**INFLAMMATORY AND** **NEURODEGENERATIVE DISEASES OF THE CENTRAL NERVOUS SYSTEM**

The central role in the regulation of all processes in the body belongs to the central nervous system. The nervous system also ensures that the body adapts to the environment. But initially, if the nervous system itself is damaged or its regulatory function is disturbed, the activity of this system becomes harmful to the body, it is maladaptive and it becomes the source of various pathologies.

The functional unit of the nervous system is the neuron. Damage to neurons disrupts their functions *(excitability of neurons, the conduction of impulses by nerve fibers, the transmission of impulses from one neuron to another one, axoplasmic current, etc.).* Because neurons do not have the ability to divide, damage to even a small number of neurons can cause permanent impairment of a given function.

**Inflammatory Diseases of the Central Nervous System**

As in all other parts of the body, inflammatory diseases can develop in the brain and its coverings. Inflammatory diseases that develop in the brain and its coverings can be both infectious and non-infectious origin. While some infectious agents damage only the nervous system (for example, rabies), others (for example, Staphylococcus, etc.) can have a pathogenic effect on all organs, including the brain.

Infectious agents may reach the nervous system through several routes: *Hematogenous spread* by way of the arterial blood supply is the most common. There can also be *retrograde venous* spread through the anastomoses between the veins of the face and the venous sinuses of the skull. *Direct implantation* of microorganisms is almost invariably due to open or penetrating trauma; rare cases can be iatrogenic, as when microbes are introduced with a lumbar puncture needle or into a surgical field. *Local extension* can occur with infections of the skull. Sources include air sinuses, most often the mastoid or frontal; infected teeth; cranial or spinal osteomyelitis. *Peripheral nerves* also may serve as paths of entry for a few pathogens — in particular, viruses such as rabies and herpes zoster.

**Meningitis**

Before clarifying the character of meningitis, let's take a brief look at the structure of the brain coverings (meninges). There are 3 layers of tissue called meninges that help protect the brain. The outer covering (called the *dura mater*), closely lines the inside of the skull. The second layer is the *arachnoid mater*, and the third layer, the *pia mater*, hugs the surface of the brain (fig. 1).

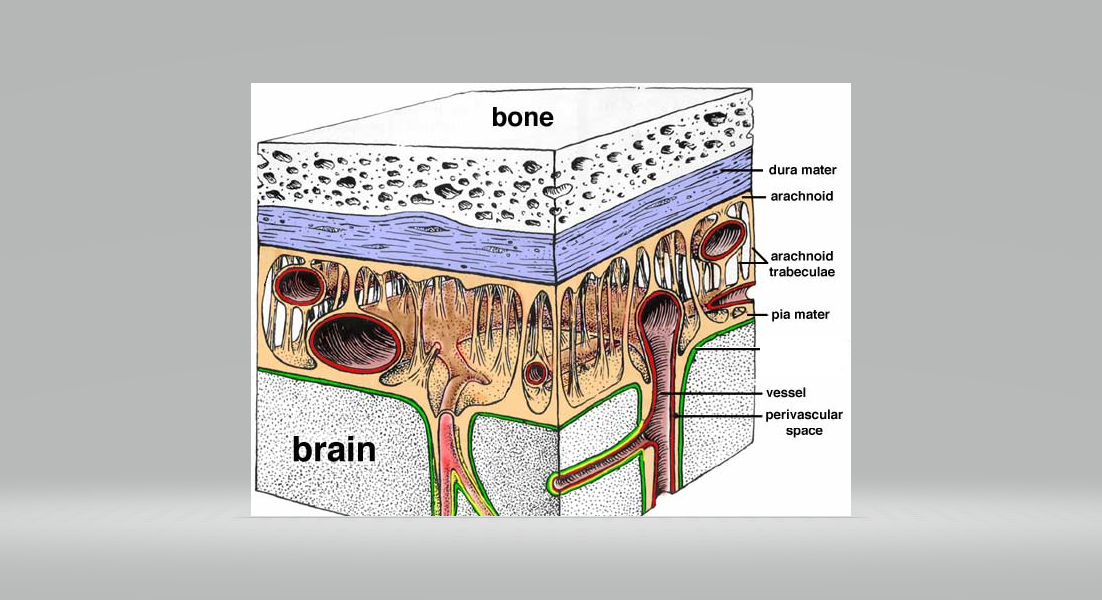
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Figure 1. The coverings of the brain.

***Meningitis***is an inflammatory process involving the *leptomeninges (arachnoid mater and pia mater)* within the subarachnoid space; if the infection spreads into the underlying brain, it is termed *meningoencephalitis.*

Meningitis and meningoencephalitis are usually infectious. However, it is possible that meningitis and meningoencephalitis might be *non-infectious.* These terms are also used in non-infectious settings such as *chemical meningitis*, a response to a nonbacterial irritant such as debris from a ruptured epidermoid cyst, and *carcinomatous meningitis,* the spread of metastatic cancer cells to the subarachnoid space.

