Prions and Rabies

NSII Module

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Prions

- The **pr**ion **p**rotein **PrP**, also known as **CD230** (cluster of differentiation 230) is encodd by the ***PRNP*** (**PR**io**N** **P**rotein) gene on the short arm of chromosome 20
- They are Proteinaceous infectious particle that lacks nucleic acid.
- It is most predominant in the nervous system and in many other tissues throughout the body

Prions protein is a coin with two faces

Good face

Ugly face

The Good face of prions

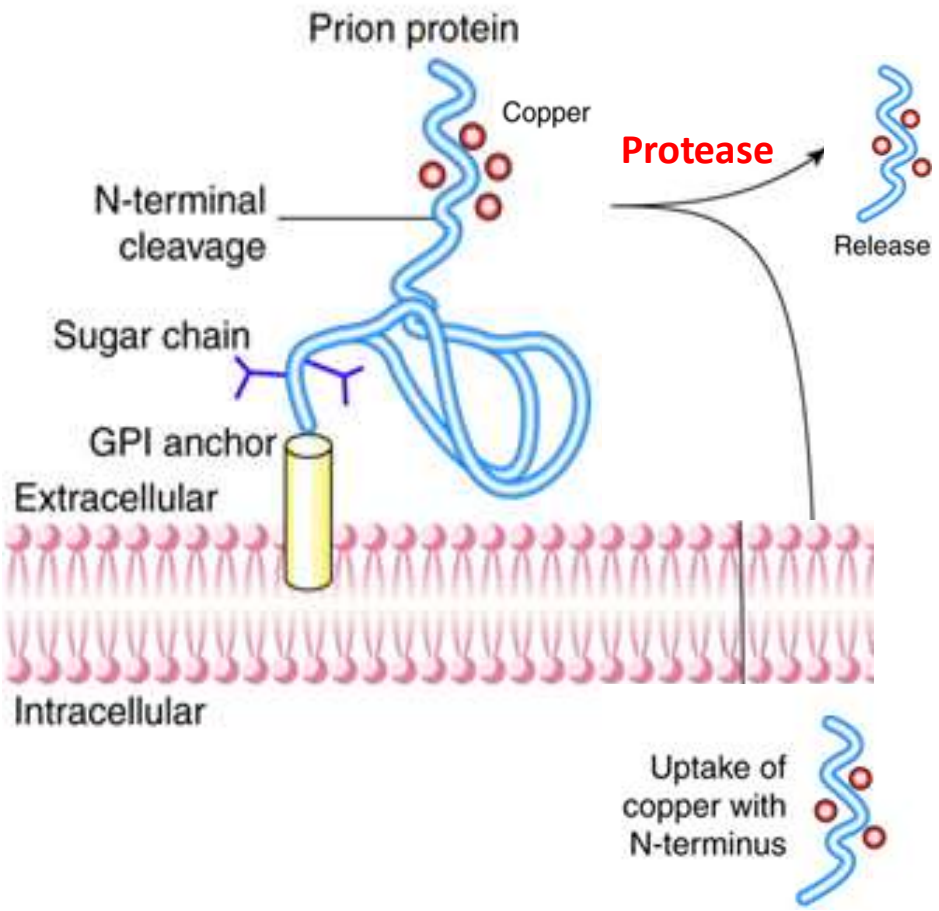
Prions have many essentail Funtions including:

- PrP protein is **important for myelin repair in Schwann Cells** and that the lack of PrP proteins caused **demyelination**.
- **Cell-cell adhesion and intracellular signaling**, and may therefore be involved in cell-cell communication in the brain.
- Maintenance of **long-term memory**
- The PrP expression on **stem cells is** necessary for an organism's **self-renewal of bone marrow**.
- Prions have **antioxidative** function epeciaplly in the at synapses which indiated a role in synaptic homeostasis.

The Good face of prions

Antioxidative function of Prions:

The amino-terminal domain of PrP^C exhibits five to six sites that bind copper Cu(II) which facilitate its uptake by cells



PrP^C + Cu (Copper)

↓

Copper is an important part pf Superoxide dismutase

(SOD)

↓

- SOD free radicals to hydrogen peroxide, which can

subsequently be reduced to water

- Prevent neuronal dysfunction

The ugly face of the prions

- During the 1960s **Stanley B. Prusiner** discovered the the caustive agents of bovine spongiform encephalopathy ("mad cow disease") and its human equivalent, Creutzfeldt–Jakob disease

- **The diseases are caused by Pro**teinaceous **in**fective particle
- It was called proin
- Proin changed to prion to sound it rhythmic.
- Prion diseases were caused by misfolded proteins.

