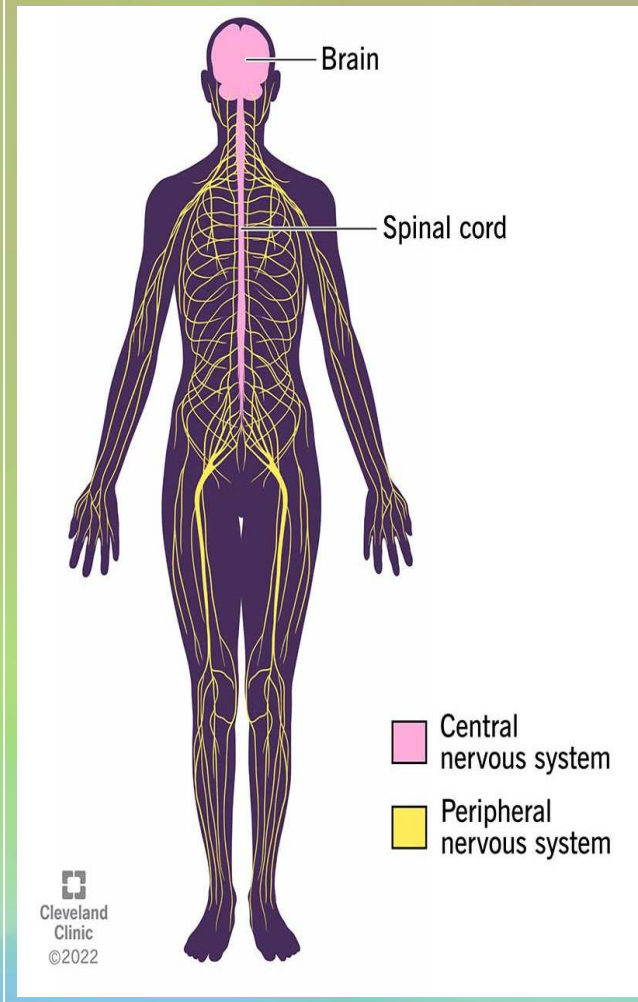
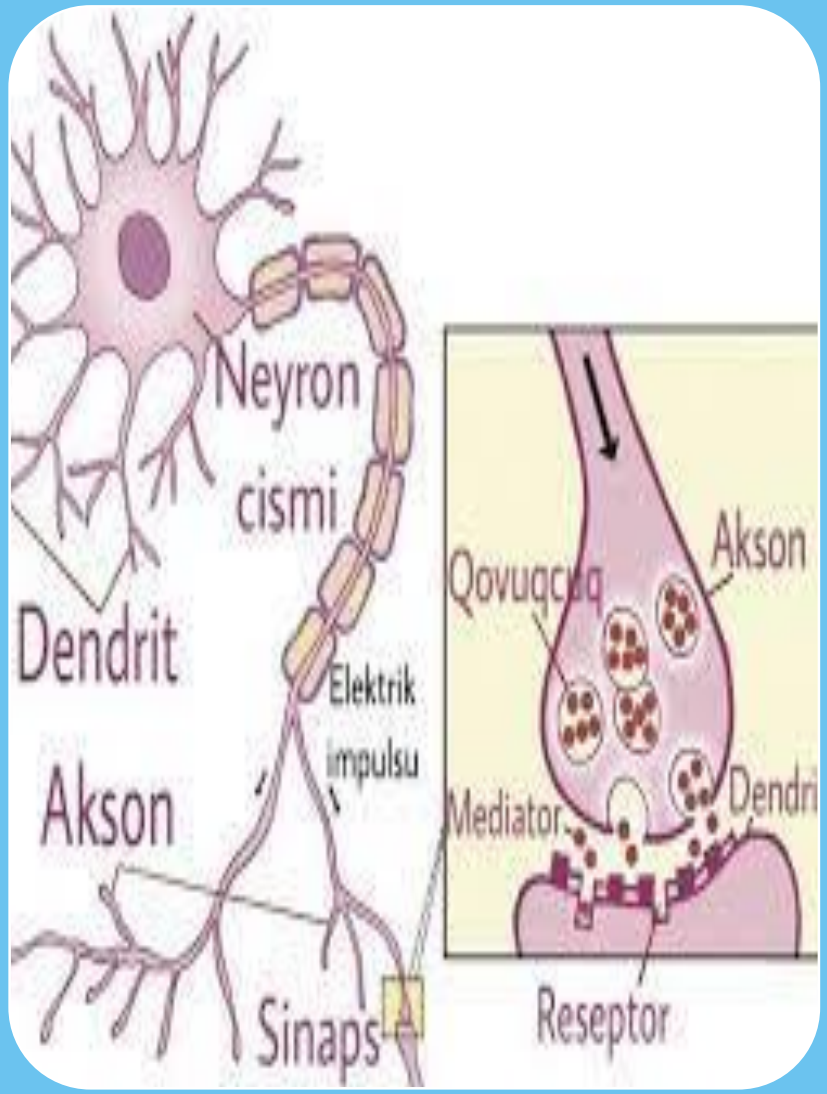
# INFLAMMATORY AND NEURODEGENERATIVE DISEASES OF THE CENTRAL NERVOUS SYSTEM

Department of Pathological Physiology



# Pathology of Nervous Cells




- *Disturbance of excitability of neurons,*
- *Disturbance of conduction of impulses throughout the nervous fibers,*
- *Disturbance of transmission of impulses from one neuron to another one,*
- *Disturbance of axoplasmatic current.*

# The Main Diagnostic Tests for Nervous System Disorders

- CT – computer tomography
- EEG – electroencephalogram
- MRI – magnet resonance tomography
- PET – positron emission tomography
- Arteriogram (also called angiogram)
- Cerebral spinal fluid analysis
- Blood tests:
    - *Complete blood count*
    - *Tests for inflammation and autoimmunity*
    - *Tests for infections*