The following forms of *infectious meningitis* are distinguished according to the composition of the cerebrospinal fluid (CSF) and the clinical picture of the disease: acute pyogenic (usually bacterial), aseptic (usually viral), and chronic (usually tuberculous, spirochetal, or fungal) subtypes. Examination of the CSF is often useful in distinguishing among the various causes of meningitis.

**Acute Pyogenic Meningitis (Bacterial Meningitis)**

The most likely causes of bacterial meningitis vary with patient age. In neonates, common organisms are *Escherichia coli* and group B streptococci. In adolescents and young adults, *Neisseria meningitidis* is the most common pathogen; in older adults, *Streptococcus pneumoniae* and *Listeria monocytogenes* are more common. Typically show systemic signs of infection along with meningeal irritation and neurologic impairment, including headache, photophobia, irritability, clouding of consciousness, and neck stiffness. Lumbar puncture reveals an increased pressure; examination of the CSF shows abundant neutrophil, elevated protein, and reduced glucose. The causative bacteria is identified in a smear made from the CSF. Untreated pyogenic meningitis is often fatal, but with early diagnosis and administration of antibiotics, most patients can be saved.

The development of leptomeningeal fibrosis and hydrocephalus is possible in patients who have recovered from purulent meningitis. Adhesive arachnoiditis can also develop after certain specific infections.

*Laboratory indices*

*Examination of the blood: Common signs of acute bacterial infection (neutrophilic leukocytosis, increased ESR, C-reactive protein), detection of causative bacteria*

*Examination of the CSF: Blurred color, increased protein, decreased glucose, neutrophilic pleocytosis (up to 90,000 neutrophils in 1 ml), finding causative bacteria in smear.*

**Aseptic Meningitis (Viral Meningitis)**

The term "aseptic meningitis" cannot be considered successful, because meningitis combined under this name in most cases has a viral and rarely a bacterial etiology. It is interesting that even when using molecular biological diagnostic methods, it is possible to determine the etiological factor only in some cases. In the case of aseptic meningitis, although the examination of cerebrospinal fluid does not reveal the causative agent, a typical clinical picture (relatively acute onset of the disease, meningeal syndrome, fever, loss of consciousness, etc.) is observed. The clinical course is milder than that of pyogenic meningitis and is usually self-limiting. At this time, the composition of liquor is also different. In aseptic meningitis, lymphocytic pleocytosis (proliferation of cells in the cerebrospinal fluid), a moderate increase in protein levels, and an almost normal glucose concentration are observed. As a rule, aseptic meningitis is self-healing and only symptomatic treatment is necessary.

*Laboratory indices*

*Blood: Lymphocytosis, increased ESR, C-reactive protein*

*CSF: Lymphocytic pleocytosis, a slight increase in protein concentration, normal glucose concentration*

**Chronic Bacterial Meningoencephalitis**

**Tuberculous Meningitis**

Tuberculous meningitis can develop both as an isolated local process and on the background of a systemic infection.

Clinical signs. The signs of tuberculous meningitis are headache, general fatigue, fainting, vomiting, etc. The development of tuberculomas makes the symptoms of the disease similar to the symptoms observed during brain tumors. Therefore, it is necessary to carry out differential diagnoses between tuberculous meningitis and tumors. During tuberculous meningitis, moderate pleocytosis (due to polymorphnuclear and mononuclear cells) is observed in the cerebrospinal fluid, the protein level is significantly increased, and the glucose concentration is usually normal or lower.

Arachnoid fibrosis is considered the most serious complication of tuberculous meningitis. The development of arachnoid fibrosis leads to the development of hydrocephalus and obliterating endarteritis, which results in the occlusion of blood vessels and cerebral infarction. If the spinal cord is involved in the process, the roots of the spinal cord nerves are damaged.

*Laboratory indices*

*Blood: Lymphocytosis and monocytosis, detection of meningococci (Latex-test method), obtaining a pure culture of the causative agent*

*CSF: Moderate pleocytosis (mainly due to mononuclear cells), the significant increase in* *protein concentration, normal or low glucose concentration, detection of meningococci (Latex-test method), obtaining a pure culture of the causative agent*

**Neurosyphilis**

*Neurosyphilis,* a tertiary stage of syphilis, occurs in about 10% of individuals with untreated *Treponema pallidum* infection. There are several patterns of CNS involvement by syphilis, which may be present alone or in combination.

*Meningovascular neurosyphilis* is a chronic meningitis, usually involving the base of the brain, often with an obliterative endarteritis rich in plasma cells and lymphocytes.

*Paretic neurosyphilis* stems from parenchymal involvement by spirochetes and is associated with neuronal loss a marked proliferation of microglial cells. Clinically, this form of the disease causes an insidious progressive loss of mental and physical functions, mood alterations (including delusions of grandeur), and eventually severe dementia.

*Tabes dorsalis* results from damage to the sensory nerves in the dorsal roots. Consequences include impaired joint position sense and ataxia; loss of pain sensation, leading to skin and joint damage.

