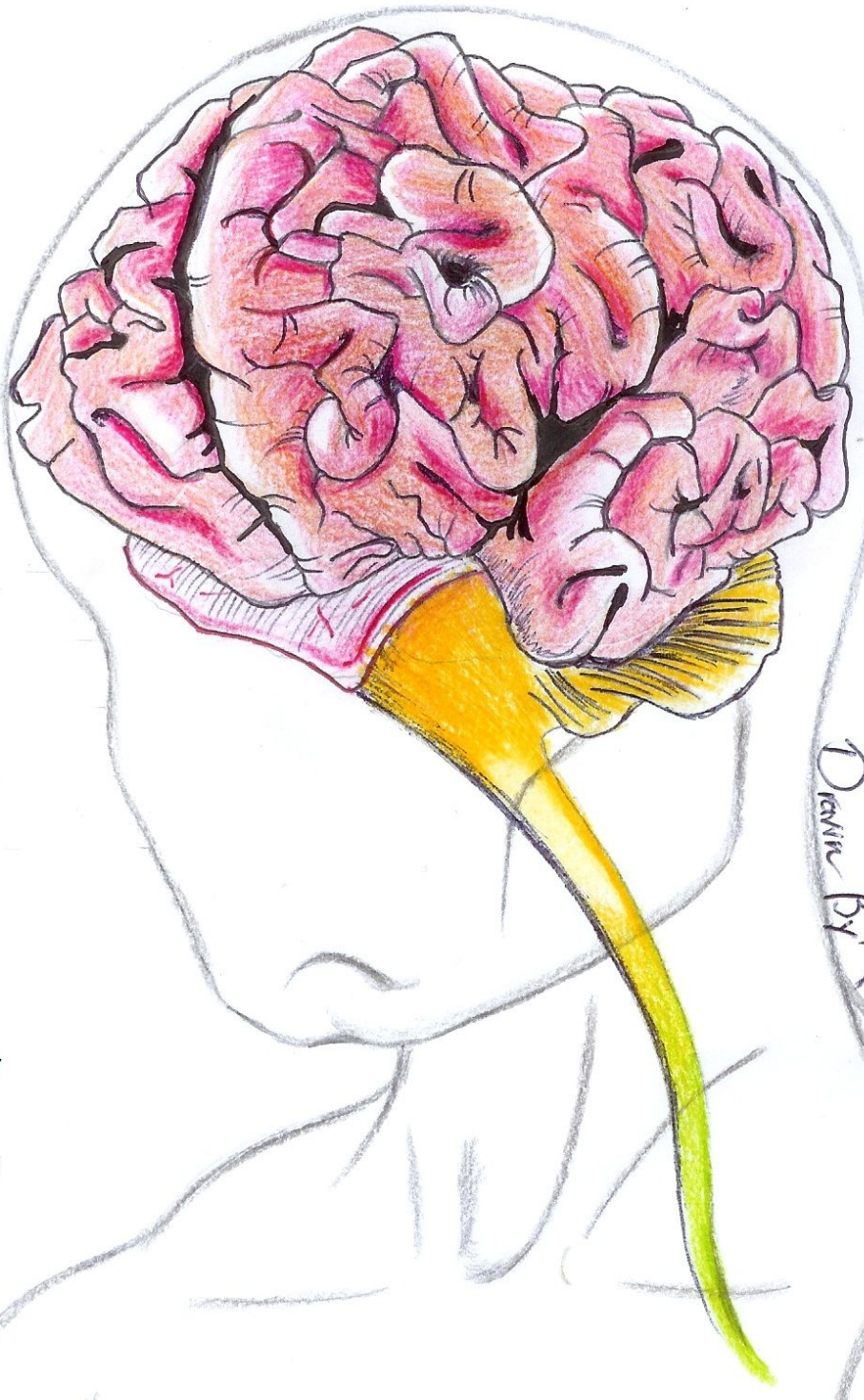
CENTRAL NERVOUS SYSTEM

- ○ Handout
- ★ Sheet
- ○ Slide

- ○ Anatomy
- ○ Physiology
- ○ Pathology
- ○ Biochemistry
- ★ Microbiology
- ○ Pharmacology
- ○ PBL



Drawn By Tariq Bushnaq...

