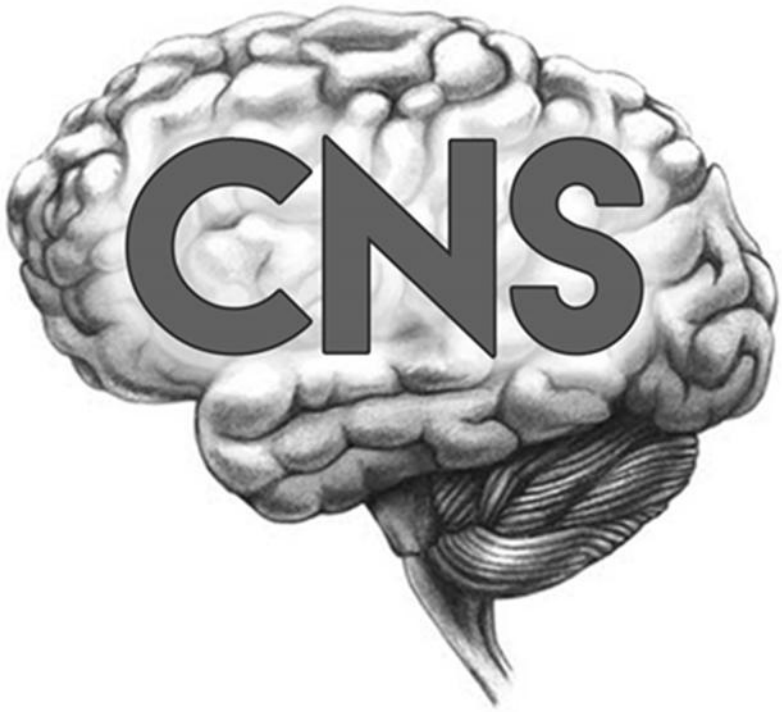

MICROBIOLOGY

☑ Sheet ○ Slide ○ Handout

Number

4

Subject

Prions

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Prions

- A prion "**PRO**teinaceous **IN**fectious particle" is an agent that consists of only one single type of protein molecule and no nucleic acid components.
- Prion protein & the gene which encodes it are also found in normal 'uninfected' cells but not in the pathological form.
- They are associated with fatal neurodegenerative diseases in humans & animals; they are called "Transmissible spongiform encephalopathies - TSEs".
- There are 2 forms of "prion protein":
  - **The normal form (PrP^{C})**
    → refers to "cellular", the form which makes part of normal human CNS.
  - **The infectious form (PrP^{Sc})**
    → refers to "scrapie; a form of prion disease that occurs in sheep".
- The most accepted theory is that they are "protein-only infectious agents", eventhough there are many research groups that are currently trying to prove this wrong by suggesting other theories such as:
  - ✕ A prion is a virus
  - ✕ A prion is a bacterial infection
  - ✕ Development of prion disease is multi-factorial, (such as the presence of prion protein).
  - ✕ Prion protein in addition to lipid & heavy metals play a role in the transformation of prion from the normal form to infectious one.

Keep in mind that all these theories are still under investigation and none of them is proved right, yet.

So, is prion a virus?

***No**, it's just an infectious protein agent.*

Why are some research groups trying to prove this "protein-only" theory wrong?

➔ Because it contradicts the central dogma of biology; which says that all kinds of living organisms need nucleic acids (DNA or RNA) in order to live.

What are the **human** illnesses that are caused by prions?

- Kuru – **Exogenous**
- Variant Creutzfeldt-Jakob disease (vCJD) – **Exogenous**
- Creutzfeldt-Jakob disease (CJD) – **Endogenous**
- Gerstmann–Sträussler–Scheinker syndrome (GSS) – **Endogenous**
- Fatal familial insomnia (FFI) – **Endogenous**

** According to the source of infection, prion diseases are classified into:*

- ***Exogenous*** *(from outside the body)*
- ***Endogenous*** *(from within the body)*

Epidemiology

- Infectious Prions are **not** the same as the prion protein that is present in our bodies.
- Prions are agents with a pathological conformation that is believed to infect and propagate the conformational changes of the native (normal) prion proteins into the abnormally-structured form.
- One part of the prion protein can induce apoptosis (programmed-cell death).

➔ Prions infect humans, sheep, cows & goats.

- Until 1996, it was believed that human infections are separate from animal infections meaning that a prion infection in animals cannot be transmitted to humans.
- The first human prion infection which was attributed to prion disease in animals was in 1996.

Mode of transmission

It is transmitted from animals to humans via consumption of raw or partially-cooked infected meat, it can transmit even via eating well-done meat.

Why is this? ➔ Because the "infectious form" of prions is resistant to heat & digestion (resistant to stomach proteases.)