*Laboratory indices*

*Blood:Lymphocytosis, an antibody against T. pallidum antigens*

*CSF: Lymphocytic pleocytosis, increased protein concentration, an antibody against T. pallidum antigens*

**Parenchymal Infections**

The entire gamut of infectious pathogens can infect the brain, often in characteristic patterns. In general, viral infections are diffuse, bacterial infections (when not associated with meningitis) are localized, while other organisms produce mixed patterns.

**Brain** **Abscesses**

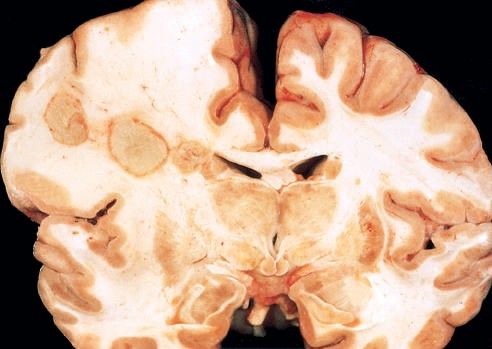
Brain abscesses are most often caused by bacterial infections.These can arise by direct implantation of organisms, local extension from adjacent foci (mastoiditis, paranasal sinusitis), or hematogenous spread (usually from a primary site in the heart, lungs, or distal bones, or after tooth extraction). Predisposing conditions include *acute bacterial endocarditis*, from which septic emboli are released that may produce multiple abscesses; and *chronic pulmonary infections,* as in bronchiectasis, which provide a source of microbes that spread hematogenously.

Abscesses are the lesions with central liquefactive necrosis surrounded by a rim of vascularized granulation and fibrous tissue (fig 2). Patients present with progressive focal deficits as well as general signs related to increased intracranial pressure. While CSF white blood cell count and protein may be elevated, lumbar puncture has little role in the diagnosis of brain abscess since organisms are more reliably cultured by draining the abscess directly. The increased intracranial pressure may cause fatal brain herniation, and abscess rupture can lead to ventriculitis, meningitis, and venous sinus thrombosis. Surgery and antibiotics reduce the high mortality rate, with earlier intervention leading to better outcomes.

*Laboratory indices*

*Blood: Leucocytosis, increased ESR, C-reactive protein*

*CSF: Pleocytosis, normal or low glucose concentration,* *bacteriological examination is usually inconclusive.*



B

Figure 2. Brain Abscesses

**Viral Encephalitis**

Viral encephalitis is a parenchymal infection of the brain that is almost associated with meningeal inflammation (meningoencephalitis). While different viruses show varying specific patterns of injury, the most characteristic histologic features are perivascular and parenchymal mononuclear cell infiltrates, microglial nodules, and neuronophagia.

The nervous system is particularly susceptible to certain viruses such as rabies virus, poliovirus, etc.

###### *Arboviruses*

###### *Arboviruses* are an important cause of epidemic encephalitis, especially in tropical regions of the world, and are capable of causing serious morbidity and high mortality. Patients develop generalized neurologic symptoms, such as seizures, confusion, delirium, and stupor or coma, as well as focal signs, such as reflex asymmetry and ocular palsies. The CSF usually is colorless but with a slightly elevated pressure and an early neutrophilic pleocytosis that rapidly converts to a lymphocytosis; the protein concentration is elevated, but the glucose is normal. Thus, CSF examination helps to distinguish viral from bacterial infections of the CNS.

*Laboratory indices*

*Blood: Antibodies against antigens of the virus (an increase in the IgG titer indicates a previous infection, and an increase in the IgM titer indicates a current infection)*

*CSF: Neutrophilic pleocytosis observed in the first days is soon replaced by lymphocytic pleocytosis, the protein concentration is high, and the glucose concentration is normal.*

*Herpesviruses*

*HSV-1* encephalitis may occur in any age group but is most common in children and young adults. It typically manifests with alterations in mood, memory, and behavior, reflecting involvement of the frontal and temporal lobes. Recurrent HSV-1 encephalitis is sometimes associated with inherited mutations, which has an important role in anti-viral defense.

*HSV-2* also affects the nervous system, usually in the form of meningitis in adults. Disseminated severe encephalitis occurs in many neonates born by vaginal delivery to women with active primary HSV genital infections.

*Laboratory indices*

*Blood: Antibodies against antigens of the virus (an increase in the IgG titer indicates a previous infection, and an increase in the IgM titer indicates a current infection)*

*CSF: Lymphocytic pleocytosis, the protein concentration is high, and the glucose concentration is normal.*

*Cytomegalovirus*

CMV infects the nervous system in fetuses and immuno- suppressed individuals. All cells within the CNS (neurons, glial cells, ependyma, and endothelium) are susceptible to infection. Intrauterine infection causes periventricular necrosis, followed later by microcephaly with periventric- ular calcification. When adults are infected, CMV produces a subacute encephalitis, which is also often most severe in the periventricular region.

