وَقُل رَّبِّ زِدْنِي عِلْمًا

PERIPHERAL NERVOUS SYSTEM

SUBJECT : Micro

LEC NO. : Lec4

DONE BY : Salsabeel almtour

Viral Encephalitis & Prions

بالبدايه المحاضره طويله
شوي بس مش صعبه ✓

اي اشي قرأه الدكتور حتلاقوه محدد باللون
او و الاشي اللي ما ذكره ما حددته

الاشي المهم كتبت عندو مهم يعني اللون مابعني
انو الاشي مهم بس حددت فيه لرووس الاقلام

Microbiology Lecture 4 PNS Module

يلا نبلش .....

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الجامعة الهاشمية
The Hashemite University

A 24-year-old male college student presents to the emergency department with a 3-day history of fever, severe headache, and progressive confusion. His roommate reports that he has been increasingly disoriented and has had several episodes of vomiting. The patient also complained of photophobia and neck stiffness. On examination, he has a temperature of 102°F (38.9°C), a heart rate of 110 beats per minute, and a blood pressure of 120/80 mmHg. He is disoriented to time and place. Nuchal rigidity is present, and there is no focal neurological deficit. A lumbar puncture is performed. CSF analysis: Opening pressure: Elevated, White blood cell count: 250 cells/µL (predominantly lymphocytes), Protein: Elevated, Glucose: Normal, CSF Gram stain: No organisms seen.

Which of the following is the most likely causative organism?

A. Herpes Simplex Virus (HSV)

B. Neisseria meningitidis

C. Streptococcus pneumoniae

D. Listeria monocytogenes

E. Cryptococcus neoformans

بما انو اغلب المعطيات بتدل انو المسبب
فايروس فالاجابه الصح حتكون A

بناءً على الاعراض اللي مذكوره (محدده بالاصفر) فالحاله
meningoencephalitis هون هي

بحالات ال meningitis وضع طبيعي يكون مرتفع

دليل على viral or fungus or mycobacterial infection but
مرتفعه WBCs بالاضافه انو ال it's not bacterial infection
شوي اما لو مثلاً مرتفعه كتير بالالف هون غالباً بكتيريا

اغلبهم بكون مرتفع البروتين كتير ما عدا ال virus بكون slight elevation

كلهم ال glucose بكون decreased عدا ال virus بكون تقريباً normal

Aseptic meningoencephalitis

VIRAL INFECTIONS IN THE CNS

Aseptic meningitis

– inflammation of meninges with sterile CSF

Encephalitis

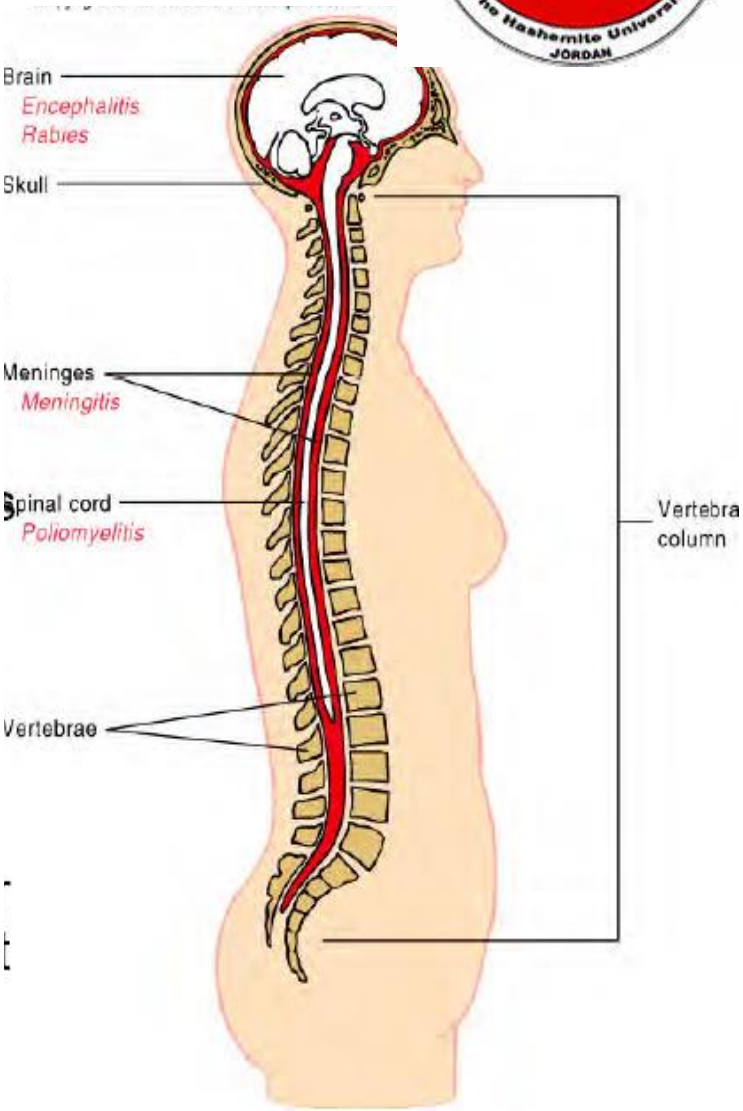
– infection of the brain parenchyma

Meningoencephalitis

– inflammation of brain + meninges

Myelitis

– inflammation of the spinal cord



What is encephalitis?

- Encephalitis is an inflammation of the brain tissue due to infection.
- Most often caused by viruses that pass the blood stream into the CSF leading to destruction of neural cells and inflammation of brain parenchyma.
  - Primary or acute encephalitis
- May also result from a viral-mediated inflammatory response in the brain following an acute, systemic infection.
  - Secondary or post-infectious encephalitis

🙂 we need to know it هاد السلايد مش محط للاسئله لكن

Secondary or post infectious encephalitis

- Subacute sclerosing panencephalitis (defective strains of hypermutated measles virus) لازم يكون hypermutated
  - CNS involvement (encephalitis) due to cytotoxic (CD8) T-cells which react with virus infected cells. بصير بعد سنوات بحيث انو previously infected cells ال at certain point of time بتطلع ال ag تاع ال measles على سطحها فبتتعرف عليه ال immune cells و بالتالي SSPE
  - SSPE (1 in 100,000) chronic measles virus infection to CNS. SSPE: personality change, intellectual deterioration, myoclonus, spasticity, tremor and ocular abnormalities
  - Occur 2-10 yrs after infection. No treatment
- Progressive postrubella panencephalitis
  - Mimics SSPE, very very rare, 6 months – 4 yrs (after infection)
  - Associated with either persistent rubella virus infection of the CNS or late sequalae of congenital rubella infection which manifests in adults. (الها نوت بالسلايد اللي بعدو)
- Progressive multifocal encephalopathy (polyomavirus JC)
  - Subacute degenerative disease of the brain found in:
    - Immunosuppressive disease: AIDS and hematologic malignancies
    - Disease requiring immunosuppressive therapy
  - No specific treatment, 50% Mortality
- Persistent Enterovirus infection
  - Seen in patients with congenital or acquired immunodeficiency where they develop chronic CNS infection
  - Headache, confusion, lethargy, seizure and CSF pleocytosis.
  - Temporary improvement with type specific immunoglobulins, relapse on withdrawal

هلاء المرأه اذا كانت pregnant و نصابت بال rubella فهون حينتقل لل fetus by vertical transmission و حيصير عندي(2 outcomes) للطفل :