# INFLAMMATORY DISEASES OF THE CENTRAL NERVOUS SYSTEM

## The Possible Routes of Infectious Agent to Entry in the Nervous System

*Hematogenous spread via the arterial blood*

*Retrograde venous spread through the anastomoses*

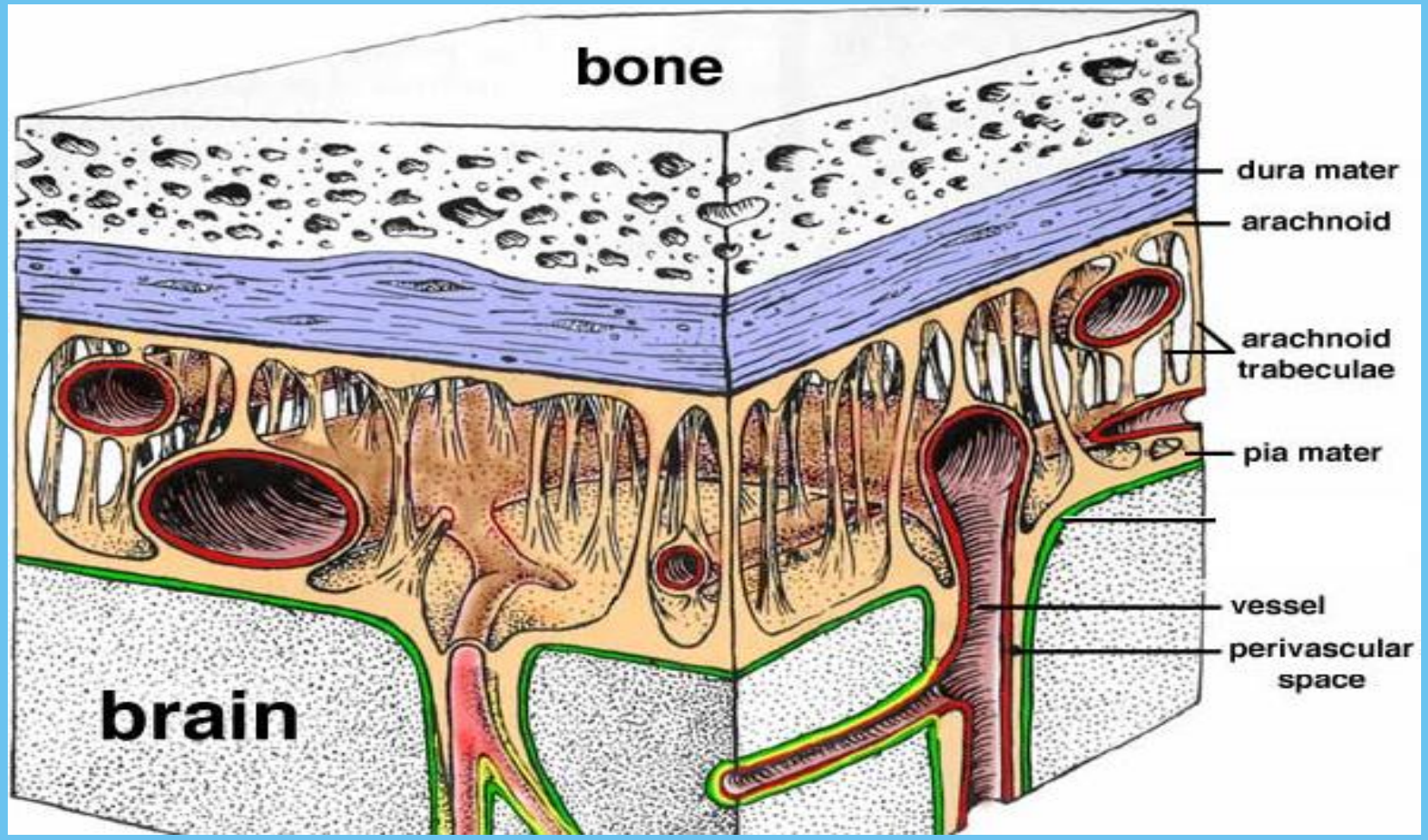
*Direct implantation of microorganisms (post-traumatic)*

*Iatrogenic spread (during lumbar puncture)*

*Local extension from air sinus (most often from the mastoid or frontal), from an infected tooth*

*Spread via peripheral nerves (for certain viruses, such as rabies and herpes zoster)*

# The structure of the brain coverings



# Meningitis

**Meningitis** *is an inflammatory process involving the leptomeninges*

**Meningoencephalitis** *is the spread of infection into the underlying brain*

**The types of meningitis and meningoencephalitis:**

**Non-infectious meningitis and meningoencephalitis** *(such as chemical meningitis, carcinomatous meningitis - the spread of metastatic cancer cells to the subarachnoid space)*

**Infectious meningitis and meningoencephalitis**

# Types of Infectious Meningitis

- ***acute pyogenic*** **(usually bacterial);**
- ***aseptic*** **(usually viral);**
- ***chronic*** **(usually tuberculous, spirochetal, or fungal)**

# Acute Pyogenic Meningitis (Bacterial Meningitis)

**Causes:**
*Escherichia coli , B qrupu streptokoklar, Neisseria meningitidis, Streptococcus pneumoniae , Listeria monocytogenes*

**Signs:**
*patients typically show systemic sings of infection along with meningeal irritation and neurologic impairment, including headache, photophobia, irritability, clouding of consciousness, and neck stiffness.*

**Aggravations:**
*Leptomeningeal fibrosis, hydrocephalus, adhesive arachnoiditis*

**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)

- **Causes:** *difficult to identify the responsible virus by culture and serologic methods*

- **Signis:** *Relatively acute onset of the disease, meningeal syndrome, disorders of consciousness, common symptoms of acute viral infection, and typically self-limiting*