*Laboratory indices*

*Blood: Antibodies against antigens of the virus (an increase in the IgG titer indicates a previous infection, and an increase in the IgM titer indicates a current infection)*

*CSF: Lymphocytic pleocytosis, the protein concentration is high, and the glucose concentration is normal.*

*Poliomyelitis*

The causative agent of this disease is an enterovirus that mainly causes subclinical or mild gastroenteritis. Sometimes the spinal cord and brain stem can be damaged as a result of the effects of this virus. Paralytic poliomyelitis develops during such injuries. The loss of motor neurons leads to the development of weak paralysis accompanied by muscle atrophy, atony, and hyporeflexia in the corresponding area of the body. During the acute development of the disease, death may occur due to paralysis of the respiratory muscles. Long after the infection has cleared (usually 25-35 years), post-polio syndrome (characterized by decreased muscle mass, progressive muscle weakness, and pain) may occur. The pathogenesis of this process is not completely clear.Laborator göstəricilər

*Laboratory indices*

*Blood: Antibodies against antigens of the virus (an increase in the IgG titer indicates a previous infection, and an increase in the IgM titer indicates a current infection)*

*CSF: Lymphocytic pleocytosis, the protein concentration is high, and the glucose concentration is normal.*

*Rabies virus*

The rabies virus is transmitted to humans from rabid animals, usually through a bite. This virus causes the development of fatal encephalitis in the human body. The host organism of the pathogen is various mammals, mainly dogs. Human contact with some species of bats can lead to virus infection, even without biting. The virus travels up the peripheral nerves from the wound site and enters the CNS, so the incubation period (usually several months) depends on the distance between the wound and the brain. The disease initially presents with non-specific symptoms such as weakness, headache and fever. As the process deepens, the CNS excitability increases; the slightest touch becomes painful, reflex contractions of the muscles begin, and these contractions gradually develop into convulsions. Contraction of pharyngeal muscles makes swallowing difficult, patients are even afraid to swallow water (hydrophobia). Periods of mania and stupor alternate and eventually result in the development of coma. Death occurs from respiratory failure, which develops as a result of damage to the respiratory center.Laborator göstəricilər

*Laboratory indices*

*Blood: Antibodies against antigens of the virus (an increase in the IgG titer indicates a previous infection, and an increase in the IgM titer indicates a current infection)*

*CSF: Lymphocytic pleocytosis, the protein concentration is high, and the glucose concentration is normal*

*Human Immunodeficiency Virus (HIV)*

In the first 15 years or so after recognition of AIDS, neuropathologic changes were demonstrated at postmortem examination in as many as 80% to 90% of cases, owing to direct effects of the virus on the nervous system *(HIV encephalitis),* along with opportunistic infections and primary CNS lymphoma. Introduction of highly active antiretroviral therapy has decreased the frequency of these secondary effects of HIV infection. When effective anti-HIV therapy is begun in the setting of established infection, there is a risk for neurologic involvement. Neuronal injury likely stems from a combination of cytokine-induced inflammation and toxic effects of HIV-derived proteins.

Aseptic meningitis occurs within 1 to 2 weeks of onset of primary HIV infection in about 10% of patients; antibodies to HIV can be demonstrated, and the virus can be isolated from the CSF. The few neuropathologic studies of the early and acute phases of symptomatic or asymptomatic HIV invasion of the nervous system have shown mild lymphocytic meningitis, perivascular inflammation, and some myelin loss in the hemispheres.

*Laboratory indices*

*Blood: Antibodies against antigens of the virus (an increase in the IgG titer indicates a previous infection, and an increase in the IgM titer indicates a current infection)*

*CSF: HIV virus, Lymphocytic pleocytosis, the protein concentration is high, and the glucose concentration is normal*

**Fungal Encephalitis**

The development of chronic fungal meningitis can be caused by hematogenous dissemination of fungal infection. Fungal species that can cause damage to the CNS include: С. albicans, Mucor spp., A. fumigatus and С. neoformans.

There are 3 main forms of fungal infection of the central nervous system: *chronic meningitis, vasculitis and parenchymal damage.*

*Chronic meningitis* is a typical opportunistic infectious disease that develops on the background of HIV infection and AIDS. This disease can develop rapidly and lead to death within 2 weeks, or it can continue gradually for several months or years. The cerebrospinal fluid contains a small number of cells, but a high concentration of protein. Yeast fungi can be found in liquor.

As a rule, *vasculitis* develops when fungi invade the vessel wall directly. Occlusion of the vascular lumen leads to cerebral infarction. At this time, a hemorrhagic component and secondary fungal infection are observed. In most cases, fungal infection of the CNS results in the entry of fungi into the parenchyma, the formation of granulomas or abscesses. At this time, the meninges are also involved in the process.

*Parenchymal damage* is observed in most of the fungal diseases of the CNS. This infection almost always results in the fungal invasion of the parenchyma, usually with the formation of granulomas or abscesses. Most fungal species penetrate the brain via the hematogenous route, but it is also possible for some fungal species to enter the brain directly.

*Laboratory indices*

*Blood: Finding the causative fungus*

*CSF: Mild pleocytosis, an increase in protein concentration is observed. Causative fungi can be found.*

**Other infections of the central nervous system**

A number of other infections can also damage the central nervous system. The most widespread of them are the following.