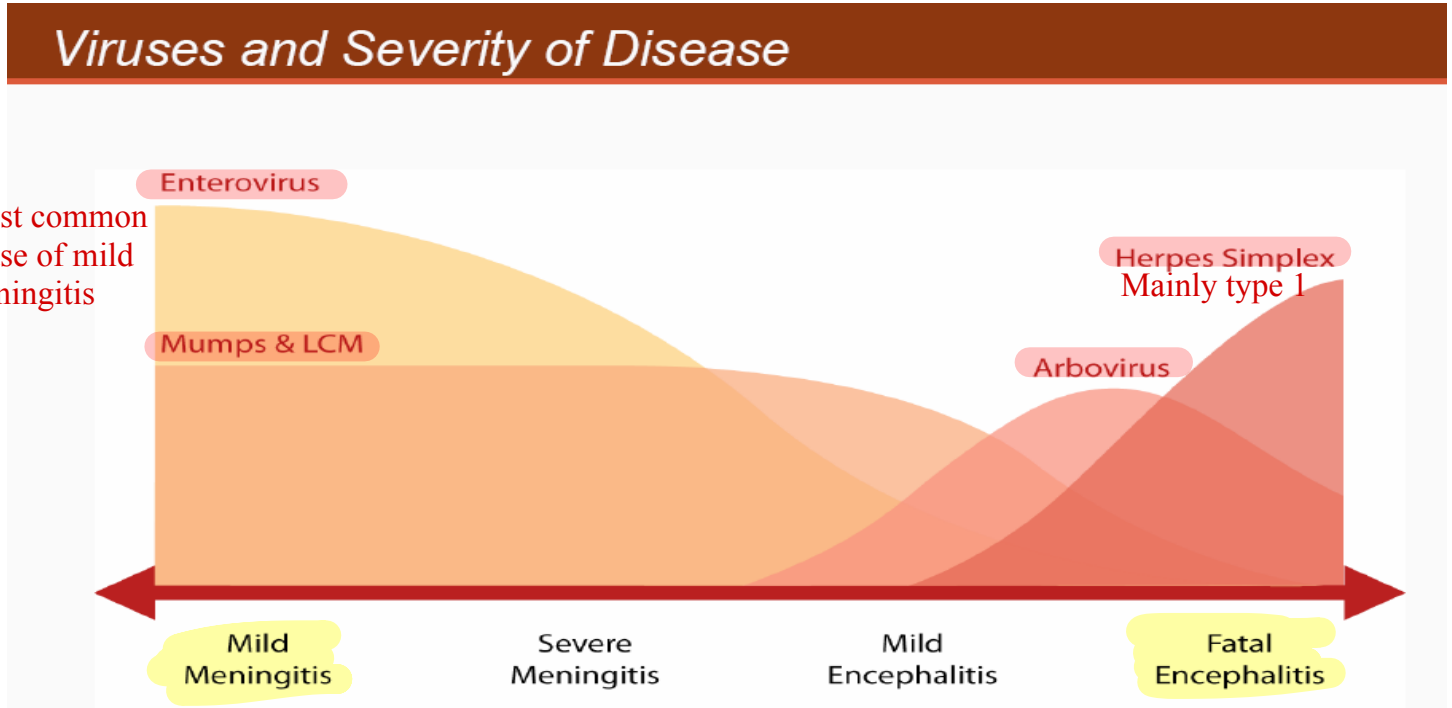
✓ اما persistent rubella واللي تحدث لسبب غير معروف بحيث بضل الفايروس يعمل replicating and shedding for a long period of time تصل للخمس سنوات من عمرهم

✓ او اللي ما بضل persistent عندهم ف بصير عندهم ال late sequalae of congenital rubella و ال mechanism بتكون نفس ال SSPE

How to distinguish encephalitis from viral meningitis?

focal بشكل عام لو كان عندي neurological deficit مشاكل بال , level of conciseness هدول يعتبرو encephalitis than meningitis اكتر

- Unfortunately, the clinical syndromes and results of routine laboratory tests are typically nonspecific and often do not help distinguish encephalitis and viral meningitis.
- Patients may have symptoms of both parenchymal and meningeal processes.
  - i.e., A patient with stiff neck and photophobia, though classic signs of meningitis, could in fact also have encephalitis! (called Meningoencephalitis)



قرأ الجدول كامل

Encephalitis vs. meningitis

Constitutional symptoms	Encephalitis	Viral Meningitis
Fever	Yes	Yes
Headache, nausea, vomiting, lethargy	Yes	Yes
Photophobia, neck stiffness	No	Yes
Neurologic dysfunction		
Seizures	Yes	Minimal
Cranial nerve palsies, paralysis	Yes	No
Altered mental status (i.e. confusion, coma)	Yes	Minimal

VIRAL MENINGITIS / ENCEPHALITIS

HERPESVIRIDAE

- Herpes simplex — Type 1 cause encephalitis; Type 2 cases meningitis
- Varicella-zoster
- Epstein Barr
- Cytomegalovirus

PARAMYXOVIRIDAE

- parainfluenzae
- Mumps
- Measles

MISCELLANEOUS

- Adenoviridae
- Rhabdoviridae
- Retroviridae (HIV)

ENTEROVIRUS

- **Polioviruses**
- **Coxsackie viruses**
- **Echoviruses**

Arboviral (Arthropod-borne Viral):

ما عنا ttt لالهم بس بعضهم الهم vaccine

1) TOGAVIRIDAE

- **Eastern equine**
- **Western equine**
- **Venezuelan equine**

have the same كلهم characteristics and structure و ال outcomes و من اسمهم بنلاحظ انو بختلفوا بال geographical location where the virus was first isolated

2) FLAVIVRIDAE

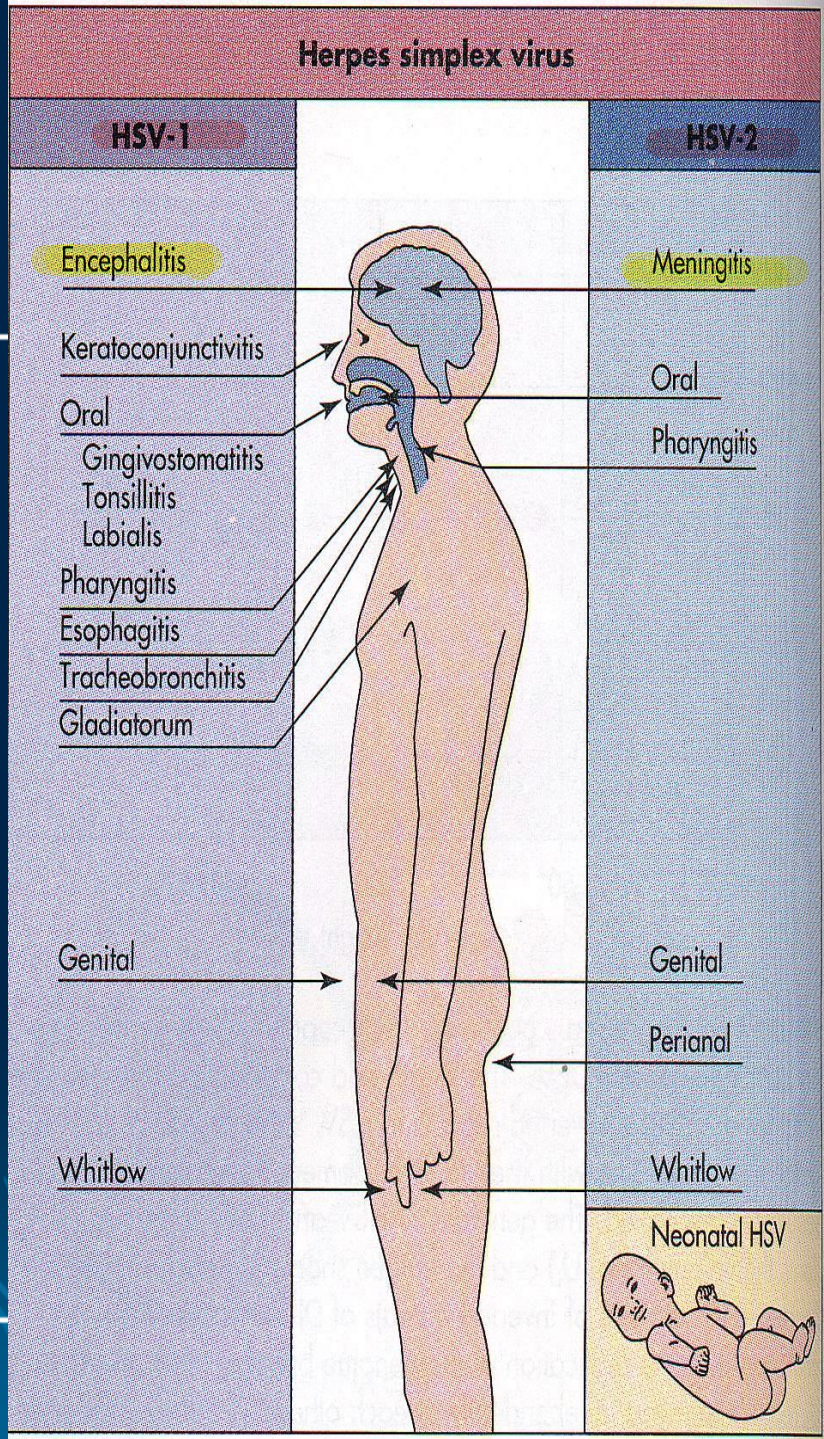
- **St. Louis**
- **West Nile**
- **Murray valley**
- **Powassan**
- **Japanese B**