Done By : **Loai Azar**

Dr. Name : **Ashraf**

Lec # : **4**

Prions

Prion are not considered as viruses but they are included in our virology lectures.

Many theories are there about the nature of prions but the most accepted theory is that prions are **infectious agents** consisting of **protein only**. Although this theory contradict the **central dogma** of biology i.e. the presence of nucleic acid is needed for the synthesis of proteins, the theory remains the most accepted one. (Central dogma = all living organisms use nucleic acids to reproduce. DNA –> RNA -> protein. The "protein-only" hypothesis: a protein structure could reproduce itself in the absence of DNA)

Other theories: 1. intoxication or increase concentration of certain components in the CNS might lead to **spongiform encephalopathy** or prion disease

2. Unknown viruses may cause spongiform encephalopathy or prion disease

3. Unknown bacteria that resemble mycoplasma (which doesn't have a cell wall) may be the cause of prions diseases.

There are two forms of the prion protein normal; normal form (PrP^{c}) and abnormal infectious nonfunctional (PrP^{sc}) form. PrP = prion protein , c= cellular sc= scrapie

The normal form PrP^{c} is normally found in the CNS without disease.

To sum up :

Prions are rather ill-defined infectious agents believed to consist of a single type of protein molecule with no nucleic acid component, prion protein & the gene which encodes it are also found in normal 'uninfected' cells but not in the pathological form. These agents are associated with diseases such as Creutzfeldt-Jakob disease in humans, scrapie in sheep & bovine spongiform encephalopathy (BSE) in cattle which **are Neurodegenerative diseases**.

Prions are proteinaceous transmissible pathogens which **doesn't carry the genetic information in nucleic acid .**

The name Prion comes from **PRO**teinaceous **IN**fectious particle.

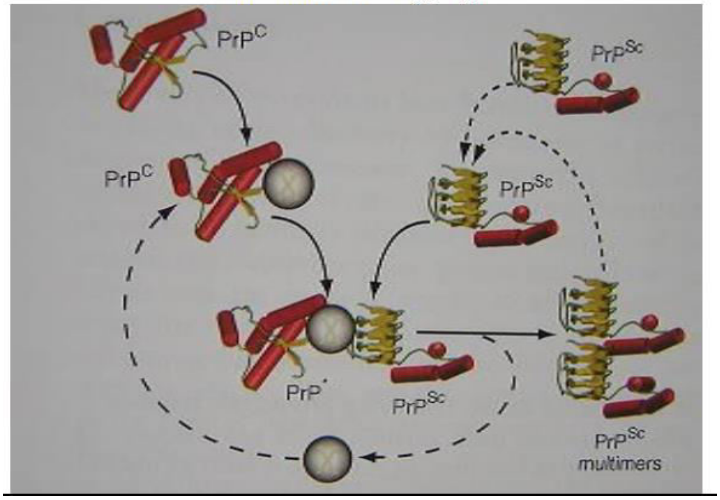
Prions are proteins with a pathological **conformation** that is believed to infect and propagate the conformational changes of the native proteins into the abnormally structured form. i.e. Once normal form of the protein come in contact with the abnormal form it is then transformed to the abnormal form. This roughly may be considered as the prion "replication cycle" but it is not a true replication cycle since there is no nucleic acid (just a protein).

Replication cycle

The presence of an initial PrP^{Sc}: exogenous (infectious forms) or endogenous (inherited or sporadic forms)

This first prion will initiate PrP^{Sc} accumulation by sequentially converting PrP^{C} molecules into PrP^{Sc} in replication cycle

PrP^{Sc} molecules aggregate



Normal prion protein is in alpha helix conformation while the abnormal one is in Beta pleated sheet conformation.