*Cerebral Toxoplasmosis*

Cerebral infection with the protozoan *Toxoplasma gondii* can occur in immunosuppressed adults or in newborns who acquire the organism transplacentally from a mother with an active infection. The consequences include the triad of *chorioretinitis, hydrocephalus, and intracranial calcifications*. In adults, the clinical symptoms are subacute, evolving over weeks, and may be both focal and diffuse. Due to inflammation and breakdown of the blood-brain barrier at sites of infection, imaging studies often show edema.

*Laboratory indices*

*Blood: Antibodies against antigens of the causative agent (increased IgG titer indicates previous infection, increased IgM titer indicates current infection).*

*CSF: Antibodies against antigens of the pathogen*

*Cysticercosis*

Cysticercosis is the consequence of an end-stage infection by the tapeworm *Tenia solium.* If ingested larval organisms leave the lumen of the gastrointestinal tract, where they would otherwise develop into mature tapeworms, they encyst. Cysts can be found throughout the body and are common within the brain and subarachnoid space. Cysticercosis typically manifests as a mass lesion and can cause seizures. Symptoms can intensify when the encysted organism dies, as occurs after therapy. Death of the encysted organism may produce an intense inflammatory reaction in the surrounding brain, often including eosinophils.

*Laboratory indices*

*Blood: Antibodies against antigens of the causative agent*

*CSF: Antibodies against antigens of the pathogen*

*Amebic meningoencephalitis*

*Amebic meningoencephalitis* manifests with different clinical syndromes, depending on the responsible pathogen. *Naegleria fowleri,* associated with swimming in stagnant warm fresh water ponds, causes a rapidly fatal necrotizing encephalitis. By contrast, various species of *Acanthamoeba* cause a chronic granulomatous meningoencephalitis.

*Laboratory indicators*

*Blood: Finding the causative agent itself, detecting antibodies against the antigens of the causative agent*

*CSF: Antibodies against antigens of the pathogen*

*Prion Diseases*

Prion diseases are a group of infectious diseases in which the causative agent is an abnormal form of a cellular protein.The causative protein, termed *prion protein* may undergo a conformational change from its normal shape to an abnormal conformation. This abnormal protein is resistant to proteolysis. More importantly, when these proteins interact with each other, occurs new conformations, a property that accounts for the “infectious” nature. Over time, this self-amplifying process leads to the accumulation of pathogenic molecules in the brain. Accumulation of prions in nerve tissue causes damage to these cells. The infectious nature of prion proteins is due to the ability of pathologically conformational changed proteins to pass from the diseased human and animal body in various ways (feces, urine, mainly through the milk of animals, sheep, deer, etc.) to the environment and back to humans (through food, milk, etc.) organism. Prion diseases include sporadic, familial, iatrogenic forms and various variants of Creutzfeldt-Jakob disease.

Creutzfeldt-Jakob Disease

This disease is a rare but well-defined prion disease that clinically manifests as rapidly progressive dementia. The disease is most common among people aged 60-70. There are well-established cases of iatrogenic transmission by contaminated deep implantation electrodes and human growth hormone preparations. Clinical presentation begins with mild changes in memory and behavior and rapidly progresses to dementia. The duration of the disease is very short (only 7 months) and soon results in death.

*Laboratory indices*

*Blood: Finding prion proteins*

*CSF: There is no pleocytosis, glucose level remains normal, prion proteins are found*

**Neurodegenerative Diseases of the Central Nervous System**

Neurodegenerative diseases are characterized by the progressive loss of neurons, typically affecting groups of neurons with functional interconnections.Different diseases tend to involve particular neural systems and therefore have relatively stereotypic presenting signs and symptoms:

●Diseases that involve the hippocampus and associated cortices present with cognitive changes, often including disturbances of memory, behavior, and language. With time these progress to dementia.

●Diseases that affect the basal ganglia manifest as movement disorders; these may be hypokinetic, as with Parkinson disease, or hyperkinetic, as with Huntington disease.

●Diseases that affect the cerebellum result in ataxia.

●When the motor system is damaged, weakness and difficulty with swallowing and respiration are often seen first, as with amyotrophic lateral sclerosis.

●There is experimental evidence that many of the protein aggregates that accumulate in neurons affected in these diseases appear to be capable of spreading to healthy neurons. Thus, aggregates can seed the development of more aggregates, and the disease process can spread, like prions. However, there is no evidence for transmission from affected to healthy individuals.

●Activation of the innate immune system is a common feature of neurodegenerative diseases. The importance of this interaction between the brain and the immune system has been further strengthened by the identification of genes that confer risk for diseases (e.g., *TREM2* for Alzheimer disease) that encode components of immune regulatory pathways.