3) BUNYAVIRIDAE

- **California**

Herpesviridae

1-Herpes simplex virus type -1	HSV-1
2-Herpes simplex virus type -2	HSV-2
3-Varicella –Zoster virus	VZV
4-Epstein- Barr virus	EBV
5-Cytomegalovirus	CMV
6-Human herpes virus type-6	HHV-6
7-Human herpes virus type-7	HHV-7
8-Human herpes virus type-8	HHV-8



Herpes Simplex Encephalitis

Have no vaccine

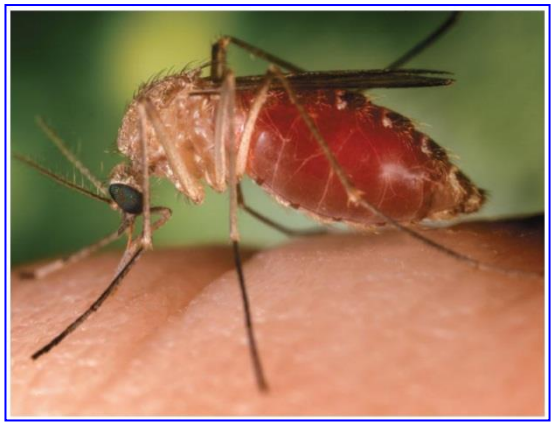
- Herpes Simplex encephalitis is one of the most serious complications of herpes simplex disease. There are two forms:
- Neonatal – there is global involvement and the brain is almost liquefied. The mortality rate approaches 100%.
- Focal disease – the temporal lobe is most commonly affected. This form of the disease appears in children and adults. It is possible that many of these cases arise from reactivation of virus. The mortality rate is high (70%) without treatment.
- It is of utmost importance to make a diagnosis of HSE early. It is general practice that IV acyclovir is given in all cases of suspected HSE before laboratory results are available.

ركزو ع هاي الفقره حسيتها مهمه

to prevent this from ال neonatal طريقة انتقاله هون بتكون من الام الpregnant للجنين و بهاي الحاله
late لو تم الكشف عن الام in early stage happening لحد الولاده اما لو acyclovir فهون بكون الاجراء انو نعطيها
Caesarean section and it is a clear contraindication for vaginal delivery فهون بنلجأ ل stage

The term ARBO is an abbreviation of "**AR**thropod **BO**rne".

Mainly mosquito



"Arbovirus" is the name given to Arthropod-borne viruses, that is, viruses that are transmitted to vertebrates, such as people and mammals, by blood-feeding insects called arthropods. Vertebrate infection occurs when the infected insect bites an animal or person and takes a blood meal.

Arboviruses

.

They can multiply in the tissues of the arthropod without evidence of disease or damage. The vector acquires a lifelong infection through the ingestion of blood from a viremic vertebrate.

All arboviruses have an RNA genome, and most have a lipid-containing envelope and consequently are inactivated by ether or sodium deoxycholate.

كيف بنتقل النا ؟ عن طريق انو بتيجي هاي ال arthropod vector على infected animal و
بتسحب منو a blood meal و هيك الفايروس بنتقل لهاي ال arthropod و بصير يتكاثر فيها
بدون ما يعمل فيها اي damage لحد ما تروح هاي ال arthropod و they bite the human
و هيك الانسان بنصاب بالفايروس و بنكون ال to take a blood meal end stage host

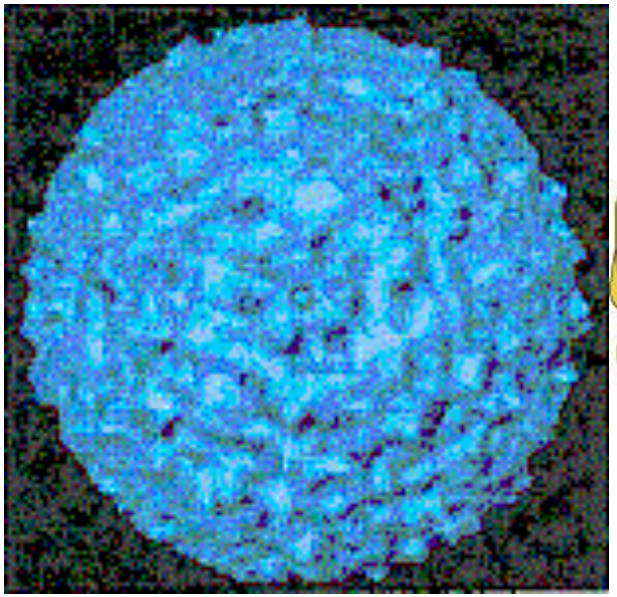
Diseases Caused

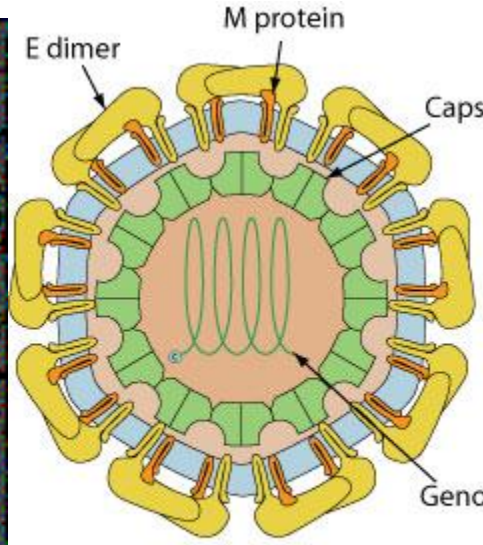
- Fever and rash - this is usually a non-specific illness resembling a number of other viral illnesses such as influenza, rubella, and enterovirus infections. The patients may go on to develop encephalitis or hemorrhagic fever.
- Encephalitis - e.g. EEE, WEE, St Louis encephalitis, Japanese encephalitis.
- Haemorrhagic fever - e.g. yellow fever, dengue, Crimean-Congo haemorrhagic fever.