Prion protein is ultraviolet radiation (that breaks down nucleid acids present in viruses and all living things) resistant, also it is protease resistant protein.

The protein that prions are made of is found throughout the body, even in healthy people and animals; the prion protein found in infectious material has a different structure and is resistant to proteases.

Normal prion protein is found on the membranes of cells, though its function has not been fully resolved; its gene has been isolated (some prion diseases can be inherited; mutations make PrPC more likely to spontaneously change into the PrPSc

The following table show the diseases caused by prions in animal and human

BSE is found in cattle (cow madness)

Disease name	Natural host	Prion name	PrP isoform
Scrapie	Sheep, goat	Scrapie prion	$OvPrP^{Sc}$
Bovine spongioform encephalopathy (BSE)	Cattle	BSE prion	$BovPrP^{Sc}$
Kuru	Human	Kuru prion	$HuPrP^{Sc}$
Creutzfeldt-Jakob disease (CJD)	Human	CJD prion	$HuPrP^{Sc}$
Gerstmann-Straussler-Scheinker syndrome (GSS)	Human	GSS prion	$HuPrP^{Sc}$
Fatal familial insomnia (FFI)	Human	FFI prion	$HuPrP^{Sc}$

Prion diseases: rare neurodegenerative disorders (one person per million)

1. Sporadic (no causative agent) (85 %) ,In the sixth or seventh decade, rapidly progressive (death in less than a year) e.g. **Creutzfeldt-Jakob disease** (CJD)

2. Familial (inherited-15%), Mutations in the PrP gene that favour the transition from the cellular form to the pathological form of PrP

e.g. **Gerstmann-Straussler-Scheinker disease** (GSS), **fatal familial insomnia** (FFI)

3. Transmissible (rare; a source of great concern)

Propagation of kuru disease in New Guinea natives (ritualistic cannibalism)

Certain tribes in New Guinea had a ritual of eating their beloved brains after their death, and this act of cannibalism was associated with Kuru disease

Recently, it has been discovered that BSE had been transmitted to humans in Europe after consumption of infected beef, producing a variant of the CJD called vCJD

4. Iatrogenic transmission (used to be transmitted by surgical instrument before knowing about the existence of prions because they are resistant to UV light, 70%alcohol, and formalin so it need extensive sterilization measures. (which were added in the 1970s to prevent iatrogenic infections, after that no cases of iatrogenic transmission has been recorded)

A patient with prion disease cannot donate blood or donate his cornea (corneal graft) because the risk of transmitting the disease.

Transmissible spongiform encephalopathies are a group of progressive conditions (neurodegenerative) that affect the brain and nervous system of humans and animals and are transmitted by prions.

The pathology they cause is vacuolear degeneration, neuronal loss, astrocytosis and amyloid plaque formation, As a result of transformation of the PrP^{c} to PrP^{SC} a protein aggregation will form causing the deposition of amyloid plaque formation.

The clinical signs: loss of motor functions (lack of coordination, ataxia, involuntary jerking movements), personality changes, depression, insomnia, confusion, memory problems, dementia, progressive tonic paralysis, death

Definitive diagnostic test: biopsy of brain tissue (histopathological examination and immunostaining for PrPSc)

There is no cure

The presence of the abnormal protein form doesn't initiate any kind of an in immunological reaction or any inflammatory reaction.

Prion transmission

1. Direct contact with infected tissues

CJD has been transmitted:

- To patients taking injections of growth hormone harvested from human pituitary glands

- From instruments used for brain surgery (prions can survive the autoclave sterilization process)

- In corneal grafts

- In electrode implants

2. Consumption of affected tissues

Kuru was transmitted through cannibalism in Papua New Guinea

Humans can contract the disease by consuming material from animals infected with the BSE (vCJD)

How can prions make their way through the gut and into the brain? Since Proteins normally are digested down to amino acids in the gut!