A pathologic process shared by most neurodegenerative diseases is the accumulation of protein aggregates, which serve as histologic hallmarks of specific disorders. Aggregates may arise because of mutations that alter the protein’s conformation or that disrupt pathways involved in processing or clearance of the proteins. In other situations, there may be a subtle imbalance between protein synthesis and clearance (due to genetic, environmental, or stochastic factors) that allows gradual accumulation of proteins. The aggregates often are resistant to degradation by normal cellular proteases, accumulate within cells, elicit an inflammatory response, and may be directly toxic to neurons. The same proteins may be present as aggregates in multiple diseases. The clinical phenotype of the neurodegenerative disease is determined more by the distribution of the aggregates than by the nature of the aggregating protein.

**Alzheimer Disease**

Alzheimer disease is the most common cause of dementia in older adults, with an increasing incidence as a function of age. The incidence is about 3% in individuals 65 to 74 years of age, 19% in those 75 to 84 years of age, and 47% in those older than 84 years of age. Most cases of AD are sporadic, but at least 5% to 10% are familial. Sporadic cases rarely present before 50 years of age, but early onset is seen with some heritable forms.

The disease usually manifests with the insidious onset of impaired higher intellectual function, memory impairment, and altered mood and behavior. Over time, disorientation and aphasia, findings indicative of severe cortical dysfunction, often develop; those in the final phases of AD are profoundly disabled, often mute and immobile. Death usually occurs from intercurrent pneumonia or other infections.

*Pathogenesis*

The fundamental abnormality in AD is the accumulation of two proteins (Aβ and tau) in specific brain regions, in the forms of plaques and tangles, respectively; these changes result in secondary effects including neuronal dysfunction, neuronal death, and inflammatory reactions. Plaques are deposits of aggregated Aβ peptides in the neuropil, while tangles are aggregates of the microtubule binding protein tau, which develop intracellularly and then persist extracellularly after neuronal death.

*Role of Aβ.* Aβ is created when the transmembrane protein amyloid precursor protein (APP) is sequentially cleaved by the enzymes β-amyloid–converting enzyme and γ-secretase (fig. 3). APP also can be cleaved by α-secretase and γ-secretase, liberating a different peptide that is nonpathogenic. Mutations in APP or in components of γ-secretase (encoded by the presenilin-1 or presenilin-2 gene) lead to familial Alzheimer disease. Once generated, Aβ is highly prone to aggregation; it first forms small oligomers, and these eventually propagate into large aggregates and fibrils. It is these aggregates that deposit in the brain and are visible as plaques. There is evidence that these oligomers decrease the number of synapses present and alter the function of those. The *APP* gene is located on chromosome 21, and the risk for Alzheimer disease also is higher in those with an extra copy of the *APP* gene, such as patients with trisomy 21 (Down syndrome).