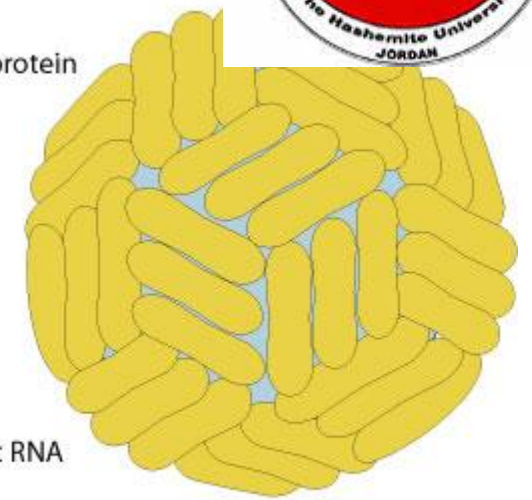
Both have vaccine

Lead to internal bleeding that will cause multi organ failure >death

Structure of Flaviviruses

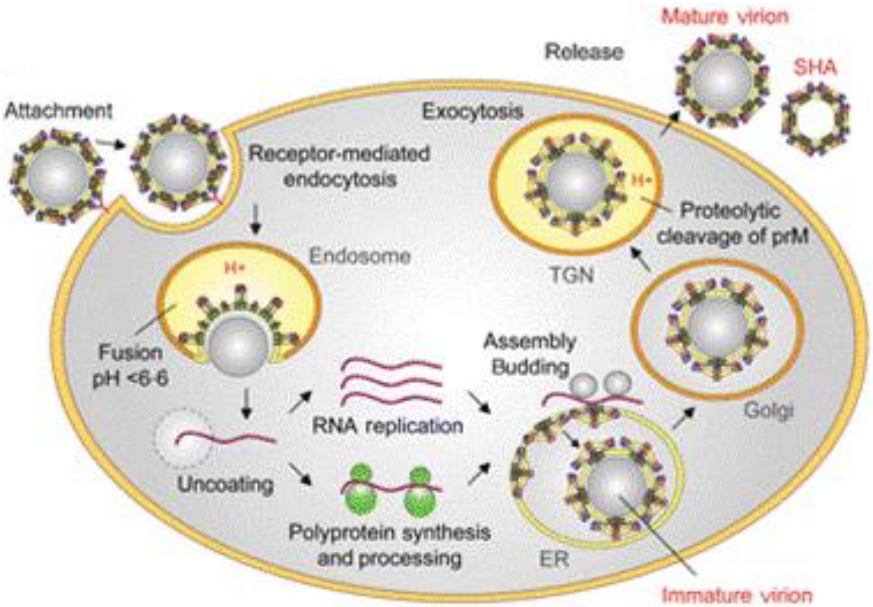






T=3-like organization of surface dimers

Positive sense, single stranded, enveloped RNA viruses with icosahedral capsid.



الجدول هاد و اللي بعدو قرأ اغلب الاشياء

Principal medically important Flaviviruses

Virus	Antigenic Clinical Syndrome	Vector	Host ركز انها جايه من animals بشكل عام و birds غالباً	Distribution
Murray valley	Encephalitis	Mosquito	wild water birds	Australia
Powassan	Encephalitis	Tick	Squirrels snowshoe hare Rabbit	Canada
St. Louis encephalitis (SLE)	Encephalitis	Mosquito	Birds	Americas

Principal medically important Flaviviruses

Virus	Antigenic Clinical Syndrome	Vector	Host	Distribution هون ما قرأ هدول بس حكى geographical في variation
Japanese encephalitis (JE)	Encephalitis	Mosquito	Pigs, birds	India, China, Japan, South-East Asia
West Nile	Febrile illness or encephalitis	Mosquito	Birds	Africa, Middle East, Europe
Tick-borne encephalitis (TBE)	Encephalitis	Tick	Rodent	Europa, Asia

Have no vaccine

Symptoms : West Nile virus

80-90% who get infected or bitten by a mosquito do not develop any symptoms and they develop immunity

- Most people do not develop symptoms
- An estimated 20% become ill 3-15 days after being bitten
  - Mild illness: fever, headache, body aches, and sometimes skin rash and swollen glands
- An estimated 1 in 150 persons infected develop a more severe form of the disease
  - West Nile encephalitis: inflammation of the brain, high fever, stiff neck, stupor, disorientation, coma, tremors, convulsions, muscle weakness, and paralysis; few cases have been fatal

(It is self limited and there is a chance for death in immunocompromised pt + extremities of age + preexisting conditions)

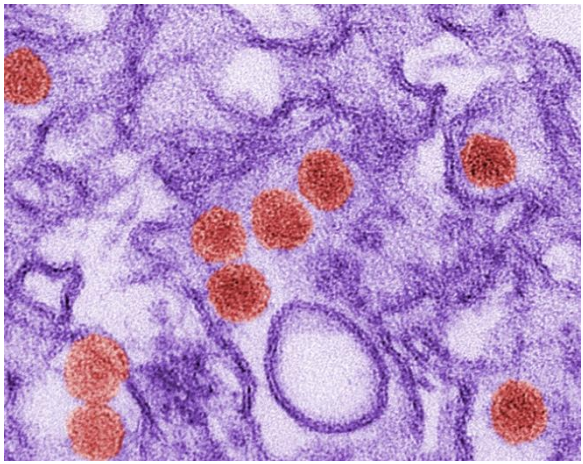
بالاغلب بال pregnant women و ازا
مش pregnant فاغلب الحالات
subclinical و لو طلع اعراض بتكون
very mild

Zika Virus

- Genus *Flavivirus*
  - Closely related to West Nile Virus, dengue, Yellow Fever viruses
- Epidemiology من زمان هاد الفايروس موجود
  - 1947: 1st isolated in Uganda
  - 2013: 1st large outbreak in French Polynesia (>28,000 cases)

The last outbreak

  - 2015: Large outbreak in S. America
    - Over 30 nations reporting local transmission
    - >1.5 million cases estimated in Brazil alone



Mostly in brazil and mexico

Transmission

- Mosquitos
  - *Aedes aegypti*
  - *Aedes albopictus*
  - Also transmit dengue and Chikungunya viruses
- Maternal-Fetal
  - Intrauterine and perinatal
  - Sexual transmission reported
  - Other possible routes
    - Bloodborne
    - Organ or tissue transplantation

مشكلة هاد الفايروس انو بنتقل من الام الحامل للجنين ف بصير عنا new borns بال anomalies

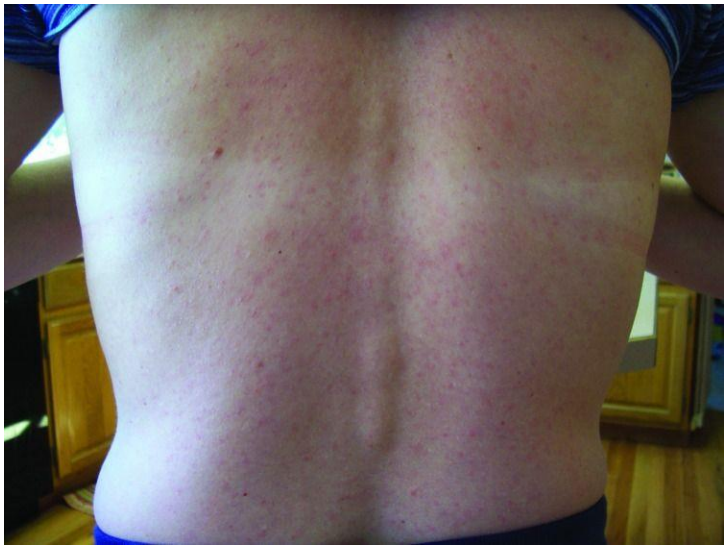
Bite from an Aedes mosquito

Blood transfusion

Sexual contact

Zika Virus Clinical Disease

- ~80% of individuals are asymptomatic
- Clinical illness is usually mild
  - Fever
  - Conjunctivitis
  - Maculopapular rash
  - Myalgia and headache



- Symptom duration: 2-7 days
- Hospitalization is uncommon and fatalities are rare