The ugly face of the prions

Whatis the pattern of inheritance?

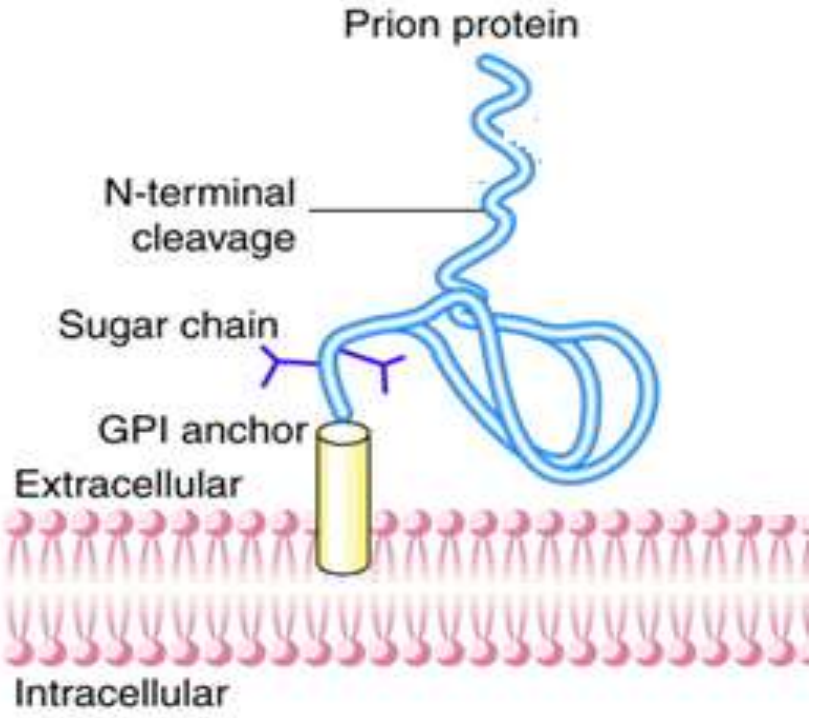
Familail

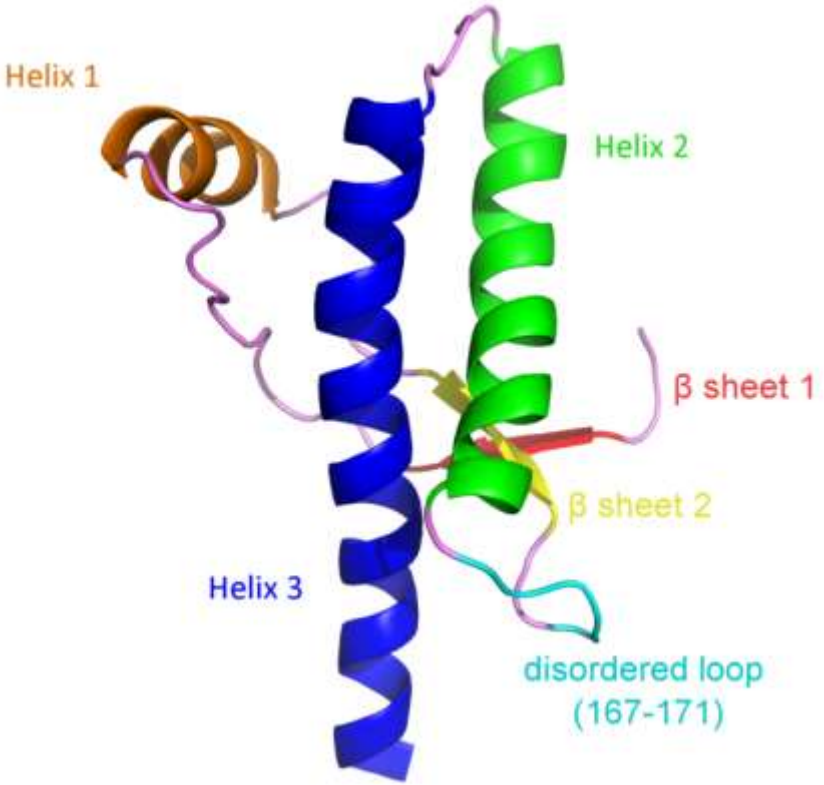
Familial spongiform encephalopathy
Fatal familial insomnia (FFI)
Familial Creutzfeldt–Jakob disease (fCJD)