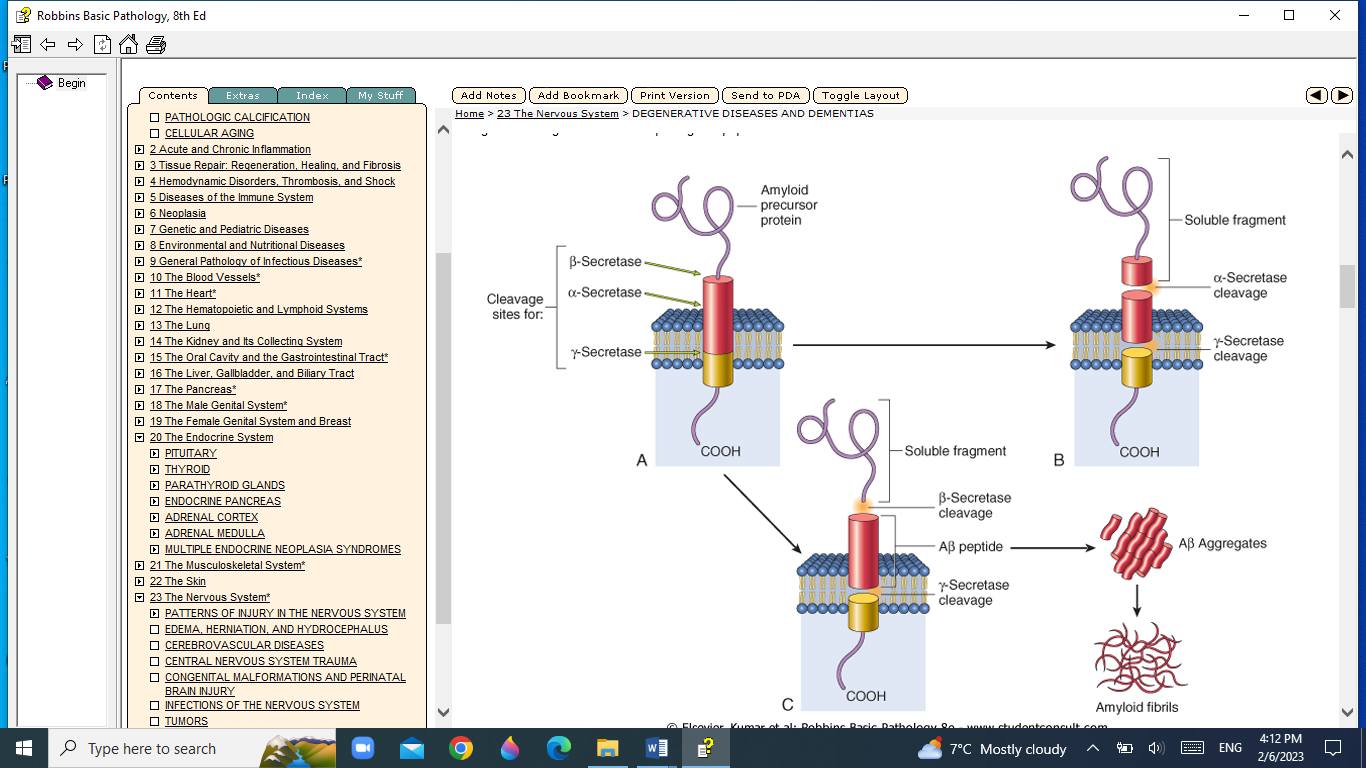


Fig. 3. Pathogenesis of Alzheimer disease

*Role of tau.* Because neurofibrillary tangles contain the tau protein, there has been much interest in the role of this protein. Tau is a microtubule-associated protein present in axons in association with the microtubular network. With the development of tangles, tau shifts to a somatic-dendritic distribution, becomes hyperphosphorylated, and loses the ability to bind to microtubules. The formation of tangles is an important component of Alzheimer disease, but the mechanism of tangle injury to neurons remains poorly understood. Two pathways have been suggested; 1) aggregates of tau protein elicit a stress response, which persists and eventually leads to cell death; and 2), the microtubule stabilizing function of tau protein is lost, leading to neuronal toxicity and death. It has been shown that tau aggregates can be passed across synapses from one neuron to the next; this may underlie some of the spread of lesions across the brain.

*Role of inflammation.* Both genetic and histologic studies have indicated that the innate immune system responds to Aβ and tau. This response probably assists in the clearance of the aggregated peptide, but also may stimulate the secretion of media- tors that cause neuronal injury over time.

*Clinical picture.* The development of Alzheimer's disease is a long and continuous process (often more than 10 years). Initial symptoms include memory impairment, speech disorders, and loss of habits that are gained all life. The terminal stage of Alzheimer's disease is characterized by the loss of control over the function of the pelvic organs and the ability to move independently. The cause of death, in most cases, is secondary infection (primarily pneumonia).

*Laboratory indices*

*Blood: Detection of Aβ and Tau proteins, mutation of presenilin-1 and presenilin-2 genes on chromosome 21*

*CSF: There is no need to examine*

**Parkinson Disease**

Parkinson disease is a neurodegenerative disease marked by a hypokinetic movement disorder that is caused by loss of dopaminergic neurons from the substantia nigra.*Parkinsonism* is a clinical syndrome characterized by tremor, rigidity, bradykinesia, and instability. Parkinsonism can be induced by drugs such as dopamine antagonists or toxins that selectively injure dopaminergic neurons.

*Pathogenesis*

Parkinson disease is associated with protein accumulation and aggregation, mitochondrial abnormalities, and neuronal loss in the substantia nigra and elsewhere in the brain. Abnormal protein and organelle clearance due to defects in autophagy and lysosomal degradation have a pathogenic role in the disease. One clue and diagnostic feature of the disease is the Lewy body, a characteristic inclusion containing *α-synuclein*, a protein involved in synaptic transmission. Point mutations and duplications of the gene encoding α-synuclein cause autosomal dominant Parkinson disease. Synuclein aggregates are cleared by autophagy, and several mutations are in genes whose products all appear to have roles in endosomal trafficking pathways implicated in autophagy.

*Clinical Features*

Parkinson disease commonly manifests as a movement disorder in the absence of a toxic exposure or other known underlying etiology. The disease usually progresses over 10 to 15 years, eventually producing severe motor slowing to the point of near immobility. While the movement disorder associated with loss of the nigrostriatal dopaminergic pathway is an important feature of Parkinson disease, it is clear that the disease has more extensive clinical and pathologic manifestations. Lesions in the brain stem (in the dorsal motor nucleus of the vagus and in the reticular formation), in advance of nigral involvement, can give rise to behavioral sleep disorder often before the motor problems. Dementia, is due to involvement of the cerebral cortex. Death usually is the result of aspiration pneumonia or trauma from falls caused by postural instability.

Movement symptoms of Parkinson disease initially respond to L-dihydroxyphenylalanine (L-DOPA), but this treatment does not slow disease progression. Over time, L-DOPA becomes less effective and begins to cause problematic fluctuations in motor function. Another treatment for the motor symptoms is deep brain stimulation, in which electrodes are implanted in the globus pallidus or subthalamic nucleus to modulate basal ganglia circuitry, often allowing a significant reduction in L-DOPA dose.