It is self limited

No antiviral drug for zika virus

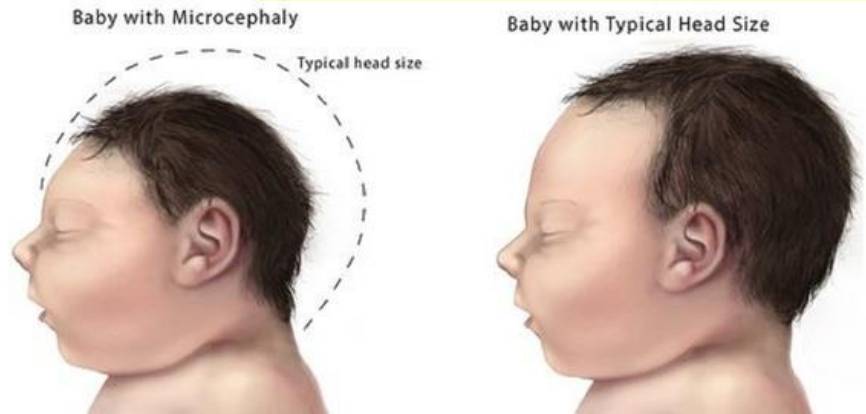
What do they develop in new borns :

Sequelae Associated with Zika Virus Infection

- **Microcephaly** Small head with distinct shape
  - 20X increase in babies born with microcephaly in Brazil since start of Zika virus outbreak
  - Zika virus was confirmed in some of these infants
  - CDC recommendation to postpone travel if pregnant

(Before travel to brazil and these countries)

- **Guillain-Barré Syndrome (GBS)**
  - Acute illness producing a lower, bilateral, symmetrical sensorimotor deficit.
  - Typically a history of infection prior to development of GBS
  - Incidence of GBS increased in all countries with Zika virus outbreak
  - Research ongoing to directly link GBS with Zika virus



Zika virus vaccine

من بعد ال outbreaks اللي صارت لل zika بلشو يحاولو يعملو
الو vaccine فلما اجى ال Covid-19 المطعوم اللي انعمل إلو
M-RNA based vaccine فعلياً هاد الابحاث كانت شغاله عليه
لل zika virus من قبل فهاد اللي خلاهم يطورو المطعوم لل
Covid-19 بشكل اسرع فالفكره انو ال zika لسا لحد الان شغالين
على المطعوم تاعو ولسا ما الو vaccine

nowadays we have clinical trials for a حالياً
vaccine for zika virus in a different bases
M-RNA based /Viral vector based / inactivated
بس هل في عنا اي approved vaccine for zika؟ للان لايوجد

لكل ال arbovirus

Diagnosis, Treatment and Prevention

- Exposure history and laboratory testing (الها نوت بالسلايد اللي بعدو)
  - NAAT for detection of Zika virus RNA
    - Specimens: serum, amniotic fluid, CSF, tissue (Looking for the virus in them)
    - Short duration of viremia (2-3 days)
  - Serology (IgM and IgG antibodies) (against a specific Ag in these viruses)
- Treatment: specific كلهم ما الهم antiviral ttt
  - Supportive care only
- Prevention: حكينا ال yellow fever وال dengue و vaccine هدول إلهم Japanese encephalitis
  - Vaccine اما ال zika ما الو vaccine
  - Avoidance of mosquito bites

Exposure history

بنشوف ازا في bite ل mosquito عند ال Pt و ال area اللي جاي منها
المريض لانو بالعاده ما بتيجي حاله وحده بكونوا عشرات او مئات الحالات زي
مثلاً بال west nile جاين كلهم مع بعض بشتكوا من نفس الاعراض

طيب هل حالياً ممكن يصير مثلاً outbreaks لل west nile بامريكا بال spring
and summer؟ yes ممكن يصير و بيجوا زي ما حكينا بمئات الحالات و لسا
subclinical بكونوا اكتر لانو اغلب الحالات

هدول ال 3 سلايدات (هاد و التنين الجاين)برضو لل arbovirus بشكل عام

Diagnosis

مش كتير معتمدين للوصل لل diagnosis

- Serology - usually used to make a diagnosis of arbovirus infections.
- Culture - a number of cell lines may be used, including mosquito cell lines. However, it is rarely carried out since many of the pathogens are group 3 or 4 pathogens.

- Direct detection tests - e.g detection of antigen and nucleic acids are available but again there are safety issues.

لما نشتغل فيهم they need to be done
in a biosafety level 3
لانهم عم ياخدو fresh sample

Prevention

- Surveillance - of disease and vector populations

نحصي الحالات و نحدد الاماكن اللي بتصير فيها outbreaks ال

- Control of vector - pesticides, elimination of breeding grounds

زي المستنقعات و المسطحات المائيه

- Personal protection - screening of houses, bed nets, insect repellants. When possible, wear protective clothing while outdoors.

خصوصاً بالمناطق الامريكيه الحاره زي ال south west states

- Vaccination - available for a number of arboviral infections e.g. Yellow fever, Japanese encephalitis, Russian tick-borne encephalitis

Treatment

- No specific therapy
- Arboviral encephalitis treated by hospitalization, intravenous fluids, respiratory support, prevention of secondary infections, and good nursing care

Supportive ttt only

- Aspirin and ibuprofen should be avoided because they increase the risk of bleeding

لانو في بعضهم حكينا بعملو hemorrhage فلازم
ننتبه لل non steroidal drugs

1. A 68-year-old woman presents to the neurology clinic with a 6-month history of progressive memory loss, confusion, and personality changes. Her family reports that she has become increasingly forgetful and irritable. Over the past month, she has developed myoclonic jerks and has had several falls. On physical examination, she is disoriented and has generalized myoclonus. There are no signs of meningismus. A brain MRI shows hyperintensities in the caudate nucleus and putamen on T2-weighted images. EEG shows periodic sharp wave complexes. Which of the following is the most likely diagnosis? *

- Alzheimer's Disease
- Vascular Dementia
- Creutzfeldt-Jakob Disease
- Lewy Body Dementia
- Normal Pressure Hydrocephalus

Prion diseases in humans :

✔Creutzfeldt-jakob disease

✔ fatal familial insomnia

✔ Kuru. (عقولة الطلاب كوري كوري😂)

✔ Gerstmann-Straussler-Scheinker Syndrome

Prions

Prions are rather ill-defined infectious agents believed to consist of a single type of protein molecule with no nucleic acid component.

Confusion arises from the fact that the prion protein & the gene which encodes it are also found in normal 'uninfected' cells.

These agents are associated with diseases such as Creutzfeldt-Jakob disease in humans, scrapie in sheep & bovine spongiform encephalopathy (BSE) in cattle.

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

1. Sporadic (85 %)

In the sixth or seventh decade, rapidly progressive (death in less than a year)

مشروحه بسلايد 46 نقطه 2 Creutzfeldt-Jakob disease (CJD) Classic CJD

2. Familial (inherited-15%)

Prion protein

Mutations in the PrP gene that favour the transition from the cellular form to the pathological form of PrP

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)

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

مشروحه برضو بسلايد 46 نقطه 1

Transmissible spongioform encephalop (TSE)=prion disease

A group of progressive conditions that affect the brain and nervous system of humans and animals and are transmitted by prions

The pathology: vacuolar degeneration, neuronal loss, astrocytosis and amyloid plaque formation

الشكل الطبيعي لل prions يكون a-helix PrPc فلما يصير abnormal بصير B-sheets PrPsc ف it form aggregate
وبتتحول ل amyloid plaques بالتالي it loses its function or gain toxicity

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 PrP^{Sc})

There is no cure

نوت اضافي للفهم :
prion infections do not stimulate adaptive immune responses in infected individuals
Because prions seem to be essentially composed of a protein PrP(Sc), identical in sequence to a host encoded protein PrP(C), the specific immune system displays a natural tolerance.

الدكتور جابها بالامتحان و سأل شو ال definitive diagnosis لل prion diseases
فمهم نعرف انو ما الو دخل موضوع انو ال prion disease ما بعمل immune
او ما بعمل response بموضوع انو ال inflammation الو definitive diagnosis
هو ال immunostaning

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 اكل لحوم البشر

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?