It was thought that the transmission of prions through food consumption is not possible due to the fact that protein get digested! Then it was found that it can be transmitted by food as in the consumption of infected cows.

Now it is known that prion protein is resistant to digestion by GIT proteases and it circumvent the normal process of intestinal absorption by passing into the

the Gut-Associated Lymphoid Tissue (GALT) to the CNS. The full mechanism is not yet well discover.

CJD is called variant CJD when it is caused by consumption of animal infected with BSE.

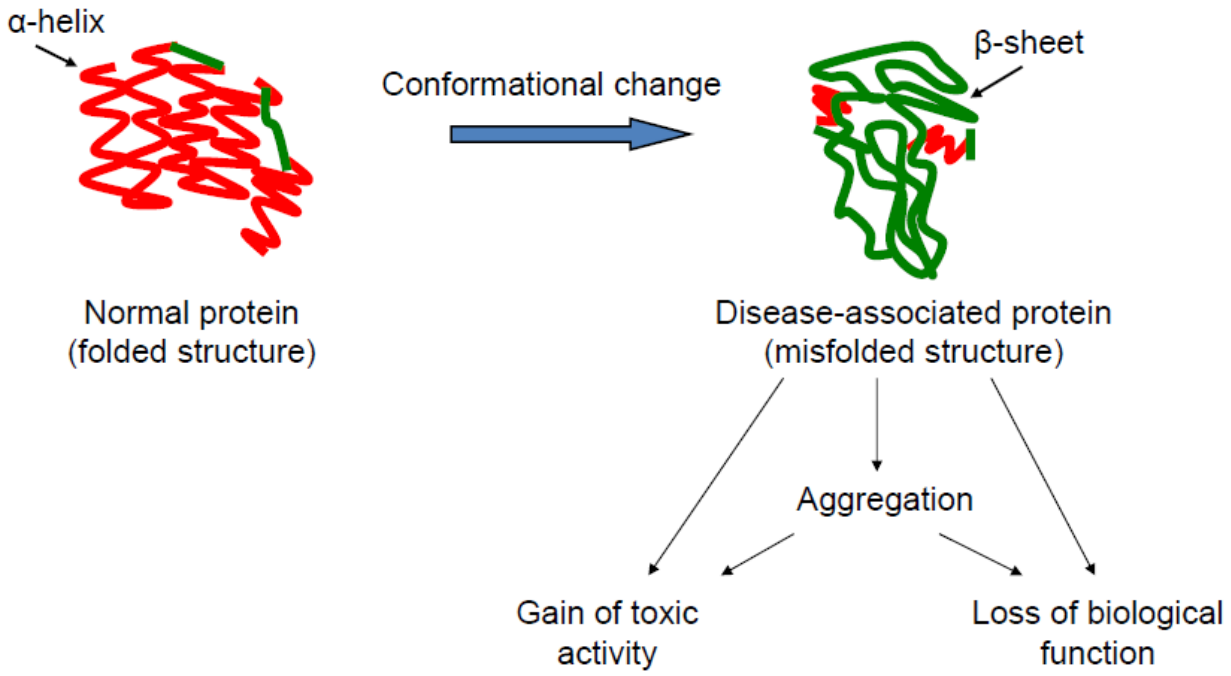
Protein misfolding diseases

Arise from abnormal conformation of specific proteins

Principle: Proteins can adopt an aberrant conformation that cause disease; two mechanisms must be considered as the diasease cause: loss of function of the native protein or gain of toxic activity of the aberrant conformation

More than 20 human pathologies

Prion diseases arise from the harmful function of the abnormal proteins; misfolded forms of proteins (rich in β-sheet structures) have a strong propensity to **aggregate** into insoluble material and form fibrils