*Laboratory indices*

*Blood: Detection of α-synuclein protein*

*CSF: Finding α-synuclein protein*

**Huntington Disease**

Huntington disease is an autosomal dominant movement disorder. Disease is caused by CAG trinucleotide repeat expansions in a gene located on 4p16.3 that encodes the protein huntingtin. Normal alleles contain 11 to 34 copies of the repeat; in disease-causing alleles, the number of repeats is increased, sometimes into the hundreds. The mutant protein can form large intranuclear aggregates. As in other degenerative diseases, smaller aggregates of the abnormal protein fragments are suspected to be toxic. These aggregates have been shown to have a range of potentially injurious actions, including sequestration of transcription factors, disruption of protein degradation pathways, and perturbation of mitochondrial function.

The disorder is characterized by involuntary jerky movements of all parts of the body; writhing movements of the extremities are typical (fig. 5). The disease is relentlessly progressive, resulting in death after an average course of about 15 years. Early cognitive symptoms include forgetfulness and thought and affective disorders, and there may be a progression to severe dementia. As a part of these early behavioral changes is an increased risk for suicide.



Figure 5. Writhing movements of the extremities in patients with Huntington disease

*Laboratory indices*

*Blood: Detection of the mutant huntingtin protein, mutation on 4p16.3 gen located in 4 chromosome*

*CSF: Detection of mutant huntingtin protein*

**Amyotrophic Lateral Sclerosis**

Amyotrophic lateral sclerosis results from the death of lower motor neurons in the spinal cord and brain stem as well as upper motor neurons in the motor cortex (fig.6).The loss of lower motor neurons results in denervation of muscles, muscular atrophy (the “amyotrophy” of the condition), weakness, and fasciculations, while the loss of upper motor neurons results in paresis, hyperreflexia, spasticity, pathological reflexes (fig.7). An additional consequence of upper motor neuron loss is degeneration of the corticospinal tracts in the lateral portion of the spinal cord (“lateral sclerosis”). Sensation usually is unaffected, but cognitive impairment is not infrequent.

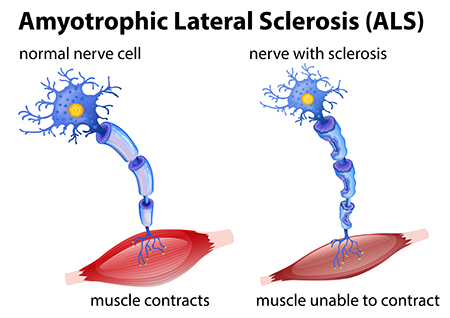


Figure 6. Healthy and sclerosed motor neuron

The disease affects men slightly more frequently than women and becomes clinically manifest in the fifth decade or later. It usually begins with subtle asymmetric distal extremity weakness. As the disease progresses, muscle strength and bulk diminish, and involuntary contractions of individual motor units, termed *fasciculations,* occur. The disease eventually involves the respiratory muscles, leading to recurrent bouts of pulmonary infection, which is the usual cause of death.

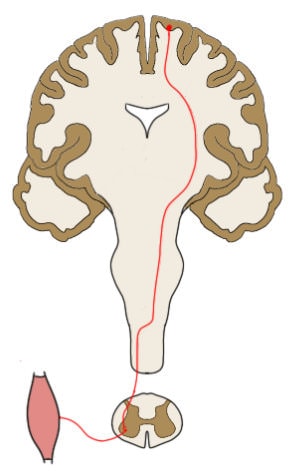


Figure 7. Upper (central) and lower (peripheral) motor neurons

###### *Pathogenesis*

While most cases are sporadic, about 10% are familial, mostly with autosomal dominant inheritance. Mutations in the superoxide dismutase gene *SOD1,* on chromosome 21 were the first identified genetic cause of amyotrophic lateral sclerosis and account for about 20% of the familial forms. These mutations are thought to generate abnormal misfolded forms of the SOD1 protein, which may trigger the unfolded protein response and cause apoptotic death of neurons. A number of other genetic loci have been identified is associated with this disease. The most common cause of familial type is hexanucleotide repeat expansion in a gene *C9orf72*. The protein encoded by *C9orf72* associates with RNA binding proteins. Familial disease begins earlier in life than sporadic disease, but once symptoms appear, the clinical course is similar in both forms.

*Laboratory indices*

*Blood: Mutations in the C9orf72 gene on chromosome 9 and the SOD1 (superoxide dismutase) gene on chromosome 21*

*CSF: There is no need to examine the cerebrospinal fluid.*

**In conclusion,** it can be noted that neurodegenerative diseases of the central nervous system cause symptoms that depend on the pattern of involvement of the brain. Diseases that affect cerebral cortex primarily (e.g., Alzheimer disease) cause cognitive change, alterations in personality, and memory disturbance. Diseases that affect basal ganglia (e.g., Huntington or Parkinson disease) have motor symptoms. Diseases that affect upper and lower motor neurons (e.g., amyotrophic lateral sclerosis) will present with weakness as the dominant feature. Many of these diseases are associated with abnormal aggregation of proteins, which may lead to loss of function or may trigger apoptosis. Familial forms of these diseases are associated with mutations in the genes.