Infectious

Kuru
Creutzfeldt–Jakob disease (CJD)
Gerstmann–Sträussler–Scheinker syndrome (GSS)
Sporadic Creutzfeldt–Jakob disease (sCJD)

Normal structure of the prion protein



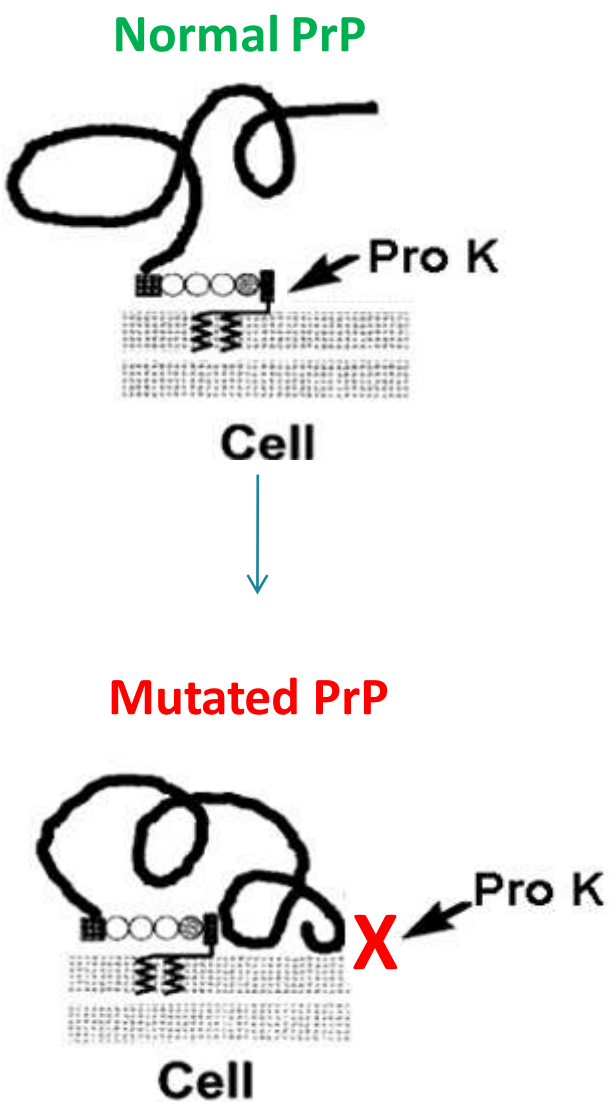


Generation of abormal structure of the prion protein

Prion proteins have an ability to undergo structural conversion from a normal "cellular" isoform (PrP^{C}) into a pathogenic conformer known as "scrapie" (PrP^{Sc})

Why is it called scrapie?