- **Laboratory indices**
- **Examination of the blood:** *Lymphocytosis, monocytosis*
- **Examination of the CSF:** lymphocytic pleocytosis, moderate protein elevation, and a normal glucose level, but bacteria cannot be cultured

# Chronic Bacterial Meningitis

## Tuberculous Meningitis

- **Causes:** *Meningococci*
- ***Signs*: *Tuberculous meningitis usually manifests with generalized signs and symptoms of headache, malaise, mental confusion, and vomiting. The development of tuberculomas makes the symptoms of the disease similar to the symptoms observed during brain tumors***
- **Complications:** *Arachnoid fibrosis, hydrocephalus, obliterating endarteritis, cerebral infarction*

- **Laboratory indices**
- **Examination of the blood:** *Lymphocytosis, monocytosis, detection of Meningococci*
- **Examination of the CSF:** *Moderate pleocytosis (mainly due to mononuclear cells), significant increase in protein concentration, normal or low glucose concentration, detection of meningococci, obtaining a pure culture of the causative agent*

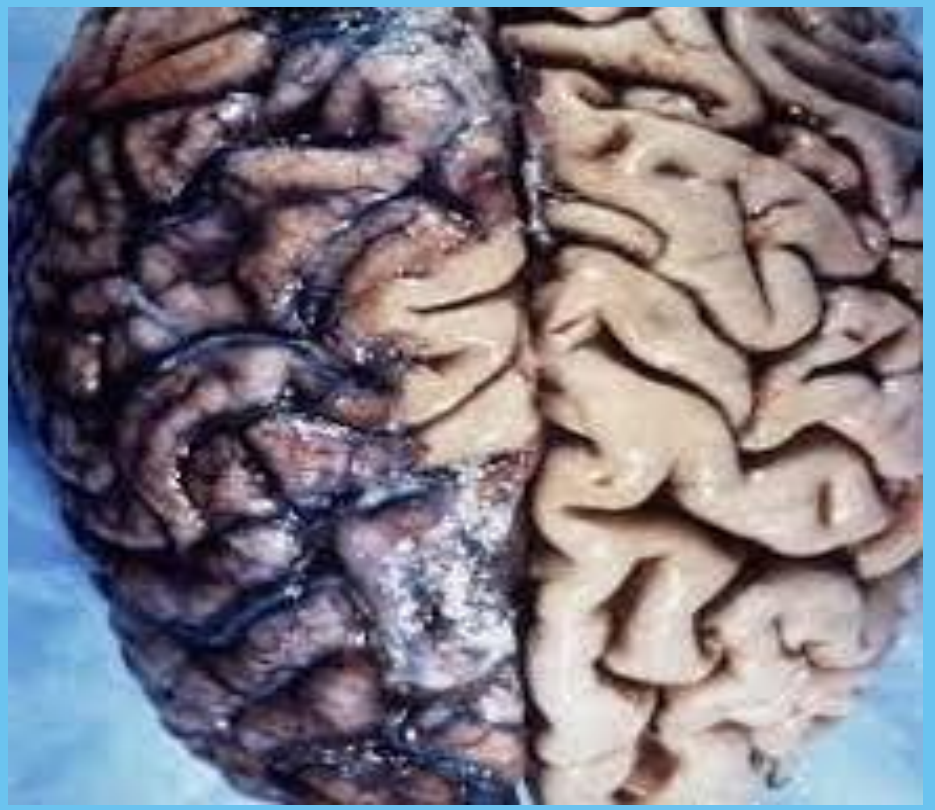
# Chronic Bacterial Meningitis
# Neurosyphilis

- **Causes:** *Treponema pallidum*

- **Types:**
- *Meningovascular neurosyphilis;*
- *paretic neurosyphilis;*
- *tabes dorsalis.*

# The Types of Neurosyphilys

- **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** *is associated with neuronal loss and marked proliferation of microglial cells. Clinically, progressive loss of mental and physical functions, mood alterations, 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 t o skin and joint damage. other sensory disturbances, and the absence of deep tendon reflexes.*



- **Laboratory indices**
- **Examination of the blood:** *lymphocytosis, antibody against T. pallidum antigens*
- **Examination of the CSF:** ***Lymphocytic pleocytosis, elevated protein concentration, antibody against T. pallidum antigens***

# Parenchymal Infections

## Characteristic:

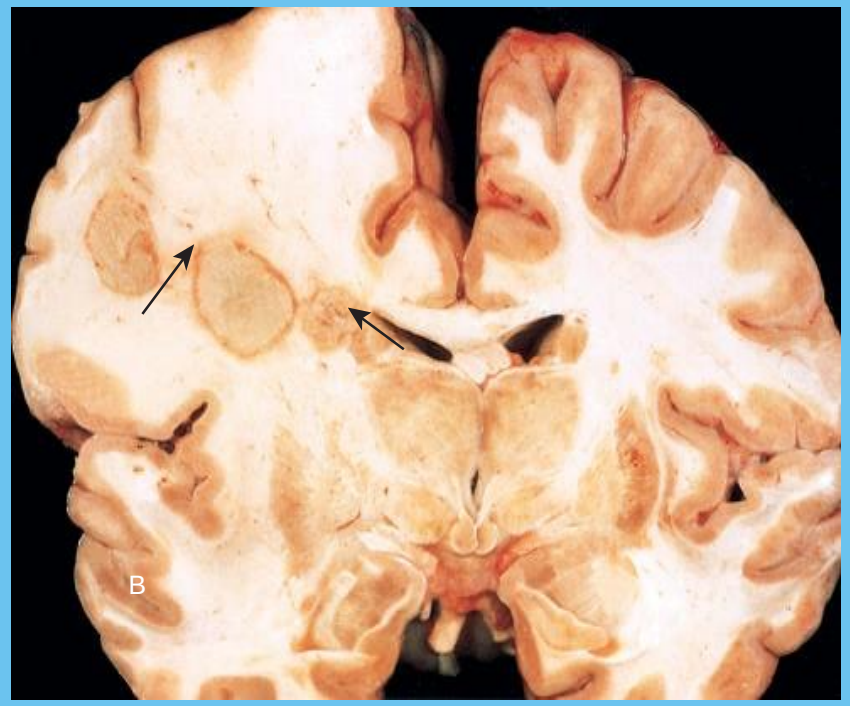
- **Bacterial infections** *are localized (when not associated with meningitis),*
- **Viral infections** *are diffuse,*
- **It is specific** *for the causative agent.*

