DISEASES OF THE CENTRAL NERVOUS SYSTEM
A: MEDICAL DISEASES

Meningitis

- Meningitis means inflammation of the meningeal coverings of the brain and spinal cord.
- Inflammation of the dura is rare and called pachymeningitis.
- Inflammation of the pia and arachnoid is much more common, and called leptomeningitis.

- **The common types of meningitis are:**
  1) Septic (suppurative) meningitis.
  2) Tuberculous meningitis.
  3) Syphilitic meningitis.
  4) Viral meningitis.

SEPTIC MENINGITIS

- **Causes:**

1) ***Meningococci:*** Are the commonest causative organisms.
- It causes **meningococcal meningitis.**
- The disease affects specially infants, children and young adults.
- It takes sporadic or epidemic forms.
- Droplet infection takes place from a patient or a carrier and causes nasopharyngitis

- The organisms in the nasopharynx invade the blood stream and are carried to the meninges and choroid plexus.

2) ***Streptococci, staphylococci, pneumococci and influenza bacilli:***

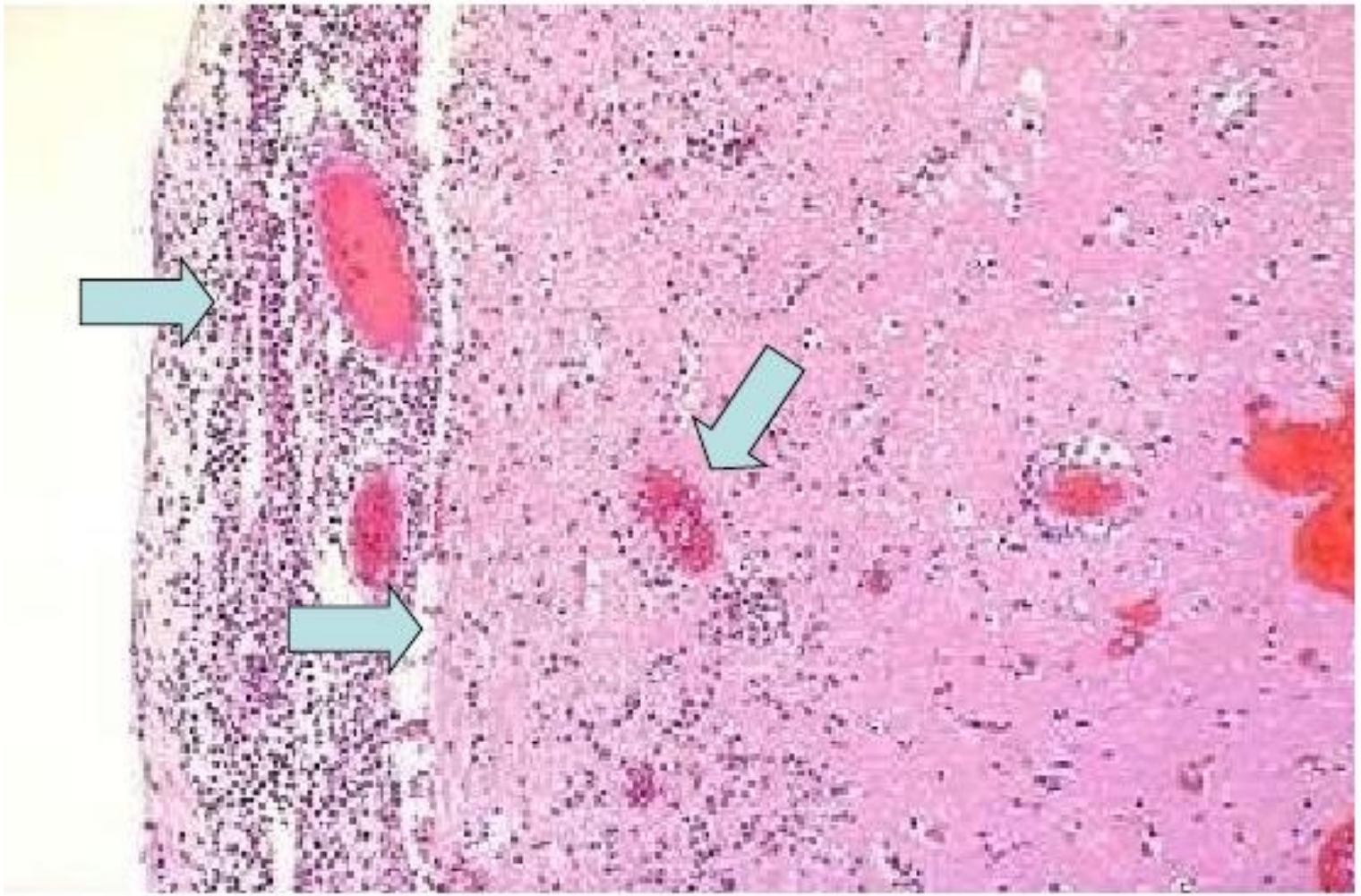
- They are rare causes of septic meningitis.
- They reach the meninges by the following routes:

A. Hematogenous from distant septic focus.
B. Direct infection from sinusitis, otitis media and brain abscess.
C. Complicating compound fractures of the skull.

- **Pathology of Meningococcal Meningitis:**
- **Gross Picture:**
- The brain is swollen and edematous.
- The meningeal and cortical vessels are dilated and congested.
- The subarachnoid space is filled with a yellowish purulent exudate.
- The exudate is most abundant at the base of the brain and on the posterior surface of the cord due to the effect of gravity.
- The ventricles are dilated and the cerebrospinal fluid (CSF) is turbid as it is mixed with pus.
- The ependymal lining is necrotic rough and the choroid plexus is congested.

- **Microscopic Picture:**
- The subarachnoid space shows dilated congested vessels and heavy infiltration by many polymorphs with some histiocytes, lymphocytes and plasma cells amidst scanty fibrin threads.

Septic Meningitis-Microscopy



- **C.S.F. Changes:**
  (1) Increased tension.
  (2) Presence of many pus cells.
  (3) Elevated protein content.
  (4) Decreased sugar content.

- **Clinically:**
  1. Headache
  2. Irritability
  3. Stiff neck
  4. Disturbed conscious level
  5. Photophobia

- **Local effects and complications:**

1. Thrombosis of the pial arteries causes infarctions in the brain and spinal cord.
2. Healing by fibrosis results in adhesions and obstruction of the foramina of Lushcka and Magendie which cause:
   A. Compression of the cranial nerves; III, IV, VI and spinal nerve roots leading to diplopia, squint, ptosis.
   B. Obstruction of the flow of C.S.F. leading to hydrocephalus.

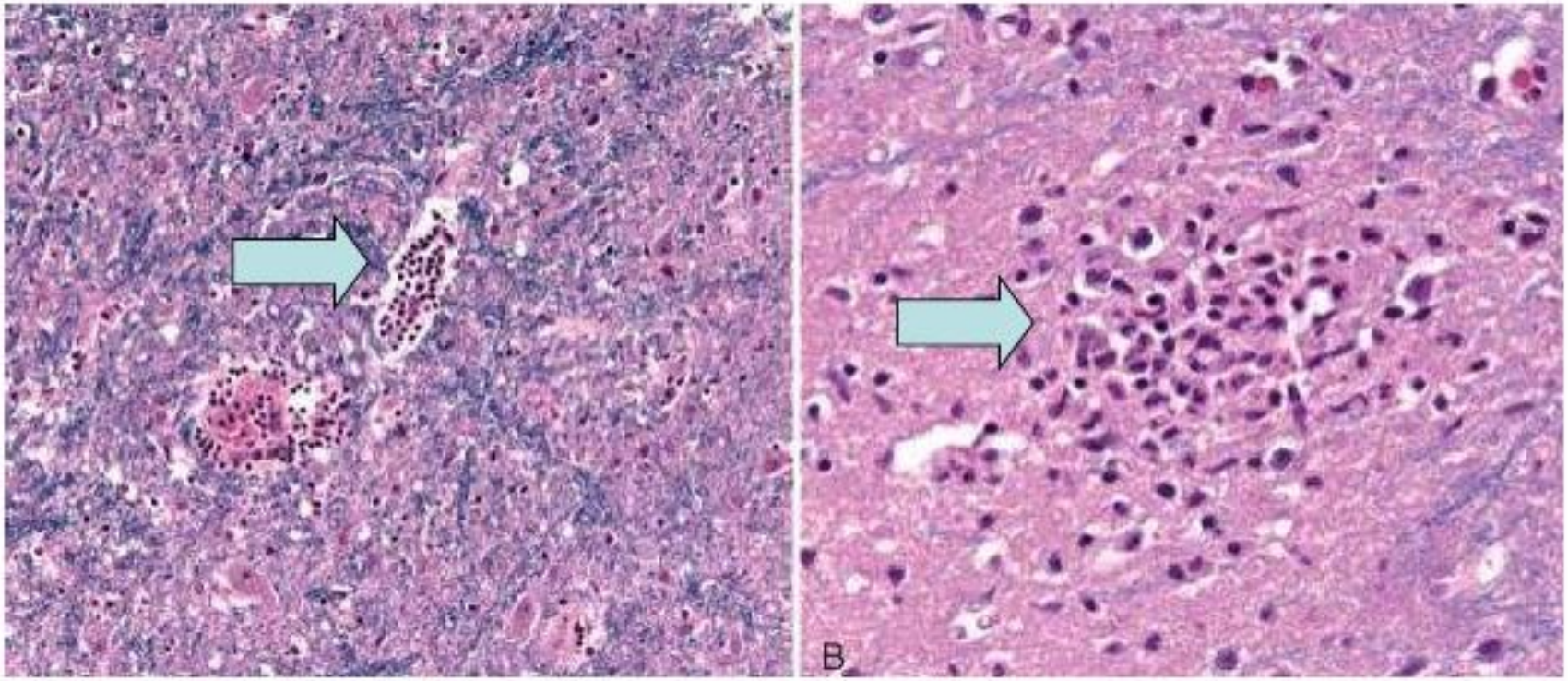
- **General effects and complications:**