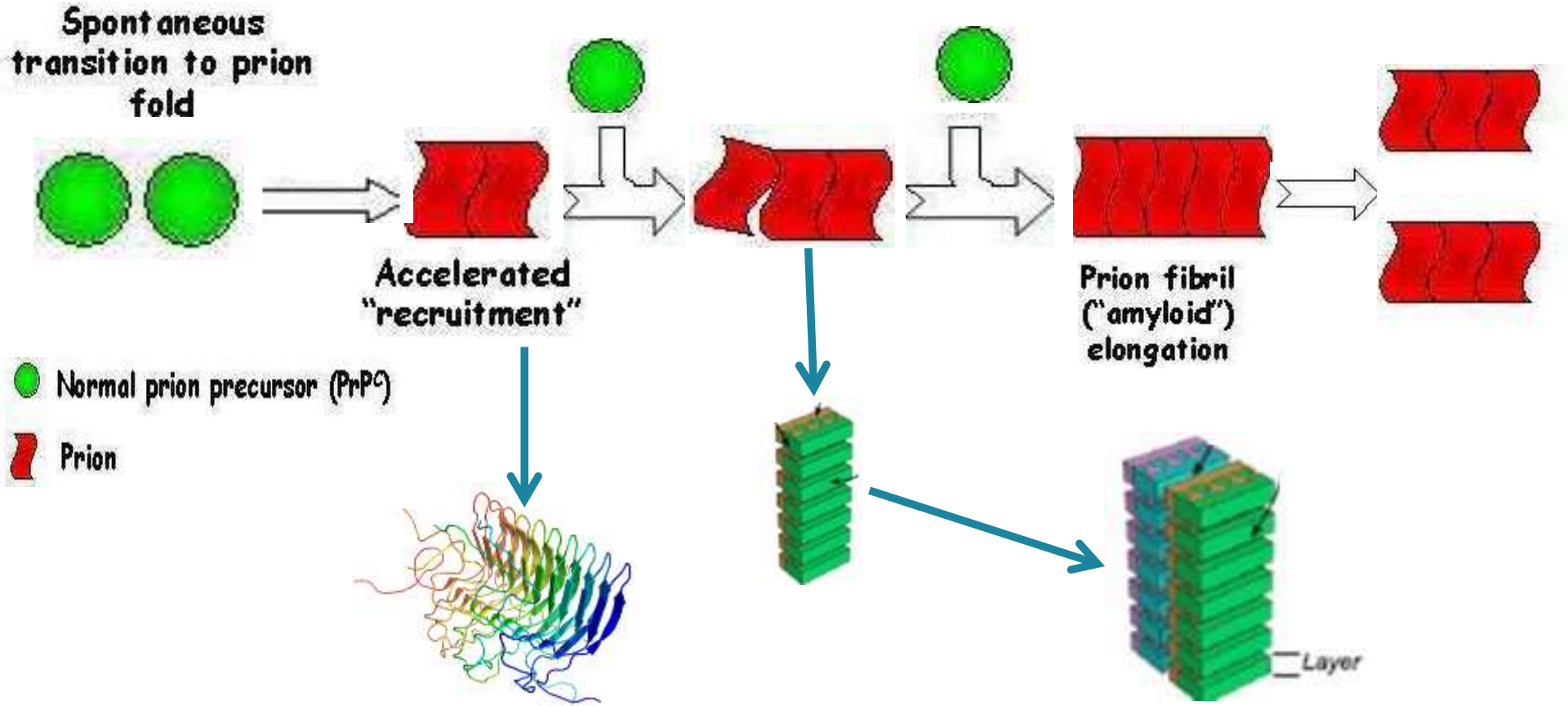
- The name scrapie is derived **from one of the clinical signs of the condition**, wherein affected animals will compulsively scrape off their fleeces against rocks, trees or fences. The disease apparently causes an itching sensation in the animals.



Generation of prions' amyloid

How does the prion replicate?

Lacking nucleic acid, **prions** cannot **reproduce**, but they reproduce by **recruiting the normal cellular isoform of the prion protein** (PrP^{C}) and stimulating its crefolding into PrP^{Sc} (**Sc**rapie)



Normal vs. pathologic struture of the prion protein

PrP^{C}	PrP^{SC}
Solubility	
Soluble	Non soluble
Structure	
Alpha-helical	Beta-sheeted
Multimerisation state	
Monomeric	Multimeric
Infectivity	
Non infectious	Infectious
Susceptibility to Proteinase K	
Susceptible	Resistant

Routes of Prion Transmission

- **Eating infected beef from cows carrying (BSE).**
- Kuru was transmitted from human to human by cannibalism (eating the brains of infected people).
- Oral, wound, and parenterally has been approved.
- Through surgical instruments or infected tissues. CJD transmitted by medical procedures is known as iatrogenic CJD.
- Body fluids such as blood or saliva.
- Corneal transplantation, contaminated EEG, electrode implantation, and surgical procedures.
- Dura mater grafts

Clinical course

- An incubation period of 1.5–2 years and it might reach 40 years years preceded the development of clinical disease.

- Most patients with CJD live 6–12 months after the onset of clinical signs and symptoms, whereas some live for up to 5 years.

Clinical features

- One third of patients with CJD develop:
  - fatigue, sleep disturbance, weight loss, headache, anxiety, vertigo, malaise, and ill-defined pain.
- Most patients with develop over weeks or months a state of profound dementia characterized by memory loss, impaired judgment, and a decline in virtually all aspects of intellectual function.
- A few patients present with either visual impairment or and coordination deficits.