Proteins normally are digested down to amino acids in the gut مشروحه لقدام

Hypothesis: They circumvent the normal process of intestinal absorption by passing into the the Gut-Associated Lymphoid Tissue (GALT)

autoclave ال و disinfectant للحراره وللل prion disease resistant ال
فحنشوف انو احدى طرق ال transmission هي ال iatrogenic فكانوا زمان لما
neurosurgical procedure يجوا يعملو
They autoclave the instrument and they reuse it once again but then they found out that the next pt got infected with the prion disease as a result
برضو autoclave لل resistant بالتالي عرفوا انو

حالياً صرنا نغير معيار ال autoclaving بحيث صرنا نرفع درجة
الحراره اكثر و نزيد الضغط و ال duration لل autoclaving اللي
might be beneficial in getting rid of prion disease

ما قرأ هاد السلايد بس تقريباً ذكرنا كلشي فيها

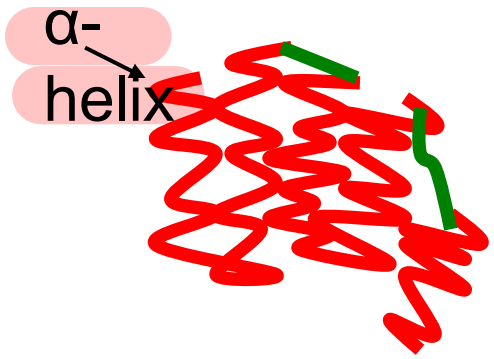
Protein misfolding diseases

Arise from abnormal conformation of specific proteins

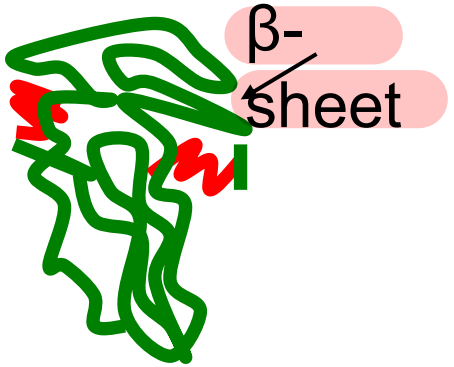
Principle: Proteins can adopt an aberrant conformation that cause disease; two mechanisms must be considered: loss of function of the native protein or gain of toxic activity of the aberrant conformation

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



Conformational change



Normal protein (folded structure)

Disease-associated protein (misfolded structure)

Aggregation

Gain of toxic activity

Loss of biological function

Genetics of prion disease

Familial forms of prion disease are caused by inherited mutations in the PRNP gene على كروموسوم 20

Mutations in this gene cause cells to produce an abnormal form of the prion protein, known as PrP^{Sc}

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

الدكتور قرأ كل الجدول

PrP^{C}	PrP^{Sc}
The normal protein	The abnormal, disease-producing protein
is called PrP^{C} (for cellular)	Form of prion disease found in sheep 🐑 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

النظريه الحاليه بتحكي انو التلامس بين الPrPc و ال PrPsc
بحول ال PrPc الى ال abnormal PrPsc و هكذا بضل يتراكم
ال PrPsc و يتجمع و يعمل aggregation

Molecular models of the structure of

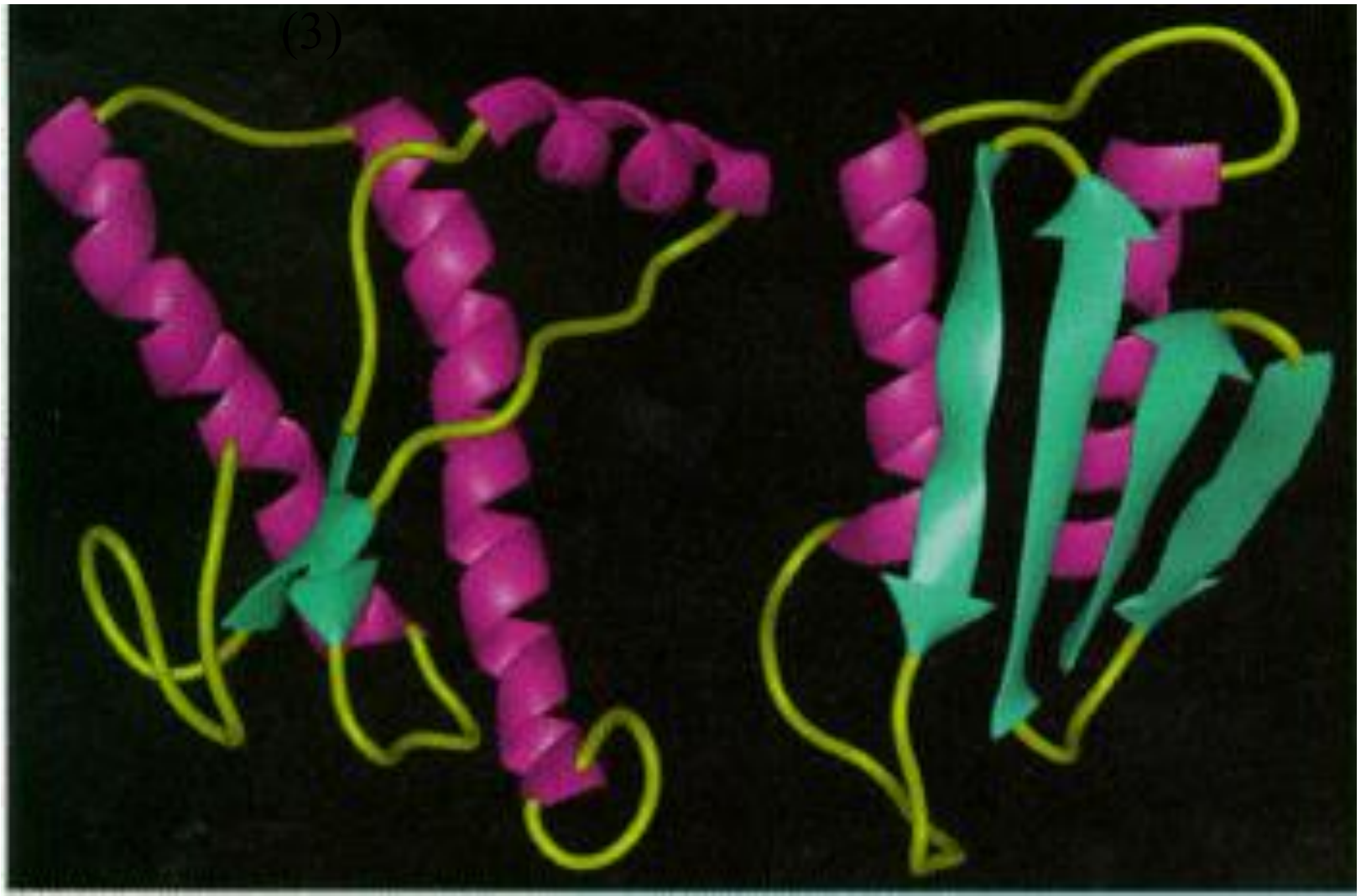
PrP^{C} https://youtu.be/AkN16QDCClg **PrP^{Sc}**