1. Septic thrombophlebitis causes septicemia and systemic pyemia.
2. Blood spread of bacteria causes' acute bacterial endocarditis, pericarditis, empyema and arthritis.
3. Adrenal cortical hemorrhage in severe cases causing acute adrenal cortical insufficiency (Waterhouse-Friderichsen syndrome).

Viral (aseptic meningitis)

- Less fulminate clinical course than in septic meningitis.
- It is self-limited and often treated symptomatically.
- **The CSF shows:**
  1. An increased number of lymphocytes.
  2. The protein elevation is only moderate.
  3. Glucose content is nearly always normal.
  4. Commonly due to enterovirus infection.

Viral Meningitis:



Perivascular cuffs of lymphocytes and Microglial nodules

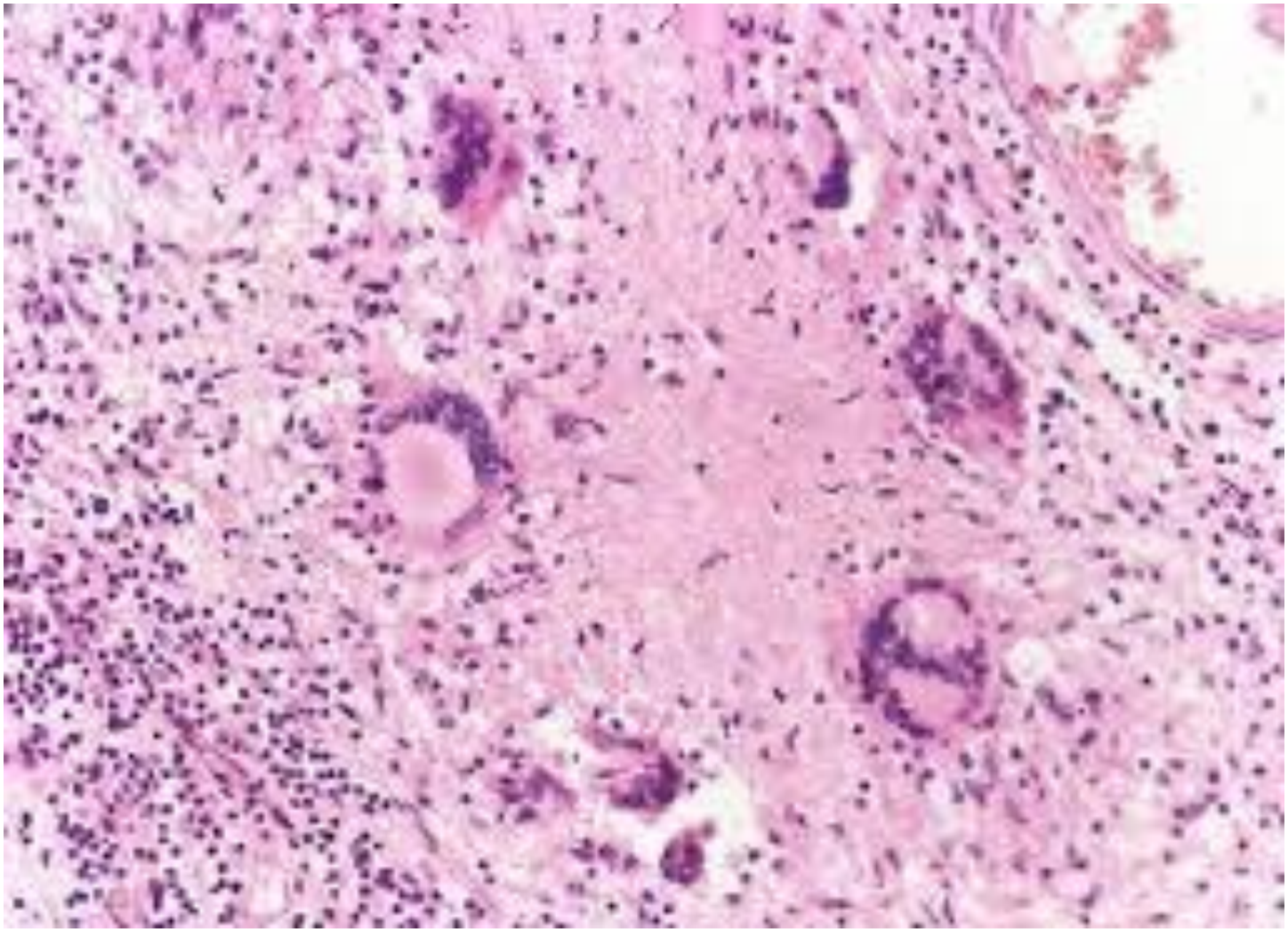
Tuberculous Meningitis

- More common in children and affects the pia-arachnoid, its blood vessels and the superficial layer of the brain.
- It is due to blood spread of a tuberculous focus in the body.
- It is one of the causes of arachinoid fibrosis which may produce hydrocephalus.

- ***Pathological features:***
- A yellowish exudate covers the surface of the brain and is marked over the base.
- The exudate is composed of fibrin, epithelioid cells, lymphocytes, scanty giant cells and shows areas of caseation.
- Healing by fibrosis may obstruct the roof of the fourth ventricle causing hydrocephalus.
- The meninges covering the spinal cord particularly in the cervical region show similar changes.

- Tubercles on the small blood vessels of the brain, choroid plexus and lining of the ventricular cavities are found.
- There are areas of softening in the cerebral cortex and basal ganglia.
- This results from tuberculous end arteritis followed by thrombosis.

TB Meningitis



- **CSF shows:**
- The fluid is clear and a fine web of fibrin forms on the surface on standing.
- Moderate increase in mononuclear cells, mainly lymphocytes.
- Protein level is elevated.
- Glucose content is moderately reduced or normal.
- Small number of bacilli could be detected in smears.

- ***Complications:***

1. Increased intracranial tension.
2. Compression of the cranial nerves leading to their paralysis.
3. Hydrocephalus.
4. Well circumscribed mass in the brain substance itself called tuberculoma.
5. Miliary tuberculosis.

Brain Abscess

- **Etiology:**
- ***Causative organisms:***
- Staphylococcus aureus, streptococcus, pneumococcus, E.coli and bacillus pyocyaneus.

- ***Routes of infections:***

(1) Direct spread of infection from otitis media, sinusitis and mastoiditis.

(2) Blood spread of infection from acute bacterial endocarditis, bronchiectasis, lung abscess or empyema through the vertebral system of veins.

(3) Infection from outside through compound fractures of the skull.

- **Sites:**
- The site of the abscess depends upon the primary site from which the infection comes.
- Otitis media causes temporal or parietal lobe abscess.
- Mastoiditis causes a cerebellar abscess.
- Sinusitis, lung infection and fracture causes frontal lobe abscess.
- Hematogenous abscesses from systemic pyemia are multiple and found at the junction of the grey and white matter.

- **Pathological Features:**
- Early the brain tissue shows edema, softening and heavy neutrophilic infiltration.
- The active liquifactive necrosis is surrounded by zone of congestion.
- Then an abscess cavity filled with pus and lined by necrotic tissue develops.
- The affected part appears swollen, the convolutions flattened and the meninges thick and adherent.
- The abscess tends to spread inwards and rupture into the ventricles.

- If pus is absorbed or evacuated spontaneous healing occurs by gliosis, but more commonly the abscess changes to chronic one.
- Chronic abscess is surrounded by a thick wall of reactive gliosis and its inner lining is smooth.

- **Clinically:**
- Progressive focal deficits.
- Increases ICT and progressive herniation which may be fatal.
- **The CSF shows:**
- White cell count is raised.
- Protein level is raised.
- Glucose content is normal.
- Rupture of abscess can lead to ventriculitis, meningitis, and venous sinus thrombosis.

