a movement disorder without a known structural defect.

**Parkinson’s Disease**

**Definition:** A neurodegenerative disease characterized by the cardinal features of bradykinesia, rigidity, resting tremor and postural instability

- Symptoms usually appear initially in the fifties and sixties and are often asymmetric
- Loss of dopamine-secreting cells in the substantia nigra
- Effective symptomatic therapies with normal life expectancy

**Clinical features**

**Epidemiology**

- Prevalence of 100 per 100,000 individuals; reaches 1-2% in patients over 70
- Men and women equally affected; rarely inherited

**Four Cardinal Symptoms:**

1. **Tremor**
   - One of the earliest symptoms, occurring in 75% of cases
   - Rhythmical, slow (4-6 Hz) resting tremor – “pill-rolling”
   - Worse with excitement or anxiety and during walking; vanishes with sleep

2. **Rigidity**
   - Increased resistance to passive movement; often detected only by examiner
   - First evident in neck and shoulder muscles
• Contributes to hypomimia (mask-like facies) and decreased arm swing during gait
• Perceived by patient as stiffness and sense of effort in moving limbs

3. Bradykinesia

• Decreased spontaneous and automatic movements, with hypomimia (masked facies), decreased blinking, impaired fine motor movements
• Related findings of micrographia, hypophonia and axial apraxia

4. Postural instability

• Stooped posture, impaired righting reflexes, freezing, festinating gait
• Impaired sense of center of gravity
• Frequent falls

Other related symptoms

• Neuropsychologic depression in 30-40%; apathy, low self-esteem, somatic complaints, diurnal swings, sleep disturbances
• Cognitive disorders in 10-30% with impaired memory and attention, psychomotor slowing, confusion, hallucinations and frank dementia in 5-10% (subcortical features)
• Constipation, hoarseness, dysphagia, bladder problems, sexual disorders, seborrhea

Differential diagnosis

1. Parkinsonism

• Drug-induced (phenothiazines, haloperidol, other neuroleptics, reserpine)
• Toxins (carbon monoxide, manganese, MPTP)
• Post-encephalitic
• Neuronal system degeneration (multiple system atrophy, Shy-Drager syndrome, progressive supranuclear palsy, striato-nigral degeneration, olivopontocerebellar atrophy, cortical basal ganglionic degeneration)

2. Tremor

• Familial tremor, alcoholism, thyrotoxicosis

3. Akinetic-rigid syndromes

• Multi-infarct dementia, communicating hydrocephalus, traumatic encephalopathy (dementia pugilistica), Alzheimer’s disease

Pathology

• Loss of dopamine-containing neurons of the substantia nigra
• Pallor of the substantia nigra on gross inspection of the brain
• Presence of gliosis and Lewy bodies (neuronal inclusions with central core and peripheral halo) on microscopic examination; predominantly found in substantia nigra, as well as brain stem, amygdala and cortex
• Disease severity is not associated with numbers of Lewy bodies; seen in normals and Alzheimer’s disease

**Neurochemistry**

• Depletion of dopamine in the putamen due to loss of dopaminergic cells in the substantia nigra
• Dopamine depletion accounts for most of the symptoms of Parkinson’s disease
• Other neurotransmitters may also be involved (norepinephrine, acetylcholine, serotonin)

**Therapy**

1. **Levodopa (L-dopa)**
   - Dopamine repletion with precursor of dopamine
   - Administered in combination with peripheral DOPA-decarboxylase inhibitor (carbidopa); trade name of Sinemet
   - Dose-dependent response, with peak-dose effects of involuntary movements and wearing-off effects within hours
   - Painful dystonias, on-off phenomena, and “freezing” may also occur (may also occur independently)
   - Other side effects include postural hypotension, confusion, hallucinations

2. **Dopamine-agonists:** pramipexole (Mirapex), ropinirole (Requip), bromocriptine (Parlodel), pergolide (Permax)
   - Act on post-synaptic dopamine receptors
   - Used in conjunction with Sinemet, often to “smooth out” dose-response curve
   - Limited by hallucinations, psychosis, nausea/vomiting, and hypotension

3. **Anticholinergic drugs:** benztropine (Cogentin), benzhexol (Artane), diphenhydramine (Benadryl)
   - Administered to decrease relative imbalance in cholinergic-dopaminergic activity in striatum
   - Typically used in early stages of the disease, especially for tremor and rigidity
   - Limited by side effects of constipation, urinary retention, and confusion

4. **Monoaminoxidase inhibitors:** selegiline, L-deprenyl (Eldepryl)
   - Inhibits enzymes which break down dopamine, thus potentially reducing toxic effect of dopamine metabolites
   - Also reduces symptoms by increasing amount of available dopamine
   - Few side-effects
Other therapies include amantadine, surgery (thalamotomy, pallidotomy), and deep brain stimulation of the thalamus, globus pallidus and subthalamic nucleus.