هاد الفيديو بلخص اغلب اللي حكيناه

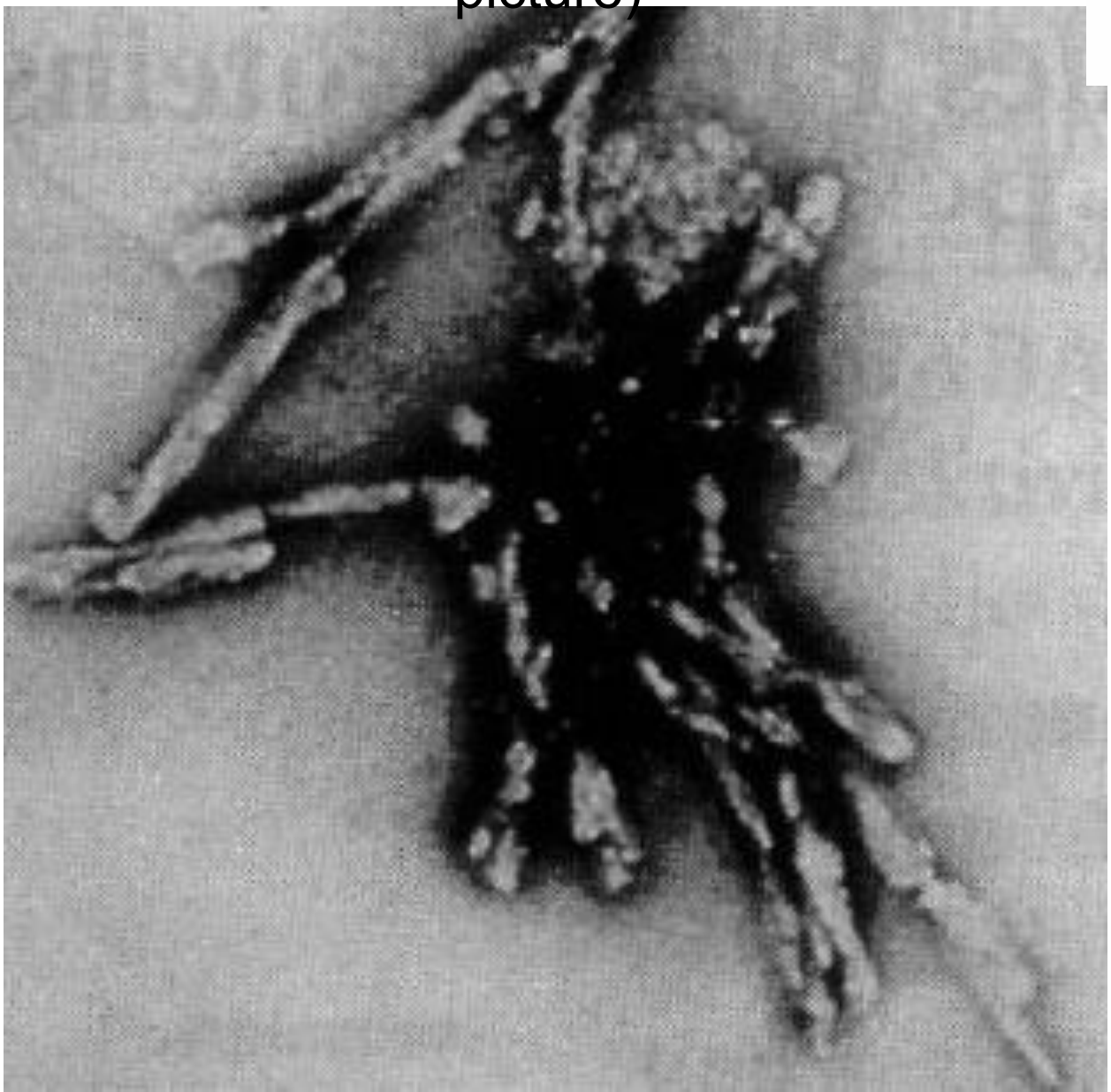
Predominantly α-helix

β-sheets (40%), α-helix (30%)

(3)



Prion aggregates (an electron microscope picture)



Aggregate of amyloid plaques

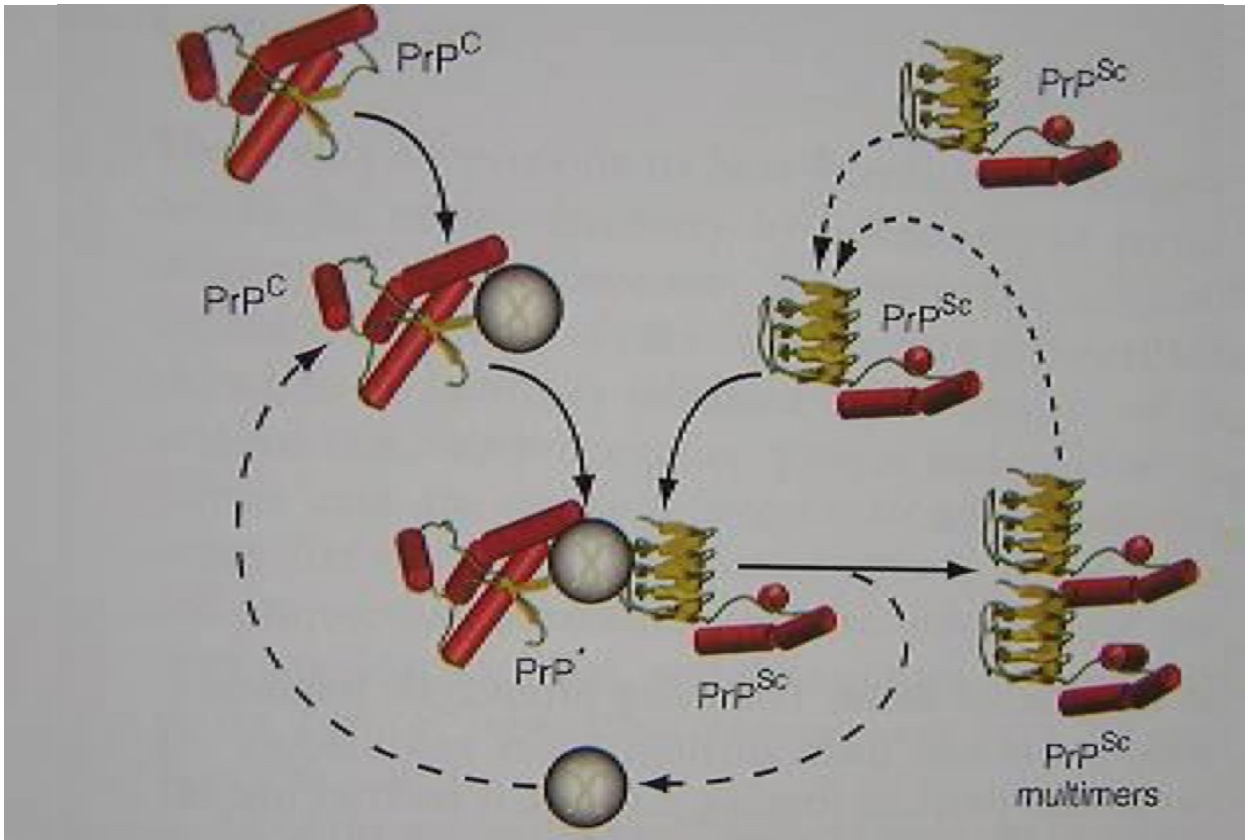
Replication cycle

ما قرأ الدكتور السلايد
بس نفس موضوع
التلامس اللي حكيناه

https://youtu.be/Xws0_I-xyOI?si=6O4xm9q4_5hwWZls
هاد الفيديو animation لطيف لفهم الموضوع

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

This first prion will initiate PrPSc accumulation by sequentially converting PrPC molecules into PrPSc



الدكتور ما قرأ عنو
بس حكى انو مرض
صار زمان وانتهى

Kuru

It's a disease of the past

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

بس الصراحه كتير
غريب موضوعه 😂

Is a prion disease incident in natives in New Guinea

(first noted in the early 1900s)

In 1950-60 epidemic

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 (vCJD occurs in younger people)

The duration of CJD is less than 1 year

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 No ttt

Forms:

1. Sporadic – most common
2. Familial – 5-10%
3. Transmitted: iatrogenic-iCJD - <1%

Through surgical instruments

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

Characteristic حسيت هاد الجدول مهم و ركز عليه الدكتور ونقرأ كامل	Classic CJD	Variant CJD
Median age at death	68 years	28 years
Median duration of illness Before death	4-5 months	13-14 months Max 2.5 years
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	بتختلف من شخص لاخر Variable accumulation of the PrP^{Sc}	Marked accumulation of the PrP^{Sc}
Presence of agent in lymphoid tissue الها نوت بسلايد47	Not readily detected	Readily detected
Presence of amyloid plaques in brain tissue	Often present	Often present

الدكتور سأل كيف ممكن نفرق بين ال classic و ال variant و هاي كانت الاجابات :

١ ال mad cow disease (bovine spongiform encephalopathy):

Mad cow disease is a severe neurological disease seen in cows. It causes damage to their brains and spinal cords.
usually People cannot get mad cow disease. But in rare cases they may get a human form of mad cow disease called variant Creutzfeldt-Jakob disease (vCJD) by Eating food contaminated with infected animal meat

contaminated meat :raw or well للحراره فلو كانت ال prion resistant و يعتبر ال cooked حتنتقل عادي

fatal. Over time vCJD destroys the brain and spinal cord.