- **Complications:**

1. Increased intracranial tension (↑ ICT), and brain herniation.
2. Septic meningitis, subdural abscess, extradural abscess and sinus thrombophlebitis.

Encephalitis

- Encephalitis means inflammation of the brain and is caused by:
  1. Pyogenic infections as brain abscess.
  2. Bacterial toxins as botulism.
  3. Fungus infections as cryptococcosis.
  4. Parasitic infections as malaria and toxoplasmosis.
  5. Viral infections as rabies, poliomyelitis, herpes zoster and herpes simplex.

Viral encephalitis

- This is infection of the brain that is invariably associated with inflammation of the meninges (meningio-encephalitis).
- The most characteristic features are perivascular and parenchymal mononuclear cell infiltrate, microglial nodules and neuronphagia.
- Certain viruses may form inclusion bodies.

Demyelinating diseases

- **Demyelinating disease** is any disease of the nervous system in which the myelin sheath of neurons is damaged.
- It is characterized by damage to the myelin with relative preservation of the axons.
- This damage impairs the conduction of signals in the affected nerves.

- In turn, the reduction in conduction ability causes deficiency in sensation, movement, cognition, or other functions depending on which nerves are involved.

MYELIN

- **Functions:**
  1. Proteolipid insulation of axon
  2. Enhances nerve signal transmittion.
  3. Supports axon function.
- Oligodendrocytes forms the myelin in the CNS.
- Schwann cells form the myelin in the PNS.

ETIOLOGY OF DEMYELINATING DISEASES:

- Some demyelinating diseases are caused by genetics, some by infectious agents, some by autoimmune reactions, and others by unknown factors.
- Organophosphates, a class of chemicals which are active ingredients in commercial insecticides will also demyelinate nerves.
- Neuroleptics can cause demyelination also.

- In multiple sclerosis, there is good evidence that the body's own immune system is at least partially responsible as evidenced by.
- T-lymphocytes are present at the site of lesions.
- Other immune system cells; macrophages and possibly mast cells contribute to the damage.
- Vitamin B12 deficiency can cause demyelination.

Classification of Demyelinating diseases:

I. Demyelinating diseases are traditionally classified depending on the underlying reason for demyelination into two kinds:
   A. **Demyelinating myelinoclastic diseases,** and
   B. **Demyelinating leukodystrophic diseases**.

- In the **first group** a normal and healthy myelin is attacked by an external substance, toxic, chemical or autoimmune substance.
- In the **second group**, myelin is abnormal and degenerates without attacks.
- The second group was denominated **dysmyelinating diseases.**

II. **Demyelinating diseases is divided into:**
   A. Those affecting the central nervous system (CNS), and
   B. Those presents in the peripheral nervous system (PNS), presenting different demyelination conditions.

III. **They are also divided according to the presence or lack of inflammation into:**
   A. Inflammatory, and
   B. Non-inflammatory.

Demyelinating disorders of the CNS

- **The demyelinating disorders of the CNS include:**

1. **Myelinoclastic disorders:**

- Standard multiple sclerosis (MS), and other disorders with immune system involvement called inflammatory demyelinating diseases.

2. **Leukodystrophic disorders:**
    a) CNS neuropathies like those produced by vitamin B12 deficiency.
    b) Myelopathies like tabes dorsalis (syphilitic myelopathy)
    c) Leukodystrophies.

- **Demyelinating disorders may be associated also with:**
  1. Optic neuritis
  2. Transverse myelitis
- These are inflammatory conditions, because inflammation and demyelination are frequently associated.
- Some of them are idiopathic, and for some others the cause has been found, like some cases of neuromyelitis optica.

- **Signs and symptoms**
- Symptoms and signs that present in demyelinating diseases are different for each condition.
- Below is a list of symptoms and signs that can present in a person with a demyelinating disease.
  1. Blurred double vision
  2. Ataxia
  3. Clonus
  4. Dysarthria
  5. Fatigue

6. Clumsiness
7. Hand paralysis
8. Hemiparesis
9. Genital anaesthesia
10. Incoordination
11. Paresthesias
12. Ocular paralysis
13. Impaired muscle coordination
14. Weakness (muscle)
15. Loss of sensation
16. Impaired vision

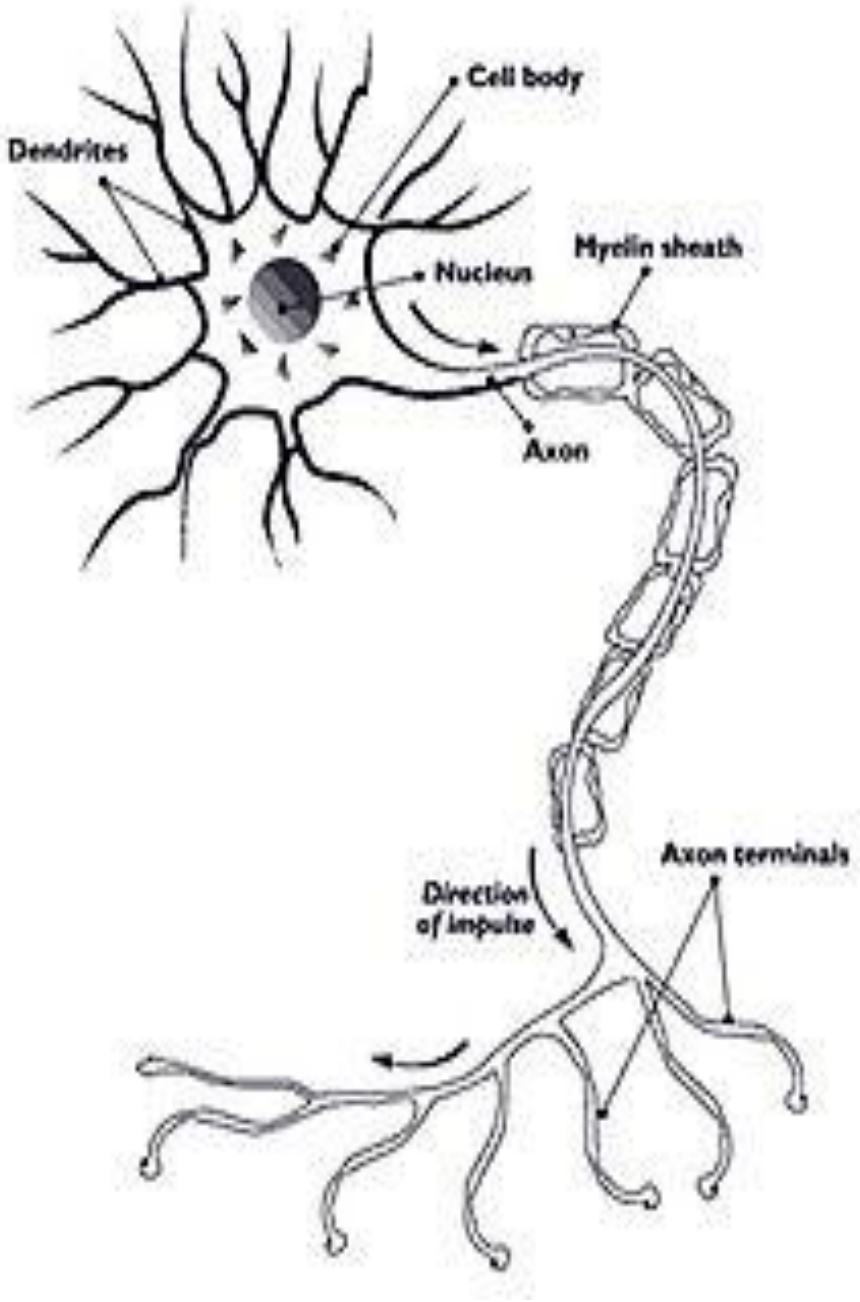
17. Neurological symptoms
18. Unsteady gait
19. Spastic paraparesis
20. Incontinence
21. Hearing problems
22. Speech problems

Multiple sclerosis (MS)