# Brain Abscesses
# (Bacterial infections)

- **Signs:**
- *Progressive focal deficits as well as general signs related to increased intracranial pressure*
- **Complications:**

*A drop in intracranial pressure can cause a brain herniation,*

*Perforation of an abscess can lead to ventriculitis, meningitis and thrombosis of venous sinuses*




- **Laboratory indices**

**Examination of the blood:** *lymphocytosis, antibody against T. pallidum antigens*

**Examination of the CSF:** *While CSF white blood cell count and protein may be elevated, lumbar puncture has little role in the diagnosis of brain abscess*

# Viral Encephalitis

**Some viruses that are tropic to nervous tissue**

*Arboviruses*

*Herpesviruses*

*Cytomegalovirus*

*Poliomyelitis virus*

*Rabies viruses*

*Human Immunodeficiency Virus*

# Viral Encephalitis
# *Arboviruses*

- **Arboviruses** *are the cause of epidemic encephalitis in tropical regions of the world, and are capable of causing serious morbidity and high mortality.*

- **Signs:**

*General: neurologic symptoms, such as seizures, confusion, delirium, and stupor or coma*

*Focal: reflex asymmetry and ocular palsies*

- **Laboratory indices**

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

**Examination of the CSF:** *early neutrophilic pleocytosis that rapidly converts to a lymphocytosis; the protein concentration is elevated, but the glucose is normal*

# Viral Encephalitis

## *Herpesviruses*

- **HSV-1 virus:**

*It typically manifests with alterations in mood, memory, and behavior, reflecting involvement of the frontal and temporal lobes*

- ***HSV-2* virus:**
  *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**

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

**Examination of the CSF:** *lymphocytosis, the protein concentration is elevated, but the glucose is normal*

# Viral Encephalitis

## *Cytomegalovirus*

- **Characteristic:**

*CMV infects the nervous system in fetuses and immunosuppressed individuals. All cells within the CNS (neurons, glial cells, and endothelium) are susceptible to infection. Intrauterine infection causes periventricular necrosis. When adults are infected, CMV produces a subacute encephalitis, which is also often most severe in the periventricular region.*

- **Laboratory indices**

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

**Examination of the CSF:** *lymphocytic pleocytosis, the protein concentration is elevated, but the glucose is normal*

# Viral Encephalitis

## *Poliomyelitis*

- **Causes:**
  *Enteroviruses*

- **Signs:**

*If the spinal cord and brain stem are damaged, paralytic poliomyelitis develops. Paralysis is accompanied by muscle atrophy and atony. Hyporeflexia occurs in the appropriate area of the body.*

- **Complications:**

*Death may occur as a result of paralysis of the respiratory muscles*
*Post-poliomyelitic syndrome (decreased muscle mass, progressive muscle weakness, and pain long after the infection has been eliminated, sometimes 25-35 years)*

- **Laboratory indices**

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

**Examination of the CSF:** *lymphocytic pleocytosis, the protein concentration is elevated, but the glucose is normal*

# Viral Encephalitis

## *Rabies viruses*

**Causes:**

*Rabies virus*

**Signs:**

*Weakness, headache, fever, increase CNS excitability, contractions of muscles, these contractions gradually rise to convulsions, difficulty swallowing, and the patient is even afraid of swallowing water (hydrophobia)*

**Complications:**

*encephalitis, coma, paralysis of the respiratory center*

- **Laboratory indices**

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

**Examination of the CSF:** *lymphocytic pleocytosis, the protein concentration is elevated, but the glucose is normal*

# Viral Encephalitis

## *Human Immunodeficiency Virus (HIV)*

- **Causes:**

*Human Immunodeficiency Virus (HIV)*

- **Signs:**

*Aseptic meningitis*
*Rapidly developing cognitive impairment,*
*Cerebral edema*
*CNS lymphoma*
*opportunistic infections (toxoplasmosis, etc.)*
**These symptoms develop when effective anti-HIV therapy is started late**

- **Laboratory indices**

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

**Examination of the CSF:** *lymphocytic pleocytosis, the protein concentration is elevated, but the glucose is normal*

# Fungal Encephalitis

- **Caues:**

*C.albicans*, *Mucor* spp., *A.fumigatus*, *C. Neoformans*

- **Types and signs:**

***Chronic meningitis*** *is a typical opportunistic infectious disease that develops on the background of HIV infection and AIDS.*

***Vasculitis,*** *as a rule, develops when fungi invade the vessel wall directly. Occlusion of the vascular lumen leads to cerebral infarction*