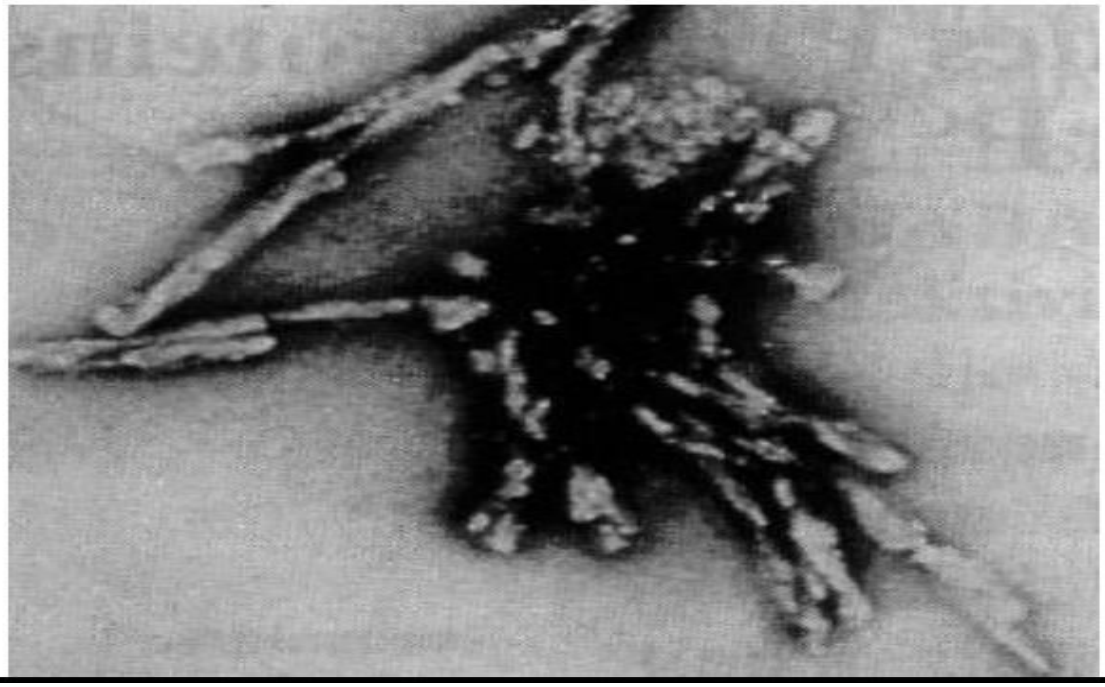
Genetics of prion disease Familial forms (15%) of prion disease are caused by inherited mutations in the PRNP gene. Mutations in this gene cause cells to produce an abnormal form of the prion protein, known as PrPSc

Most cases of prion disease are sporadic, they occur in people without gene mutations. Familial forms of prion disease are inherited in an **autosomal dominant pattern.**

CJD, Gerstmann-Straussler-Scheinker syndrome (GSS), Fatal familial insomnia **these 3 are inherited.**

PrP^C	PrP^{Sc}
The normal protein	The abnormal, disease-producing protein
is called PrP^C (for cellular)	is called PrP^{Sc} (for scrapie)
is a transmembrane glycoprotein (neurons, lymphocytes); its function is unknown	has the same amino acid sequence (primary structure)
has dominant secundary structure α-helix	has dominant secundary structure β-sheets
is easily soluble	is insoluble
is monomeric and easily digested by proteases	is multimeric and resistant to digestion by proteases
is encoded by a gene designated PRNP located on the chromosome 20	When PrP^{Sc} comes in contact with PrP^C, it converts the PrP^C into more of itself These molecules bind to each other forming aggregates

Prion aggregates (an electron microscope picture)



Kuru

(a native word meaning “trembling with cold and fever“)

Is a prion disease incident in natives in New Guinea

Cannibalism: relatives ate their dead relative's brains as a sign of mourning

In the 1950's, the practice was banned, thereby preventing any further possible transmission; (incubation period of 4 to 20 years)