5. Physiotherapy

- Physical, occupational and speech therapy
- Emphasis on gait training, assistive devices, exercise programs

**Huntington’s Disease**

**Definition:** A genetic, neurodegenerative disease characterized by movement disorders, dementia and behavioral disturbances

- Autosomal dominant inheritance, short arm of chromosome 4
- Signs and symptoms appear in early childhood
- Selective and progressive neuronal degeneration primarily in the basal ganglia

**Clinical features**

**Epidemiology**

- Prevalence of 5-10 per 1000,000; 25,000 in the U.S. with HD; 125,000 at risk
- Age at onset of HD is variable with average age of 38 years; mean duration of 19 years
- Juvenile onset: dystonia and parkinsonian features, 90% from affected father
- Late adult onset; slower progression, 50:50 inheritance

**Four Cardinal Symptoms:**

1. **Movement disorders**

   - Chorea initially, with dystonia appearing later, resulting in characteristic choreoathetosis
   - Speech and swallowing affected with severe dysarthria and recurrent aspiration
   - Impaired ocular motility (impaired saccades and loss of smooth pursuit)

2. **Intellectual decline**

   - Impairment of memory and performance skills
   - Subcortical features with relative preservation of cortical functions

3. **Behavioral features**

   - Personality changes, depression with biologic signs (insomnia, anorexia, weight loss)
   - Frank psychosis with hallucinations, paranoia and thought disorders
• May appear either early or late in course of HD
• Increased risk of suicide

4. **Functional decline**

• Dementia and personality changes impair domestic and occupational skills early
• Self-care deteriorates as motor impairment worsens, requiring increased care

**Diagnosis**

• Clinical findings in the setting of a confirmatory family history
• Caudate atrophy on imaging studies
• Decreased metabolism in basal ganglia on PET studies
• Genetic testing (rarely sporadic)

**Pathology**

• Changes largely confined to basal ganglia (striatum and globus pallidus) – “selective vulnerability”
• Atrophy, neuronal loss, reactive gliosis
• Minor changes in cerebellum, cortex and brain stem

**Neurochemistry**

• Decreased GABA transmission
• Relative “hyperactivity” of dopaminergic systems
• Excitotoxic effect of glutamate

**Genetics**

• Localization to chromosome 4 using markers (restriction fragment length polymorphism)
• Actual gene identification in 1993 (trinucleotide repeat); genetic product unknown
• Autosomal dominant inheritance with exceedingly rare mutations
• Genetic defect can now be determined with nearly 100% accuracy; ethical concerns

**Experimental therapeutics**

1. **Replacement therapies**

• GABA replacement ineffective (unlike successful replacement of dopamine in Parkinson’s disease)

2. **Neuroprotective therapies**

• Focus on blocking excitotoxic effects of glutamate
Therapy

1. Movement disorder
   - In general are limited by transient effectiveness, side effects and inability to slow degenerative process
   - Anti-dopaminergic medications (phenothiazines, haloperidol, reserpine)

2. Behavioral disturbance
   - Tricyclic antidepressants, serotonin-reuptake inhibitors for depression
   - Anti-psychotics for schizophrenia-like symptoms
   - No treatment available for intellectual decline

3. Supportive care
   - Attention to social and psychological consequences of HD
   - Full disclosure of clinical and hereditary features of HD
   - Social services
   - Genetic counseling

Essential Tremor

Definition: A disorder of the nervous system characterized by a postural and kinetic tremor, particularly of the upper extremities

- Also known as familial, senile and benign essential tremor, depending on family history and age of onset
- Wide range of severity; often unreported

Clinical features

- Insidious onset, usually beyond 60 years of age; can occur in adolescents
- May have unilateral presentation but eventually becomes bilateral
- Evident when maintaining posture (i.e., outstretched arms) but may worsen with movement (kinetic tremor) and interfere with eating, drinking and writing
- Usually involves upper extremities, but legs, trunk and head (tutubation) can be affected
- Speech may also be affected; fluctuating and rhythmical, unusually seen in isolation
- Remarkably responsive to ethanol in some individuals
- Can be extremely debilitating in some individuals

Pathology

- No known central nervous system lesion; pathophysiology remains unclear
Genetics

- May occur sporadically
- Autosomal dominant when familial

Treatment

- Propranolol (Inderal) (60-240 mg/day – may be effective in up to 70% of patients
- Primidone (Mysoline) (50-500 mg/day) – limited by sedation
- Clonazepam (Klonopin) (0.5-2.0 mg/day) – also limited by sedation