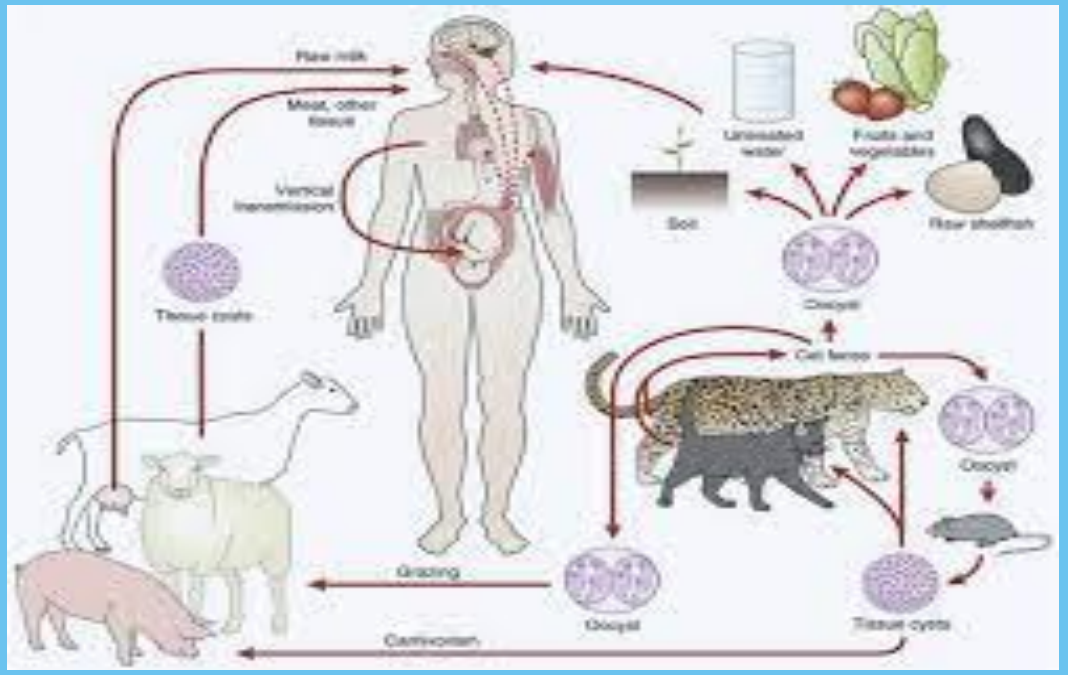
***Parenchymal lesions*** *is observed in most of the fungal diseases of the CNS. It usually results in the formation of granulomas or abscesses.*

- **Laboratory indices:**

**Examination of the blood:** *Finding the causative fungus*

**Examination of the CSP:** *Slight pleocytosis, an increase in protein concentration is observed. Causative fungi can be found.*

# Cerebral Toxoplasmosis




- **Causes**:

*Toxoplasma gondii*

occur in immunosuppressed adults or in newborns who acquire the organism transplacentally from a mother with an active infection.

**Signs:**

*The classic triad – chorioretinitis, hydrocephalus and intracranial calcification develops*

- **Laboratory indices**

**Examination of the blood:** *Antibodies against antigens of Toxoplasma gondii*

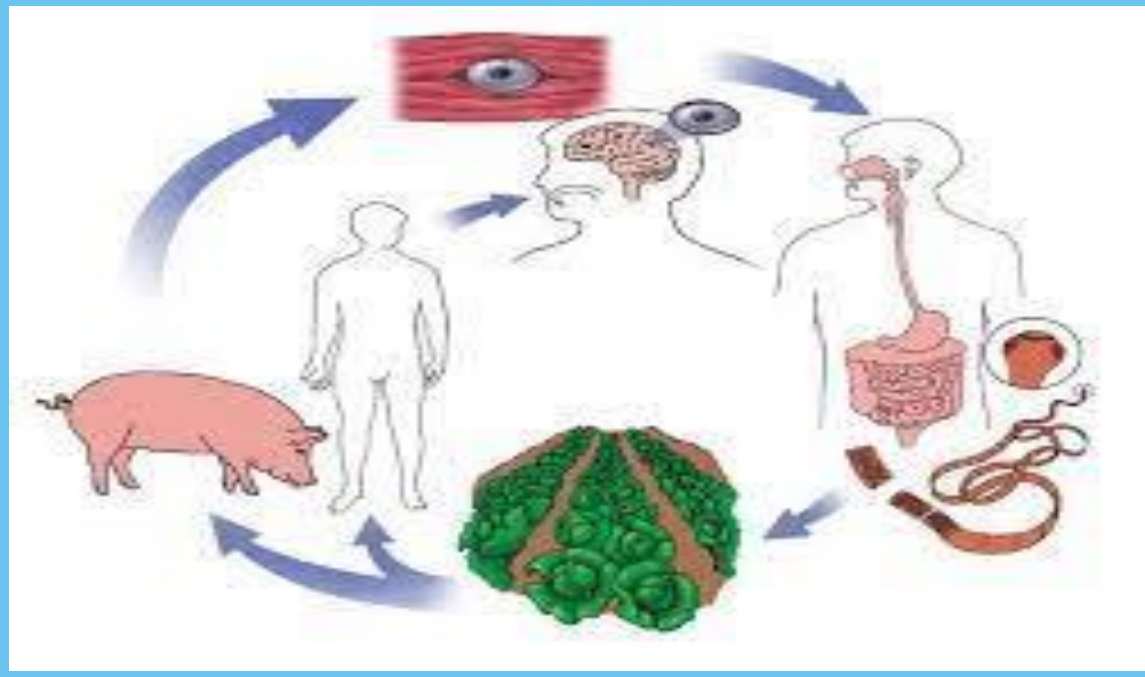
*are found (an increase in IgG titer indicates a previous infection, and an increase in IgM titer indicates a current infection)*

**Examination of the CSF:** *Antibodies against antigens of Toxoplasma gondii*

# Sistiserkoz

- **Causes:**

*Tenia solium*



- **Signs:**

*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 cause seizures. Symptoms can intensify when the encysted organism dies, as occurs after therapy (Death of the encysted organism produces an intense inflammatory reaction in the surrounding brain).*

- **Laboratory indices**

**Examination of the blood:** *Antibodies against antigens of Tenia solium*

**Examination of the CSF:** *Antibodies against antigens of Tenia solium*

# Amebic meningoencephalitis

- **causes:**

*Naegleria fowleri*

*Acanthamoeba*

- **Signs:**

*Naegleria fowleri*, associated with swimming in stagnant warm fresh water ponds,
causes a rapidly fatal necrotizing encephalitis

*Acanthamoeba* cause a chronic granulomatous meningoencephalitis.