Symptoms: 3 stages; gradually deterioration of motor and mental functions

The first stage, exhibits unsteady gait, decreased muscle control, tremors, deterioration of speech and dysarthria (slurred speech).

second stage, incapable of walking without support, suffers ataxia (loss of muscle coordination), severe tremors and depression.

final stage, the patient suffers severe ataxia, is unable to speak, is incontinent, has dysphagia (starvation), is unresponsive to their surroundings

An infected person usually dies within 3 months to 2 years after the first symptoms, often because of pneumonia or pressure sores infection

Creutzfeldt-Jakob disease (CJD)

is the most common of the prion disease

usually affects people aged 55-65 mean age 68(vCJD occurs in younger people)

The duration of CJD is less than 1 year, death occur shortly in 4 to 6 months.

Symptoms: Dementia, hallucinations, motoric dysfunction, ataxia and seizure

Diagnosis: symptoms, EEG, MRI, CSF analysis

The definitive diagnostic test: biopsy of brain tissue

Treatment: fatal disease, searching for viable treatments

Forms:

1. Sporadic

2. Familial

3. Transmitted: iatrogenic-iCJD, via consuming -vCJD

Blood donor restrictions: prions can be transmitted by blood transfusions; there is no test to determine if a blood donor is infected; restrictions for blood donors

Classic CJD vs vCJD

Characteristic	Classic CJD	Variant CJD
Median age at death	68 years	28 years
Median duration of illness	4-5 months	13-14 months
Clinical signs and symptoms	Dementia; early neurologic signs	Prominent psychiatric/behavioral symptoms; delayed neurologic signs; hallucinations
Specific changes on MRI	Often present	Often present
Specific changes on EEG	Often present	Often absent
Immunohistochemical analysis of brain tissue	Variable accumulation of the PrP^{Sc}	Marked accumulation of the PrP^{Sc}
Presence of agent in lymphoid tissue	Not readily detected	Readily detected
Presence of amyloid plaques in brain tissue	Often present	Often present

note the presence of agent (prion) in lymphoid tissue in case of vCJD while it is absent in classic CJD, and this reflect the fact that classic form starts from inside the brain i.e. mutation while the variant is by food consumption.

Diagnosis

Gold standard: brain biopsy (histopathological examination and immunostaining for PrPSc)

• CSF: elevated protein 14-3-3 and S100

•CT and MRI: Normal, if abnormal not diagnostic

•EEG: abnormal pattern in 2/3 of Creutzfieldt-Jakob disease

Therapeutic strategies

There is no cure yet to any of the prions diseases but these are strategies that are under investigation.

1. Compounds can be designed to specifically disrupt the replication cycle of the PrPSc by binding it and preventing it to bind the normal protein thus preventing further transformation. Design of such compounds had proven successful in cell-based models but must now be extended to animal models and human clinical trials
2. Vaccine design: The abnormally folded proteins expose a side chain of amino acids which the properly folded protein does not expose. Antibodies specifically coded to this side chain amino acid sequence stimulate an immune response to the abnormal prions
3. Design of peptides that break the β-sheet structures
4. Gene therapy by modification of the prion gene, because the fact that animals who doesn't have this gene can't get any of these prion diseases. Genetic engineering research: cattle lacking a necessary gene for prion production - thus theoretically making them immune to BSE (December 2006)

Summary

The prions are proteins that carry information for self-reproduction (contradict the central dogma of modern biology)

The prions are expressed in cells of healthy humans and animals; their abnormal conformations (PrPSc) are insoluble, resistent to digestion and aggregate

The PrPSc attacks the native prion PrPC, changes its conformation into an abnormal form and causes an exponential production of insoluble proteins; they aggregate and form the fibrillar structure

Prion disease are rare fatal degenerative disorders; a portion of them can be transmitted; this mechanism is not clear (e.g. transmision of BSE to human)

One part of the prion protein can cause apoptosis, or programmed cell death

Prions induce no immune reactions within the human

DONE.