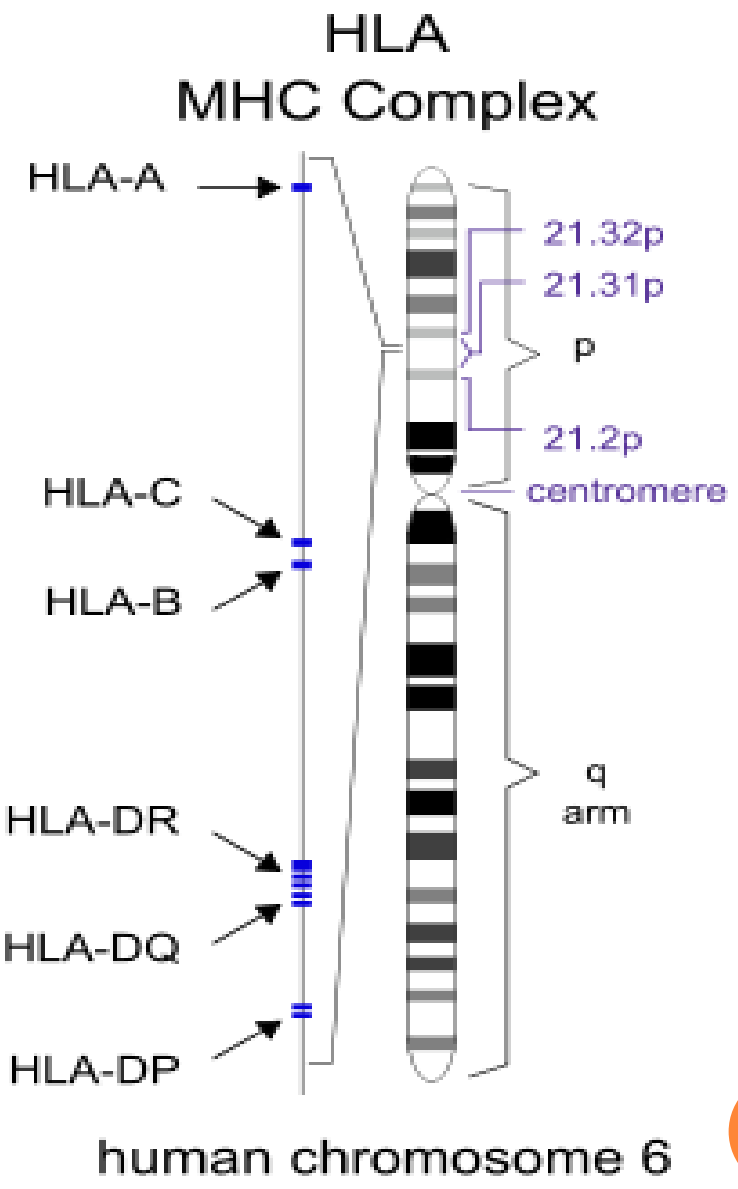
- **Multiple sclerosis** is a demyelinating disease in which the insulating covers (myelin sheets) of the nerve cells in the brain and spinal cord are damaged.
- It is the most common autoimmune disorder affecting the CNS.

- **Etiology of MS:**
- Autoimmune disease due to combination of environmental and genetic factors resulting in loss of tolerance to self proteins (myelin antigens).
- A transmissible agent (virus) has been proposed but not yet identified.
- Genetic lineage of MS susceptibility to HLA-DR-2 is established.

- **Nerve axon with myelin sheath**



- HLA region of Chromosome 6. Changes in this area increase the probability of getting MS.



- **Pathogenesis of MS:**
- The cause is not clear.
- The underlying mechanism in which the insulating covers of nerve cells in the brain and spinal cord are damaged is thought to be either destruction by the immune system or failure of the myelin-producing cells.
- Proposed causes for this include genetics and environmental factors such as being triggered by a viral infection.

- Damage of myelin sheets disrupts the ability of parts of the nervous system to communicate.
- This results in a range of signs and symptoms, including physical, mental, and sometimes psychiatric problems.
- Sites of predilection of this disruption are; optic nerve, paraventricular area, brain stem, spinal cord, and cerebral white matter.
- The function of white matter cells is to carry signals between grey matter areas; where the processing is done, and the rest of the body.

- The PNS is rarely involved by MS.
- MS is usually diagnosed based on the presenting signs and symptoms and the results of supporting medical tests.

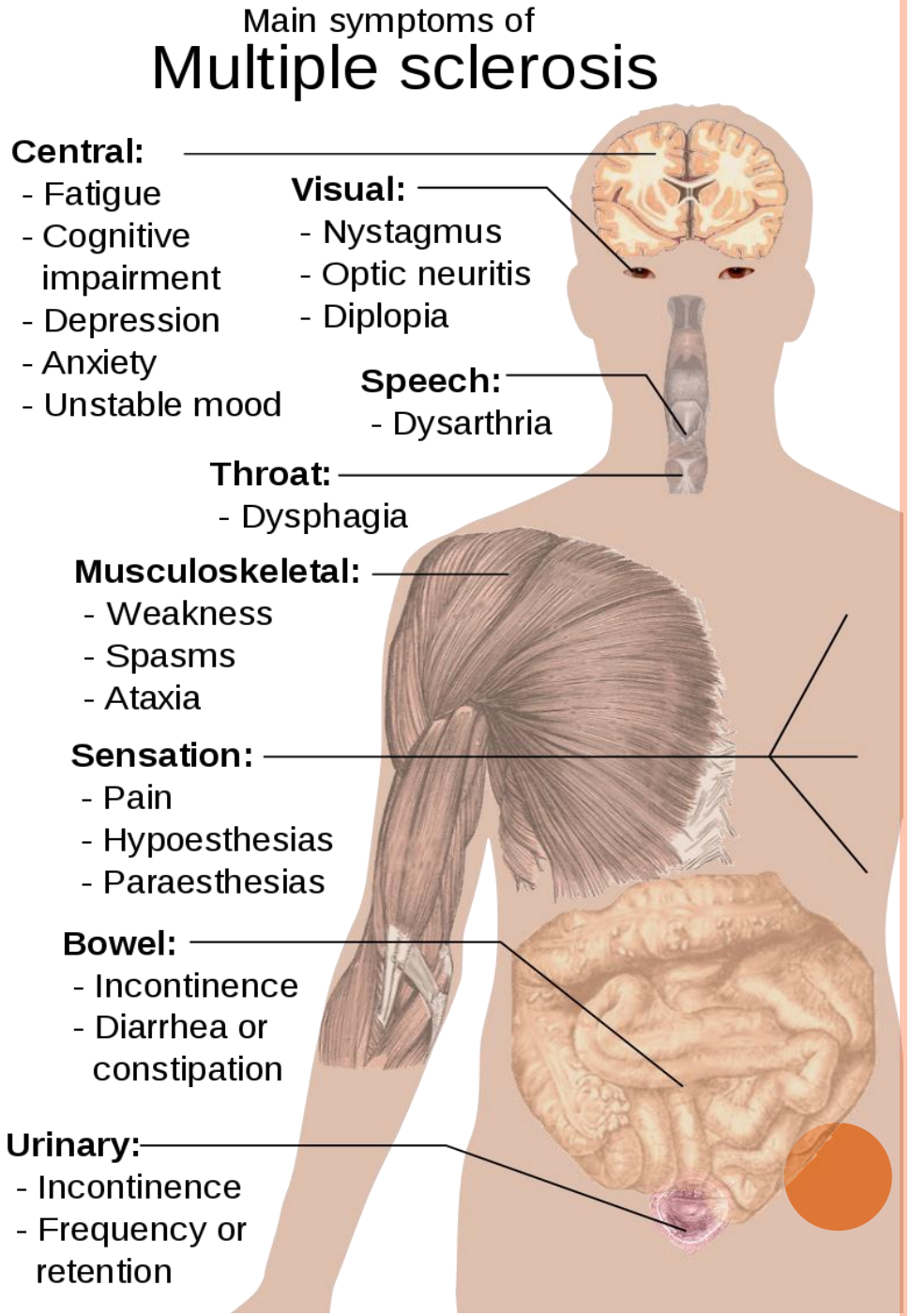
- **Grossly:**
- The name ***multiple sclerosis*** refers to the **scars** known as ***plaques*** of demyelination in the nervous system.
- Any area of the brain can be affected.
- The lesions most commonly affect the white matter in the optic nerve, brain stem, basal ganglia, and spinal cord, or white matter tracts close to the lateral ventricles.
- These plaques are *perivenular* and appear as irregular well demarcated *grey* or *translucent* lesions with a diameter ranging between 0.1cm to several centimeters.

- **Microscopic:**
- Plaques show demyelination and ***tangled masses*** of preserved axons.
- *Lymphocytic infiltration* is present in areas of *recent* demyelination.

- **Clinically:**
- The disease is characterized by *episodic* ***relapses*** and ***remissions*** over many years.
- The clinical manifestations depend on the area of the brain affected and include *abnormalities of vision, cerebellar dysfunction, parasthesia, weakness and spinal cord dysfunctions*.
- Specific symptoms include *double vision, blindness in one eye, muscle weakness, trouble with sensation, or trouble with coordination*.

- MS takes several forms, with new symptoms either occurring in isolated attacks ***(relapsing forms)*** or building up over time ***(progressive forms)***.
- Between attacks, symptoms may disappear completely; however, permanent neurological problems often remain, especially as the disease advances.

- **Main symptoms of multiple sclerosis**



Degenerative diseases of CNS

- **Neurodegeneration** is a progressive loss of structure or function of neurons, including their deaths.
- Neurodegenerative diseases including Parkinson's, Alzheimer's, and Huntington's occur as a result of neurodegenerative processes.
- Such diseases are incurable → progressive degeneration and/or death of neuron cells.