Clinical features

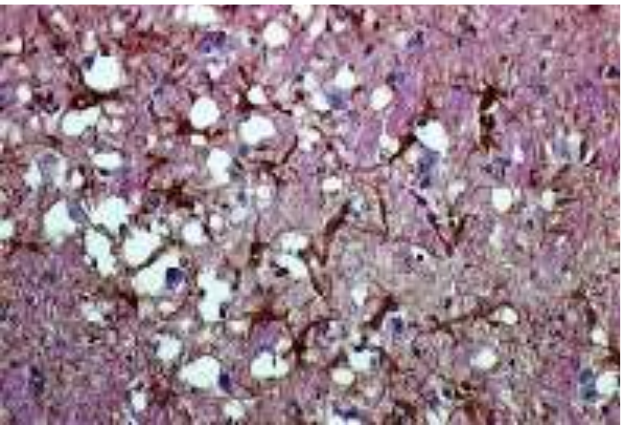
Other symptoms and signs include:

- Difficulty walking
- Hallucinations
- Muscle stiffness
- Confusion
- Fatigue
- Difficulty speaking

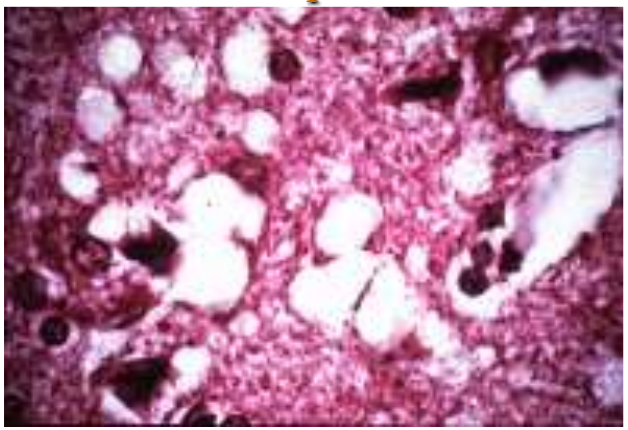
Diagnosis

- The most widely used method involves the detection of PrP by immunoassay after denaturation.
- **Brain biopsy** if PrPsc is detected.
- Magnetic resonance imaging (**MRI**).
- **At autopsy**, immunoassay and immunohistochemistry of tissue section.
- Sequencing of the PRNP gene must be performed.
- CT may be normal or show cortical atrophy.
- **CSF is nearly always** normal but may show protein elevation and, rarely, mild pleocytosis.
- **The EEG** is often useful in the diagnosis of CJD, although only about 60% of individuals show the typical pattern.