- **Laboratory indices**

**Examination of the blood:** *Finding of causative agent, antibodies against antigens of causative agent*

**Examination of the CSF:** *Antibodies against antigens of causative agent*

# Prion Diseases

- **Causes:**
- *Prion protein (an abnormal form of a cellular proteins)*

*The infectious nature of prion proteins is due to their ability to pass from the diseased human band animal body in various ways (feces, urine, mainly through the milk of animals, sheep, and deer, etc.) to the environment and back to human (through food, milk, etc.).*

- **Types:**

sporadic, familial, iatrogenic

- **Signs:**

*memory and behavior disorders,*
*rapidly developing dementia*
*It results in death in 6-7 months*

- **Laboratory indices**

**Examination of the blood:** *Finding of prion proteins*

**Examination of the CSF:** *Finding of prion proteins*

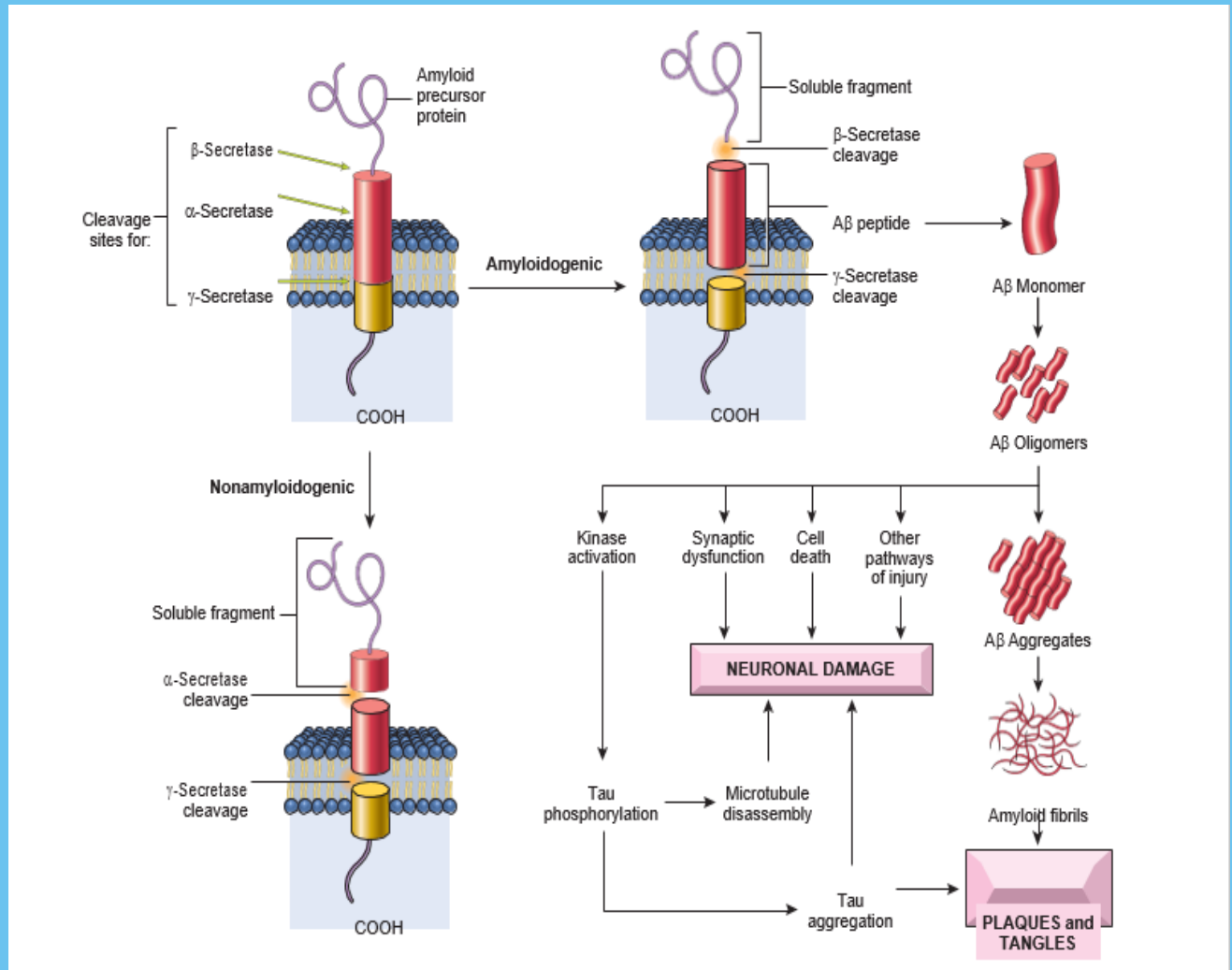
# Neurodegenerative Diseases of the Central Nervous System
## Characteristic Features

- *No toxic effect or other clearly visible external etiological factor can be found*
- *Progressive loss of neurons*
- *Protein aggregates that accumulate in damaged neurons can spread to healthy neurons*
- *Diseases that involve the hippocampus and associated cortices present with cognitive changes, including disturbances of memory, behavior, and language. With time these progress to dementia*
- *Diseases that affect the basal ganglia manifest as movement disorders;*
- *Diseases that affect the cerebellum or its input and output circuitry result in ataxia, as seen in the spinocerebellar ataxias*
- *the genes involved in the immune regulation mechanisms are also important in the development of these diseases*

# Neurodegenerative Diseases of the Central Nervous System

## Alzheimer Disease

- **Pathogenesis:**
- ***Role of Aβ.*** Transmembrane amyloid precursor protein (APP), can be cleaved in two ways. If APP is cleaved by α-secretase and γ-secretase non-pathogenic (soluble) peptide is formed. When APP is broken down by β-secretase and γ-secretase, the pathogenic (insoluble) Aβ protein is accumulated.
- ***Role of Tau.*** Tau is a microtubule-associated protein present in axons in association with the microtubular tau shifts network. With the development of tangles, to a somatic-dendritic distribution, becomes hyperphosphorylated, and loses the ability to bind to microtubules.
- *Role of inflammation.* Accumulation of Aβ and Tau aggregatesin neurons leads to the development of inflammation.