- Many similarities appear that relate these diseases to one another on a sub-cellular level.
- Discovering these similarities offers a hope for therapeutic advances that could ameliorate many diseases simultaneously.

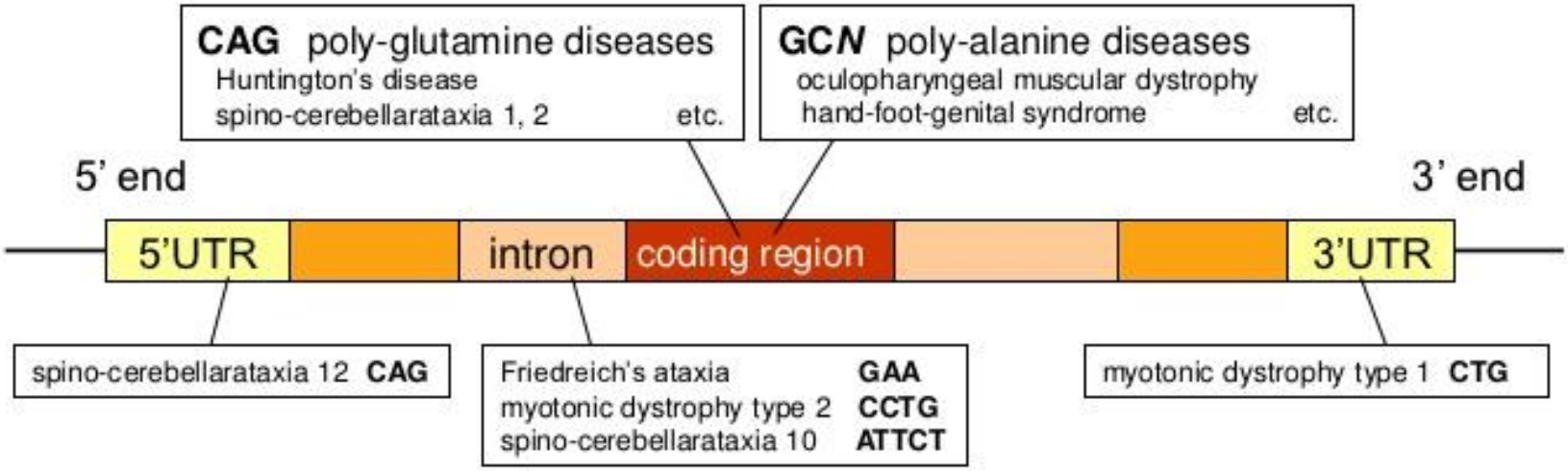
Etiology & pathogenesis/ mechanisms:

I. **Genetics:**

- Many neurodegenerative diseases are caused by genetic mutations, most of which are located in completely unrelated genes.
- In many of the different diseases, the mutated gene has a common feature: a repeat of the CAG nucleotide triplet.
- CAG encodes for the amino acid glutamine.
- A repeat of CAG results in a polyglutamine (polyQ) tract.
- Diseases showing this are known as polyglutamine diseases.

Triplet repeat disease

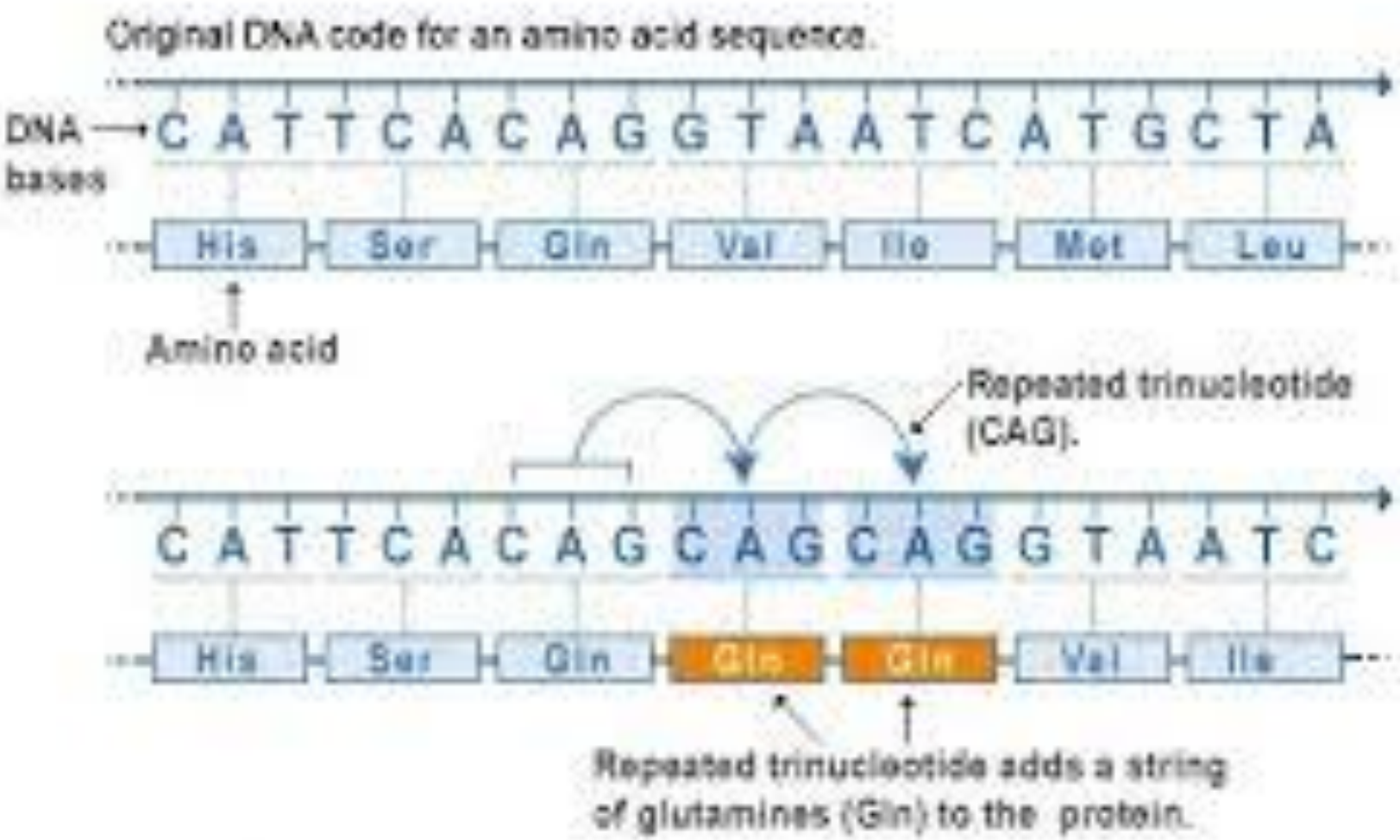
- General term of hereditary diseases caused by abnormal expansion of triplet repeats



e.g. triplet repeat length

	Normal	Patient
Huntington's disease	11～34	36～121
Myotonic dystrophy type 1	5～37	50～5000

Repeat expansion mutation



II. **Protein misfolding:**

- Several neurodegenerative diseases are classified as ***proteopathies*** as they are associated with the aggregation of misfolded proteins.
- **Intracellular mechanisms:**

A. ***Protein degradation pathways:***

- Parkinson's disease and Huntington's disease are associated with the accumulation of *intracellular toxic proteins*.

- Diseases caused by the aggregation of proteins are known as ***proteinopathies***, and they are primarily caused by aggregates in the following structures:
  a) cytosol, e.g. Parkinson's & Huntington's.
  b) nucleus, e.g. Spinocerebellar ataxia type1
  c) endoplasmic reticulum (ER), (familial encephalopathy with neuroserpin inclusion bodies)
  d) extracellularly excreted proteins, amyloid-ß in Alzheimer's disease

B. ***Membrane damage:***

- Damage to the membranes of organelles by *monomeric or oligomeric proteins* could also contribute to these degenerative diseases.

C. ***Mitochondrial dysfunction:***

- The most common form of cell death in neurodegeneration is through the intrinsic mitochondrial apoptotic pathway.
- Reactive oxygen species (ROS) are normal byproducts of mitochondrial respiratory chain activity.
- Over production of ROS ***(oxidative stress)*** is a central feature of all neurodegenerative disorders.

- There is a strong evidence that mitochondrial dysfunction and oxidative stress play a causal role in neurodegenerative disease pathogenesis, including Alzheimer's, Parkinson's, Huntington's, and Amyotrophic lateral sclerosis.

D. ***Axonal transport:***

- Axonal swelling has been observed in many neurodegenerative diseases.
- This suggests that ***defective axons*** may cause certain pathological insult due to *accumulation of organelles*.
- When axonal transport is severely disrupted a degenerative pathway known as Wallerian-like degeneration is often *triggered*.