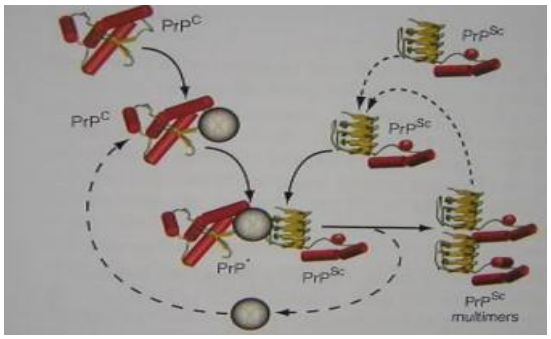
Causes of infection

- **Sporadic** (85%): The cause of infection is unknown.
- **Familial**: Mutation in the *PRNP gene*, resulting into the formation of PrP^{Sc}.
  - e.g.) Fatal familial insomnia / Gerstmann–Sträussler–Scheinker syndrome
  - Around 400 families and a total of 1500 people from around the world
- **Iatrogenic**:
  - As a physician, you might accidently infect the patient, mostly after a surgery when you do instrument autoclaving (تعقيم) to sterilize the instruments by heat but prions are resistant to heat and therefore, nowadays they use more extensive sterilization measures**.**
  - Prions can be transmitted in grafts (corneal donation, blood transfusion, etc..)
  - Injections of growth hormone taken from another human's pituitary gland. Fortunately, nowadays hormones are created via recombination technologies.
- **Transmissible**

Pathogenesis

Transmissible spongiform encephalopathies are characterized by:

- Spongiform matter around area of infection
- Absence of inflammation & immune reaction!
- Vacuolar degeneration, neuronal loss, astrocytosis & amyloid plaque formation



Mechanism of transformation: Once the infectious form of prion protein (PrP^{Sc}) comes into contact with the normal form (PrP^{C}), it's going to induce its transformation into the abnormal form (PrP^{Sc}).

Ps.) One molecule of PrP^{Sc} will be enough to induce all the bad action.

- Infectious prions have a misfolded conformation & different protein composition:
  - ⌘ Normal PrP^{C}: Has an alpha-helix conformation
  - ⌘ Infectious PrP^{Sc}: Has a beta-pleated sheet conformation

  Therefore, there are 2 mechanisms by which pathology occur:
  1) Loss of function of the normal alpha-helix prion protein
  2) Toxicity effect of the aggregated beta-pleated prion protein

[Important] Although both normal & infectious types of prions have different conformations, but **they have the same amino acid sequence!**

- **The clinical signs:** loss of motor functions, personality changes, depression, insomnia, confusion, memory problems, dementia, paralysis, death.
- **Definitive diagnostic test:** Biopsy of brain tissue after death (autopsy) then do a histopathological examination and immunostaining for the abnormal protein (PrP^{Sc})
- There is no cure or vaccine. ➔ Again, once infected عظم الله أجركم

How can prions make their way through the gut and into the brain?

Since proteins normally must get digested down to amino acids in the gut in order to be absorbed, it was thought that the transmission of prions through food consumption is not possible due to the fact that infectious prions are insoluble & resistant to digestion.

But later it was found that it **can** really be transmitted via food, *but how is that possible?*

➔ It circumvents (يتحايل على) the normal process of intestinal absorption by passing into the **Gut-Associated Lymphoid Tissue (GALT)**, then from there passing to the CNS.

When a prion is present in the GALT ➔ It's Variant Creutzfeldt-Jakob disease (vCJD)

Let's talk more about each prion disease…

❖ Creutzfeldt-Jakob disease (CJD) –

- **It is the most common prion disease**
- It occurs after the age of 60 years, and it's considered as **endogenous.**
- Mean age of death is 68
- The duration of CJD is less than 1 year then death.
- Symptoms: Dementia, hallucinations, motor dysfunction, ataxia and seizures.
- Symptomatic diagnosis, CSF analysis shows high *14-3-3 protein* & S100
  EEG (changes in most of the cases, but not all)
  CT & MRI (Normal, but NOT diagnostic if abnormal)
  The definitive diagnostic test: biopsy of brain tissue.

❖ Variant Creutzfeldt-Jakob disease (vCJD)

- Transmitted via consumption of raw or even well-done infected meat, and according to that, it's classified as **exogenous**.
- Affects younger people
- Mean age of death is 28, but duration of vCJD is longer than this of CJD.

❖ Kuru

It was a ritual (تقليد) in Papua New Guinea that when someone you love dies, you take out his brain and make a brain soup out of it (شوربة مخ حبيبي :p) as a mourning cannibalism, that's why it's considered **exogenous.** Due to the fact that they were banned from doing this ritual in the middle of 1960s, Kuru is no longer seen.

According to the progression of symptoms, it's classified into 3 stages:

1) **The first stage** –unsteady gait, tremors, dysarthria (slurred speech), decreased muscle control.
2) **The second stage** – depression, ataxia (loss of muscle coordination), incapable of walking without support.
3) **The final stage** – severe ataxia, mute, incontinence, dysphagia (starvation), unresponsive to their surroundings.

   An infected person usually dies within 3 months to 2 years.

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

Therapeutic strategies

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

1) **Compounds can be designed to specifically disrupt the replication cycle of the PrP^{Sc} 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 only but must now be extended to animal models and human clinical trials
2) **Vaccine design:** Antibodies specifically target a side chain of amino acids that only the abnormal (infectious) prion possesses, this will stimulate an immune-response to the abnormal prions only.
3) **Design of peptides that break the β-sheet structures**
4) **Gene therapy by modification of the prion gene**, because they tested it and animals who doesn't have this gene can't get any of these prion diseases!

- This was the last sheet in the Central Nervous System
- Best of luck w el hamdulillah 3al salameh :D♥