# Neurodegenerative Diseases of the Central Nervous System

## Alzheimer Disease

**Signs:**

*develops within 10-15 years*

*altered mood and behavior, memory impairment*

*impaired higher intellectual function*

*disorientation and aphasia, often mute and immobile*

*loss of habits that are gained all life, loss of control over the function of the pelvic organs*

*Death usually occurs from intercurrent pneumonia or other infections*

- **Laboratory indices**

**Examination of the blood:** *Detection of Aβ and Tau proteins, mutation of presenilin-1 (encodes APP) and presenilin-2 (encodes γ-secretase) genes on chromosome 21*

**Examination of the CSF:** *no need to examine the CSF.*

# Neurodegenerative Diseases of the Central Nervous System
# Parkinson Disease

- **Pathogenesis:**

*mitochondrial abnormalities,*

*pathologies in autophagy and lysosomal breakdown,*

*impaired removal of abnormal proteins and organelles,*

*accumulation of protein aggregates (in particular, α-synuclein protein) in the substantia nigra and other brain cells,*

*loss of dopaminergic neurons from the substantia nigra.*

# Neurodegenerative Diseases of the Central Nervous System

## Parkinson Disease

- **Signs:**

*develops within 10-15 years,*

*movement disorders (tremors, rigidity, bradykinesia, and instability),*

*gradual full immobility,*

*progressive mental disorders.*

*Death usually is the result of aspiration pneumonia or trauma from falls caused by instability.*

- **Laboratory indices:**

**Examination of the blood:** *Detection of α-synuclein protein*

**Examination of the CSF:** *no need to examine the CSF*

# Neurodegenerative Diseases of the Central Nervous System
# Huntington Disease

- **Pathogenesis:**

*autosomal dominant way of inheritance, CAG trinucleotide repeat expansions in a gene located on 4p16.3 that encodes the protein huntingtin. Mutant proteins form large intranuclear aggregates.These aggregates break down transcription factors, disrupt protein degradation pathways, and cause mitochondrial dysfunction.*

## Clinical Features:

involuntary movements of all parts of the body;

writhing movements of the extremities are typical;

early cognitive symptoms;

forgetfulness and thought and affective disorders,

dementia, increased risk for suicide.