III. Programmed cell death (PCD):

- PCD is mediated by an intracellular program.
- This process can be activated in neurodegenerative diseases including Parkinson's disease, amytrophic lateral sclerosis, Alzheimer's disease and Huntington's disease.
- There are also other situations in which these pathways are artificially stimulated due to injury or disease.

IV. Transglutaminase:

- Transglutaminases are *enzymes* present in human body and in the brain in particular.
- The *main function* of transglutaminases is ***bind proteins and peptides intra- and inter-molecularly*** in a reaction termed transamidation or cross-linking.
- Transglutaminase binding of these proteins and peptides make them clumping together and the resulting structures are turned *extremely resistant to chemical and mechanical disruption*.

- Most relevant neurodegenerative diseases share the property of *the presence of abnormal structures made up of proteins and peptides*.
- Each one of these neurodegenerative diseases have one (or several) specific main protein or peptide which are made up:
  a) in *Alzheimer's* disease they are amyloid-beta and tau,
  b) in *Parkinson's* disease it is alpha-synuclein,
  c) in *Huntington's* disease it is huntingtin.
- In Alzheimer's, Parkinson's and Huntington's diseases the expression of the transglutaminase enzymes are increased.

Alzheimer's disease

- **Alzheimer's disease** (**AD**), also referred to simply as **Alzheimer's**, is a chronic neurodegenerative disease that usually starts slowly and worsens over time.
- It is the cause of 60% to 70% of cases of dementia.
- The most common early symptom is difficulty in remembering recent events ***(short-term memory loss)***.

- As the disease advances, symptoms include problems with language, disorientation, easily getting lost, mood swings, loss of motivation, not managing self-care, and behavioral issues.
- As a person's condition declines, they often withdraw from family and society.
- Gradually, bodily functions are lost, ultimately leading to death.
- Although the speed of progression can vary, the average life expectancy following diagnosis is three to nine years.

ETIOLOGY:

- The cause of AD is poorly understood.

I. **Genetic hypothesis:**

- The genetic heritability of AD based on
- reviews of twin and family studies.
- About 70% of the risks is believed to be genetic with many genes usually involved.

A. Around 0.1% of cases are familial forms of **autosomal dominant** inheritance, which have an onset before the age 65 years.

- This form of disease is known as early onset familial Alzheimer's disease.

- Most of autosomal dominant familial AD is attributed to mutations in one of three genes: those encoding amyloid precursor protein *(APP) and presenilins 1 and 2.*
- Most mutations in the APP and presenilin genes increase the production of a small protein called ***Aβ42***, which is *the main component of senile plaques.*
- Some mutations merely alter the ratio between Aβ42 and the other major forms of proteins, particularly Aβ40 without increasing Aβ42 levels.

B. Most cases of AD do **not exhibit autosomal-dominant** inheritance and are termed sporadic AD, in which environmental and genetic differences may act as risk factors.

- The best known genetic risk factor is the inheritance of the ***ε4 allele*** of the apolipoprotein E (APOE).
- Between 40 and 80% of people with AD possess at least one APOEε4 allele.
- The APOEε4 allele increases the risk of AD by three times.

- Environmental effects and genetic modifiers result in incomplete penetrance.
- More recent *genome-wide association studies* (GWAS) have found 19 areas in genes that appear to affect the risk.

c. Mutations in ***TREM2*** gene have been associated with a 3 to 5 times higher risk of developing Alzheimer's disease.

- A suggested mechanism of action is that when TREM2 is mutated, white blood cells in the brain are no longer able to control the amount of beta amyloid present.

II. **Cholinergic hypothesis:**

- The oldest, on which most currently available drug therapies are based, is the ***cholinergic hypothesis***.
- It proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine.
- The cholinergic hypothesis has not maintained widespread support, largely because medications intended to treat acetylcholine deficiency is not very effective.
- Other cholinergic effects, for example, is initiation of large-scale aggregation of amyloid, leading to generalized neuro-inflammation.

III. Amyloid hypothesis

- ***Amyloid hypothesis*** postulated that extracellular amyloid beta (A_{β}) deposits are the fundamental cause of the disease.
- Support for this postulate comes from the location of the gene of the amyloid precursor protein (APP) on chromosome 21, together with the fact that people with *trisomy 21 (Down Syndrome)* who have an extra gene copy almost universally exhibit at least the earliest symptoms of AD by 40 years of age.

- Also, a specific isoform of apolipoprotein, APOE4, is a major genetic risk factor for AD.
- While apolipoproteins enhance the breakdown of beta amyloid, some isoforms are not very effective at this task (such as APOE4), leading to ***excess amyloid buildup in the brain***.

IV. Tau hypothesis

- The ***tau hypothesis*** proposes that tau protein abnormalities initiate the disease cascade.
- Hyperphosphorylated tau begins to pair with other threads of tau.
- Eventually, they form ***neurofibrillary tangles*** inside the nerve cell bodies.
- When this occurs, the microtubules disintegrate, destroying the structure of cell's cytoskeleton which collapses the neuron's transport system.
- This may result first in *malfunctions in the biochemical communication between neurons and later in cell death*.

V. **Other hypotheses**

a) **Neurovascular hypothesis:** states that poor functioning of the blood-brain barrier as in cases of *hypertension* may be involved.

b) **The cellular homeostasis of biometals:** such as *ionic copper, iron, and zinc* is disrupted in AD, though it remains unclear whether this is produced by or causes the changes in proteins.

- These ions affect and are affected by tau, APP, and APOE, and their dysregulation may cause oxidative stress that may contribute to the pathology of AD.

c) **Retrogenesis is a medical hypothesis:** about the development and progress of AD.

- The hypothesis is that just as the fetus goes through a process of **neurodevelopment** *beginning with neurulation* and *ending with myelination*, the brains of people with AD go through a reverse **neurodegeneration** process *starting with demyelination* and *death of axons* (white matter) and *ending with* the *death of grey matter*.
- Likewise the hypothesis is, that as infants go through states of *cognitive development*, people with AD go through the reverse process of *progressive cognitive impairment.*

- **Other risk factors include:**

1. A history of head injuries, depression, or hypertension.
2. There is tentative evidence that exposure to air pollution may contribute to the development of AD.
3. An infection with Spirochetes bacteria in gum disease may cause dementia and may be involved in the pathogenesis of AD.
4. Smoking is a significant AD risk factor.
5. The majority of researchers do not support a causal connection with *aluminium*.

PATHOGENESIS:

- Exactly how disturbances of production and aggregation of the beta-amyloid peptide give rise to the pathology of AD is *not known*.
- The amyloid hypothesis points to the *accumulation of beta-amyloid peptides* as the *central event triggering neuron degeneration*.
- Accumulation of *aggregated amyloid fibrils*, which are the *toxic form of the protein* responsible for *disrupting the cell's calcium ion homeostasis*, induces *apoptosis*.

- It is also known that A_β selectively *builds up* in the mitochondria in the cells of Alzheimer's-affected brains.
- It also inhibits certain enzyme functions and utilization of glucose by neurons.
- Various inflammatory processes and cytokines may also have a role in the pathology of AD.
- Inflammation is a general marker of tissue damage in any disease, and may be either secondary to tissue damage in AD or a marker of an immunological response.

- Obesity and systemic inflammation may promote disease progression.
- Alterations in distribution of neurotrophic factors and in the expression of their receptors such as brain-derived neurotrophic factor (BDNF) have been described in AD.