٢ عند الكبار بالعمر بصير ال classic و اللي السبب بإنوا اغلب الحالات sporadic:

there is a chance يوجد بجسمنا طبيعي و هو كبروتين مش معروف شو وظيفته بالزبط لكن ال prions of introduction of mutation in prions with increase in age
structural and functional changes حيصير فيه prions بال mutation ما يصير في once بالتالي
B-sheets بصير abnormal يصير بس ف a- helix يكون structure واللي الطبيعي ال

Presence of agent in lymphoid tissue

حكينا انو ال prions لو انتقلو من بعد اكلنا ل steak 🥩 هون ال prions
حيدخلو جسمنا و يبلشوا يعمل aggregates واللي اصلاً resistant to
Proteases طيب احنا بنعرف انو اي بروتين عشان يعاد امتصاصه لازم نكسره
لاجزاء صغيره حتى نقدر ناخده طيب كيف ممكن هاي ال aggregates توصل
الدماغ و هي اصلاً ما قدرنا نعيد امتصاصها ؟ وجدوا انو بنتقل through the
lymphatics towards the CNS عشان هيك حنلاقيه بال lymphatic عند
vCJD ال

هاي نوت زياده لما ننسى انو ال prions مش بس
موجوده بالدماغ :

Normal prion protein is widely distributed throughout the body, but has its highest concentrations in brain, nerve, and related tissue.

Fatal familial insomnia

Inherited

- **Cause:**
  - There is a mutation in PRNP (codes for prion protein) on chromosome 20. This mutation makes the protein insoluble.
  - When it converts, the protein causes plaque to form in the thalamus, which is the region responsible for regulation of sleep.
- **Inheritance:**
  - The dominant gene responsible for FFI has only been found in 28 families worldwide.
  - 5 of these are in the U.S.
  - If only one parent has the gene, the offspring have a 50% chance of getting the disease.

Fatal familial insomnia

بصير عندهم ارق شديد

- **Symptoms/Signs of the Disorder**
- Four stages:

1. Increasing insomnia, paranoia, phobias (4 months)
2. 2. Hallucinations (5 months)
3. 3. Complete inability to sleep, rapid weight loss (3 months)
4. 4. Dementia; person becomes unresponsive/mute (6 months)
5. Death occurs between 7 to 36 months from onset.

- **Treatment/Prevention:**
  - There is no cure for Fatal Familial Insomnia.
  - Gene therapy has been unsuccessful so far.
  - Sleeping pills don't help; they can actually speed disease progression.
  - Some scientists believe that a cure could be found in the next 10-15 years.

مهم هاي النقطه
بحيث they tried modulating the gene 🧬 but it was unsuccessful

- **Prognosis**
  - Life expectancy ranges from 7 months to 6 years; with an average of 18 months

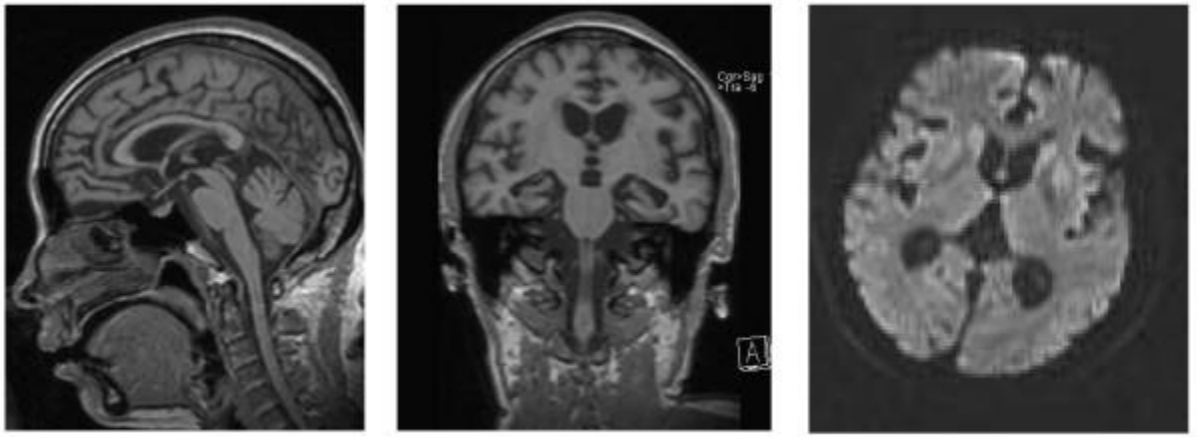
Gerstmann–Sträussler–Scheinker syndrome

- Cause:
  - There is a mutation in PRNP (codes for prion protein) on chromosome 20.
- Inheritance:
  - Autosomal-dominant gene
  - found in few families worldwide.

- Symptoms/Signs of the Disorder
  - slowly developing dysarthria (difficulty speaking)
  - cerebellar truncal ataxia (unsteadiness)
  - Progressive dementia
  - Loss of memory can be the first symptom of GSS.
  - Many patients also exhibit nystagmus (involuntary movement of the eyes), visual disturbances, and even blindness or deafness.

Gerstmann–Sträussler–Scheinker syndrome

- Diagnosis
  - Genetic testing to detect the mutated gene at certain codons.
- Treatment/Prevention:
  - There is no cure for GSS.
- Prognosis
  - Duration of illness can range from 3 months to 13 years with an average duration of 5 or 6 years



A B C

هون لل prions disease بشكل عام

مهم السلايد هاد

Diagnosis

- Gold standard: brain biopsy (histopathological examination and immunostaining for $PrP^{Sc)}$
- 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

all these are therapeutic strategies , some of them are not realistic and they did not make any progress towards doing farther research or to become applicable

Therapeutic strategies

We have no ttt or cure or vaccine
all the pt will eventually die

1. Compounds can be designed to specifically disrupt the replication cycle of the PrP^{Sc}

Design of such compounds had proven successful in cell-based models but must now be extended to animal models and human clinical trials

لو عرفنا شو اول منطقه ممكن يرتبط فيها ال abnormal مع ال normal و نعمللها ف block
progression in the early stages of disease بنقلل ال

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

لما يتحول البروتين من a-helix ل B-sheets تنكشف مناطق كانت مخبيه فيه ف ازا قدرنا نحدد هاي
الاماكن اللي صارلها expose حنقدر نعمل AB specific لالهم و بالتالي نتخلص منهم

3. Design of peptides that break the β-sheet structures

هاد ممكن كمان بس مشكلته انو ال B-sheets توجد ببروتينات تانيه
it might affect other proteins as will بالتالي

4. Gene therapy: modification of the prion gene

Genetic engineering research: cattle lacking a necessary gene for prion production - thus theoretically making them immune to BSE (December 2006)

بتمنى اكون فدتكم و ما تنسونا من صالح دعائكم .....🤍

Summary ملخص للافكار اللي حكيناها

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

The prions are expressed in cells of healthy humans and animals; their abnormal conformations (PrP^{Sc}) are insoluble, resistent to digestion and aggregate

The PrP^{Sc} attacks the native prion PrP^{C}, 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