- **Laboratory indices:**

*Blood: Detection of mutant huntington protein, mutation on 4 chromosome*

*CSF: Detection of mutant huntington protein,*

# Neurodegenerative Diseases of the Central Nervous System
# 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.**

- **Pathogenesis:**

**Mutations in the superoxide dismutase gene (*SOD1*), on chromosome 21 lead to:**

*autosomal dominant way of inheritance,*

*accumulation of abnormal proteins*

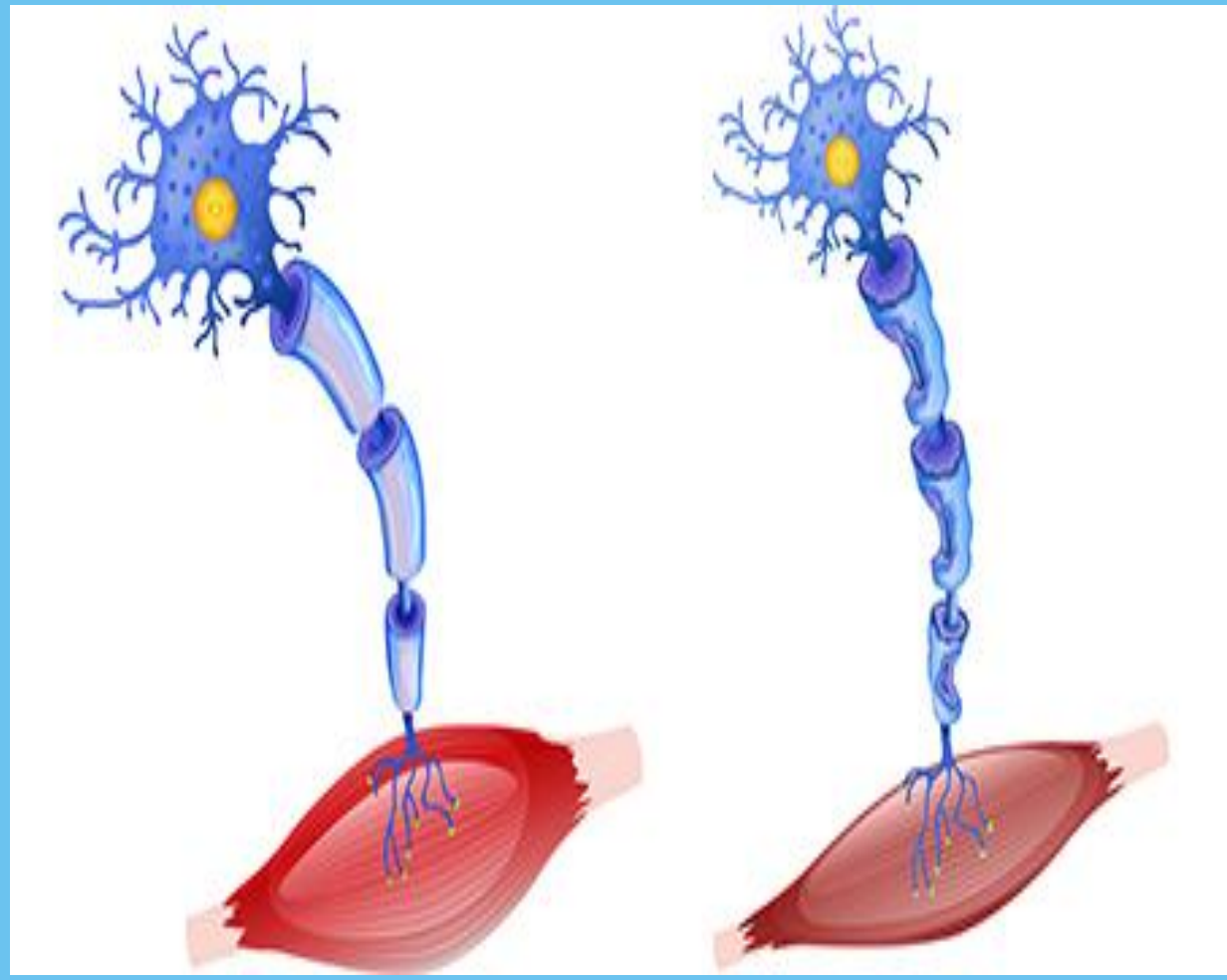
*apoptotic death of neurons occurs*

**Mutation in C9orf72 gen (9 chromosome)**

**leads to:**

*Didorders of RNA bimding*

.

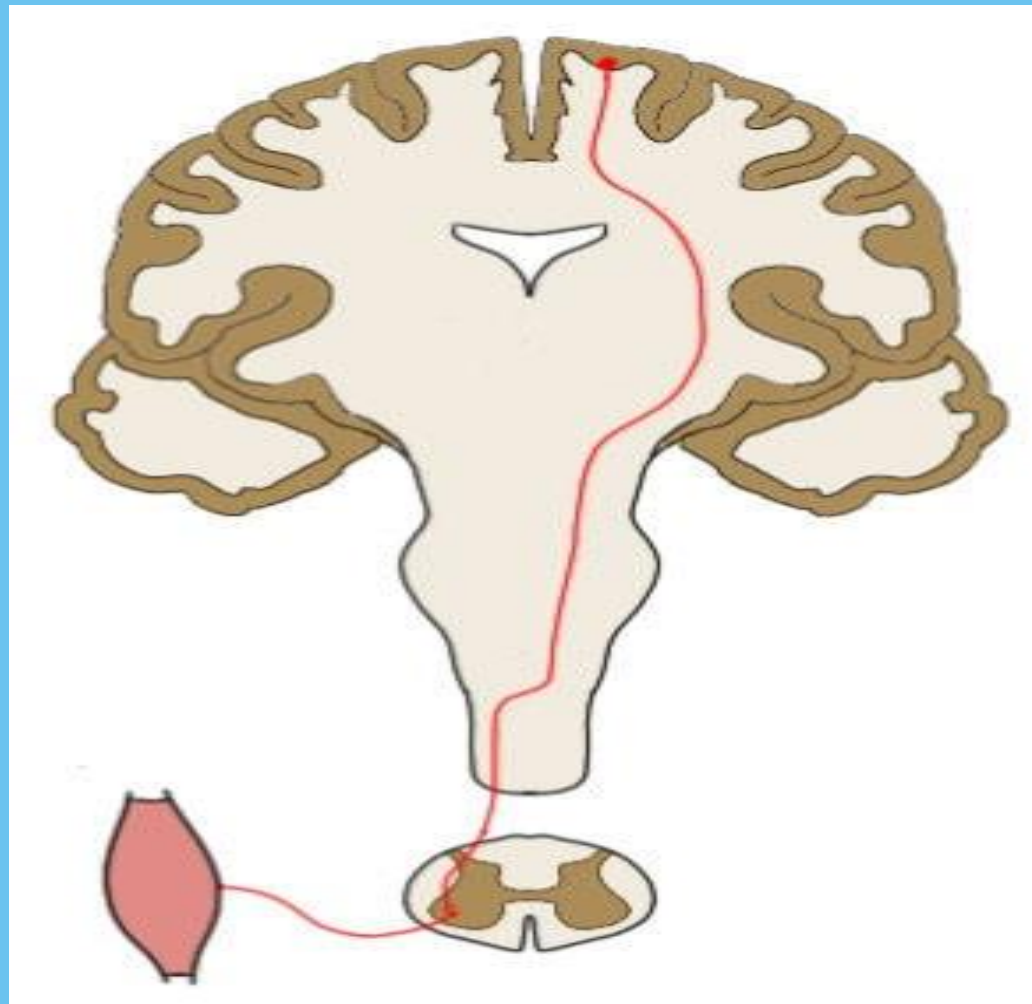


# Neurodegenerative Diseases of the Central Nervous System
# Amyotrophic Lateral Sclerosis

- **Clinical features:**

*The loss of **lower (peripheral) motor neurons** results in denervation of muscles, muscular atrophy (the "amyotrophy" of the condition), weakness, athony and fasciculations (peripheral paresis or paralysis)*

*The loss of **upper (central) motor neurons** hyperreflexia, and spasticity, pathological with a Babinski sign (central paresis or paralysis). An additional consequence of upper 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 frequent.*



- **Laboratory indices:**

*Blood: Mutation on 9 chromosome (gen C9orf72), mutation on 21 chromosome ( gen SOD1 )*
*CSF: No need examine*

# Neurodegenerative Diseases of the Central Nervous System Summary

- Neurodegenerative diseases cause symptoms that depend on the pattern of involvement of the brain.
- Diseases that affect cerebral cortex primarily (e.g., Alzheimer disease) are more likely to cause cognitive change, alterations in personality, and memory disturbance.
- Diseases that affect basal ganglia (e.g., Huntington or Parkinson disease) have motor symptoms. Parkinson disease is caused by loss of dopaminergic neurons, and Huntington disease is caused by trinucleotide repeat expansions.
- 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.
- Familal forms of these diseases are associated with mutations in the genes encoding these proteins.