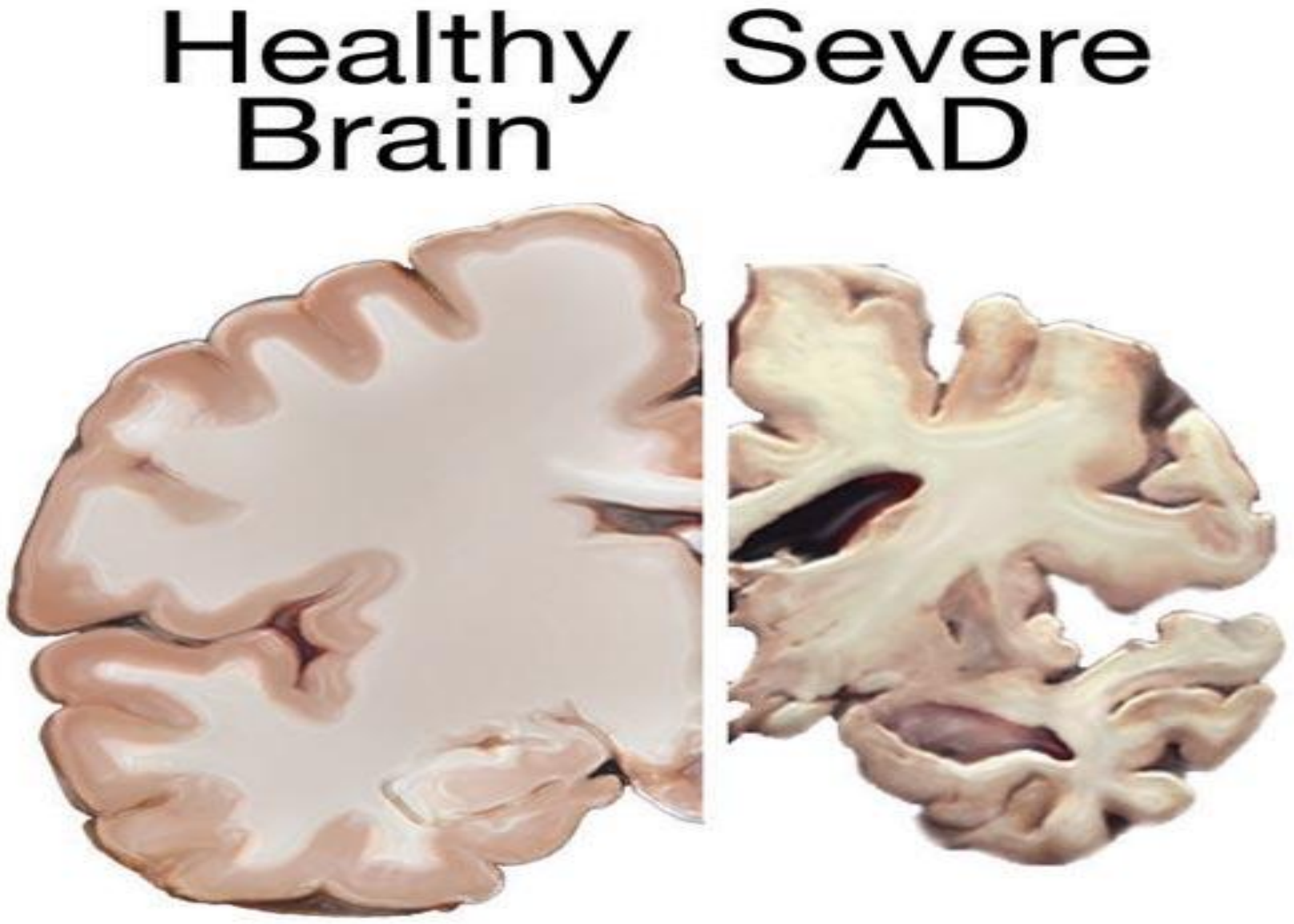
PATHOLOGICAL FEATURES:

- **Gross:**
- Gyri are narrowed and sulci widened specially in frontal, temporal and parietal lobes.
- The disease process is associated with ***neuritic plaques*** and ***neurofibrillary tangles*** in the brain.
- **Microscopic:**
- *Neurofibrillary tangles*; bundles of argrophilic paired helical filaments in neuronal cytoplasm.
- *Neuritic plague*.
- *Amyloid angiopathy*.

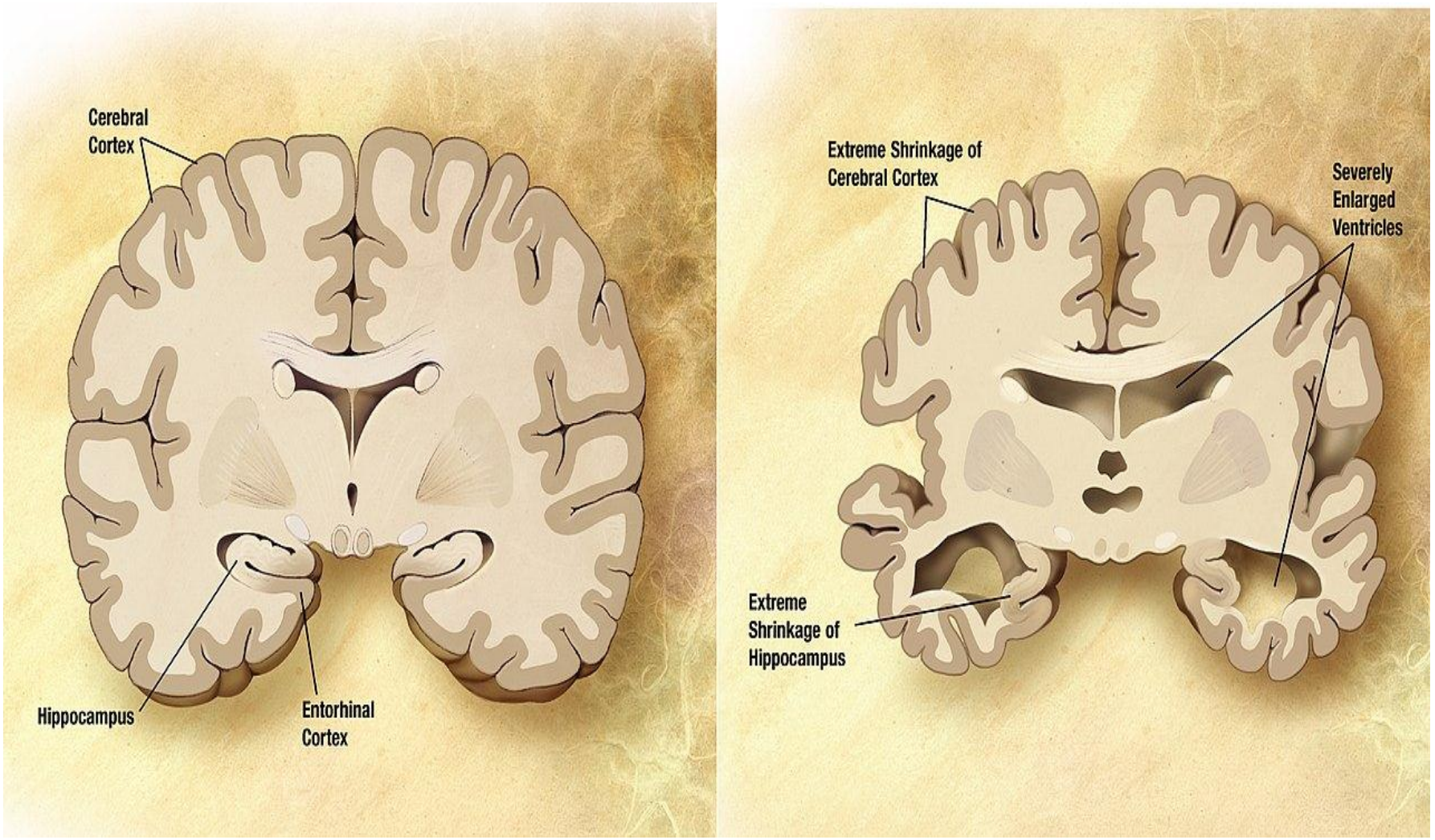
CLINICAL PICTURE AND PROGNOSIS:

- Principle clinical manifestation is dementia.
- Usually begins after the age of 50 years.
- Initial symptoms are often mistaken for normal ageing.
- A probable diagnosis is based on the history of illness and cognitive testing with medical imaging and blood tests to rule out other possible causes.
- Examination of the brain tissue is needed for a definite diagnosis.

- Mental and physical exercise, and avoiding obesity may decrease the risk of AD; however, evidence to support these recommendations is not strong.
- There are no medications or supplements that decrease the risk.



Brain atrophy in severe Alzheimer's



Comparison of a normal aged brain (left) and the brain of a person with Alzheimer's (right).

Pick's disease

- ***Pick's disease*** is a term that can be used in two different ways.
- It has traditionally been used as a term for a group of neurodegenerative diseases with symptoms attributable to frontal and temporal lobe dysfunction.
- Common symptoms that are noticed early are personality and emotional changes, as well as deterioration of language.

- This condition is commonly called frontotemporal dementia by professionals.
- The second use of the term is to mean a specific pathology that is one of the causes of frontotemporal lobar degeneration.
- It is known as **Pick disease** or **PiD** (not to be confused with pelvic inflammatory disease (PID) or Parkinson's disease (PD).

- A defining characteristic of the disease is ***build-up of tau proteins*** in neurons, accumulating into silver-staining, spherical aggregations known as ***"Pick bodies"***.

Clinical features:

- **The symptoms of Pick's disease include:**
- Difficulty in language and thinking, efforts to dissociate from family, behavioral changes, unwarranted anxiety, irrational fears, CBD (Compulsive buying disorder, or oniomania).
- In addition to impaired regulation of social conduct (e.g., breaches of etiquette, vulgar language, tactlessness, disinhibition, misperception), passivity, low motivation (aboulia), inertia, over-activity, pacing and wandering.

- It is a characteristic of Pick’s disease that dysfunctional, argumentative, or hostile social conduct is initially exhibited towards family members and not initially exhibited in a workplace or neutral environment.
- The changes in personality allow doctors to distinguish between Pick's disease and Alzheimer's disease.
- Pick's disease is one of the causes of the clinical syndrome of frontotemporal lobar degeneration.
- Pick's disease is associated with frontotemporal dementia and progressive nonfluent aphasia.

ETIOLOGY:

- Excess of a protein called ***β-amyloid*** (Aß) in neural cells has been linked to neural degeneration.
- Buildup of Aß within cells causes inflammation, leading to cell destruction by the immune system.
- Proteins associated with Pick's disease are present in all nerve cells, but those with the disease have an ***abnormal amount***.
- Mutations in the ***tau gene*** *(MAPT)* have been associated with this disease.

PATHOLOGICAL FEATURES:

- PiD was first recognized as a distinct disease separate from other neurodegenerative diseases because of the presence of *large, dark-staining aggregates of proteins in neurological tissue as well as the ballooned cells*, which are known as ***Pick cells***.
- ***Pick bodies*** are almost universally present in patients with PiD.
- Some cases of atypical Pick's disease have come to light that *lack* noticeable *Pick bodies*.

- Immunohistochemical staining using *anti-tau and anti-ubiquitin antibodies* have proven the most efficient and specific in visualization of Pick bodies and Pick cells.
- *Hematoxylin and eosin* staining allows visualization of another population of Pick cells, which are both tau and ubiquitin protein negative.
- *Silver impregnation* stains have been used to allow PiD to be distinguished from Alzheimer's disease.

- **Differences from Alzheimer's disease**
- In Alzheimer's disease, a*ll six isoforms of tau proteins* are expressed.
- In addition, the presence of *neurofibrillary tangles* that are a hallmark of Alzheimer's can be stained with antibodies to *basic FGF*, *amyloid P*, and *heparan sulfate glycosaminoglycan*.
- *Another difference is that in Pick's disease, a personality change occurs before any form of memory loss, unlike Alzheimer's, where memory loss typically presents first*.

Parkinsonism:

- **Parkinsonism** is a clinical syndrome characterized by tremors, *bradykinesia*, *rigidity*, and *postural instability*.
- Parkinsonism is found in Parkinson's disease (after which it is named)
- **Parkinsonian syndrome:**

1. Occurs with diseases, drugs, or toxins that selectively injure *dopaminergic neurons* in the *substania nigra*.

2. A wide range of causes may lead to symptoms of parkinsonism, including some toxins, metabolic diseases, and neurological conditions other than Parkinson's disease.

- About 7% of people with parkinsonism have developed their symptoms following treatment with particular medications.
- Side effect of medications, mainly neuroleptic antipsychotics especially phenothiazines, thioxanthenes and haloperidol, and rarely, antidepressants may cause symptoms of parkinsonism.

- The incidence of drug-induced parkinsonism increases with age.
- Drug-induced parkinsonism tends to remain at its presenting level, not progress like Parkinson's disease.

- **Pathogenesis of Parkinsonism:**
- Most cases are *sporadic*, both *autosomal dominant* and *autosomal recessive* forms do exist.
- There is defect in *α-synuclein*; a protein involved in *synaptic transmission*.
- **Lewy body:** an *inclusion* containing α-synuclein.

- **Grossly:**
- *Pallor* of the substantia nigra and locus ceruleus.

- **Microscopic:**
- *Depigmented* substantia nigra.
- ***Lewy bodies*** appear as single or multiple *intracytoplasmic, eosinophilic, round to elongated* in lesions with *dense core surrounded by a pale halo*.

- **Clinical features:**
- Commonly manifests as movement disorder.
- Progresses producing severe motor slowing over 10-15 years.
- Death usually is the result of inter current infection or trauma from frequent falls caused by *postural instability*.
- Dementia (*Lewy body dementia*) arises within one year of the onset of motor symptoms.

Dementia

- **Dementia** refers to progressive long term decline in the intellectual functions, and the ability to think and remember which is severe enough to interfere with person's normal daily activities and social relationships.
- Diagnosis requires a change from a person's usual mental function and a greater decline than one would expect due to aging.
- Other common symptoms include emotional problems, problems with language, and a decrease in motivation.

- Person's consciousness is usually not affected.
- It is a symptom of disease rather than a single disease entity.
- The most common type of dementia is Alzheimer's disease, which makes up 50% to 70% of cases.
- Other common types include vascular dementia (25%), Lewy body dementia (15%), and frontotemporal dementia.
- Less common causes include normal pressure hydrocephalus, Parkinson's disease, syphilis, and Creutzfeldt-Jakob disease.
- A small proportion of cases run in families.

- Dementia is a consequence of diffuse disease of the brain hemispheres, maximally affecting the cerebral cortex and hippocampus.
- Efforts to prevent dementia include trying to decrease risk factors such as high blood pressure, smoking, diabetes, and obesity.
- More than one type of dementia may exist in the same person.

Diagnosis of dementia:

- **Memory** must be impaired to make the diagnosis of dementia.
- Loss of memory for recent events is the earlist feature of dementia.
- Subsequent symptoms include abnormal behavior, loss of intellect, mood changes, and difficulty coping with ordinary routes.
- **Insight** may be retained initially, but is then usually lost.
- Ultimately, there is **loss of self-care**, wandering, incontinence, and often paranoia.

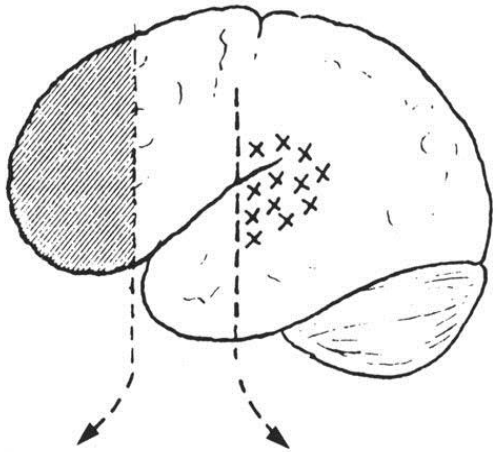
- **Differential diagnosis:**
  1. Dementia has to be distinguished from **delirium** which is an acute disturbance of cerebral function with impaired conscious level, hallucinations and autonomic overactivity as a consequence of toxic, metabolic or infective conditions.
  - It develop over a short period of time in some surgical patients, surgical intensive care unit patients, medicinal inpatients and AIDS patients.
  2. **Depression** can mimic the initial phases of dementia and it is termed ***"pseudodementia"*** which is amenable to antidepressant medication.

Classification of dementias based on the cause:

1. **Alzheimer's disease** (~60% of all dementias).
2. **Cerebrovascular** (multi-infarction state, subcortical small vessel amyloid angiopathy) (~20%).
3. **Neurodegenerative** (MS, Pick's disease, Huntington's chorea, Parkinson's disease).
4. **Infectious** (Creutzfeld-Jakob disease, HIV infection, progressive multifocal leucoencephalopathy).
5. **Normal pressure hydrocephalus**.

5. **Nutritional** (thiamine deficiency in alcoholics, B12 deficiency, folate deficiency).
6. **Metabolic** (hepatic disease, thyroid disease, parathyroid diseases, Cushing‘s syndrome).
7. **Chronic inflammatory diseases.**
8. **Trauma** (head injury, Punch drunk syndrome).
9. **Tumors** (e.g. subfrontal meningioma).

Classification of dementias based on the site:



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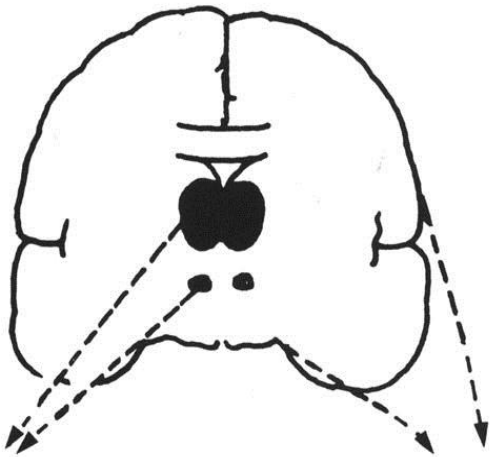

Anterior
(Frontal premotor cortex)
↓
Behavioural changes/loss of inhibition, antisocial behaviour, facile and irresponsible
↓
e.g. Normal pressure Hydrocephalus
Huntington's chorea
Metabolic disease

Posterior
(Parietal and temporal lobes)
↓
Disturbance of cognitive function (memory and language)
without marked changes in behaviour
↓
ALZHEIMER'S DISEASE

Subcortical
Apathetic
Forgetful and slow, poor ability to use knowledge
Associated with other neurological signs and movement disorders
↓
e.g. PARKINSON'S DISEASE
AIDS DEMENTIA COMPLEX

Cortical
Higher cortical abnormalities
– dysphasia
– agnosia
– apraxia
↓
e.g. ALZHEIMER'S DISEASE

Thank You