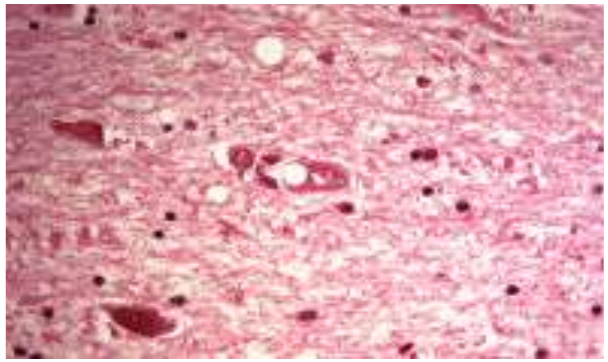
Microscopic changes



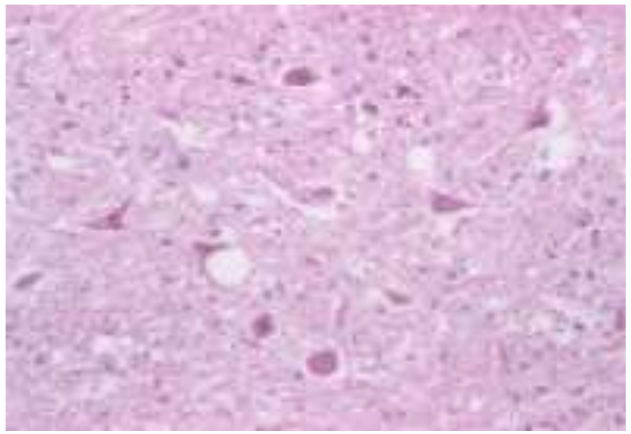
Scrapie

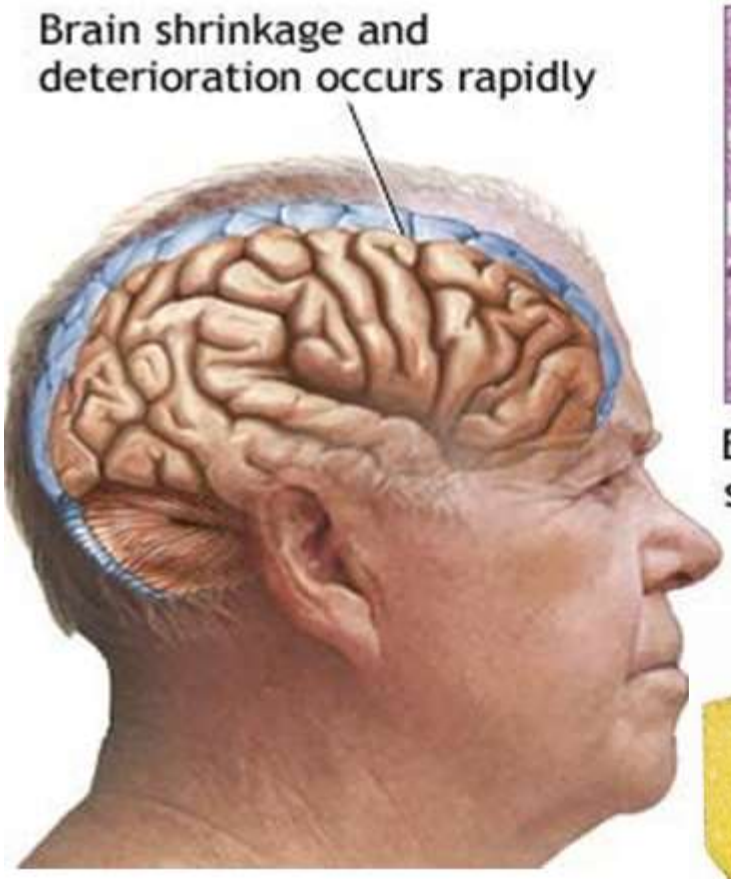


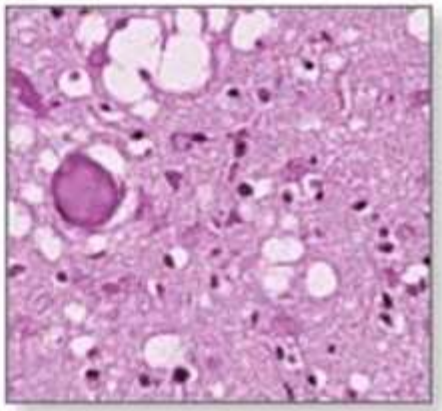
Kuru



CJD







Brain section showing spongiform pathology characteristic of Creutzfeldt-Jakob

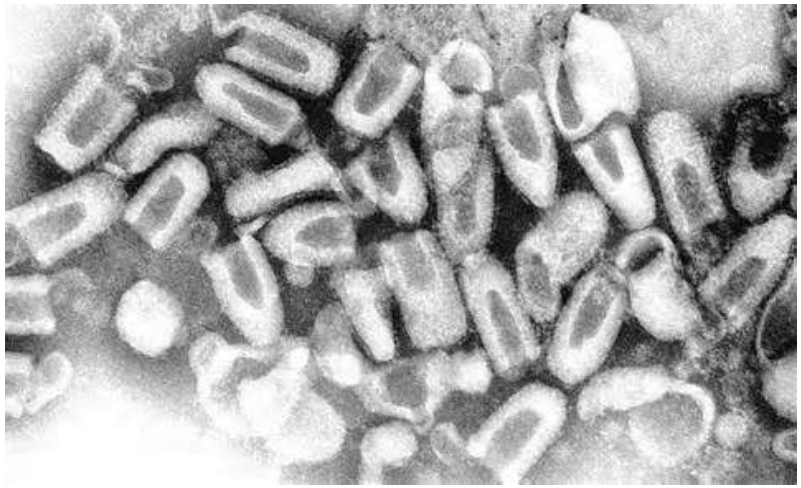
Treatment

- **There's no proven cure for Creutzfeldt-Jakob disease (CJD)**
- At present, treatment involves trying to keep the person as comfortable as possible and reducing symptoms through the use of medicines.

Rabies

Definition of Rabies

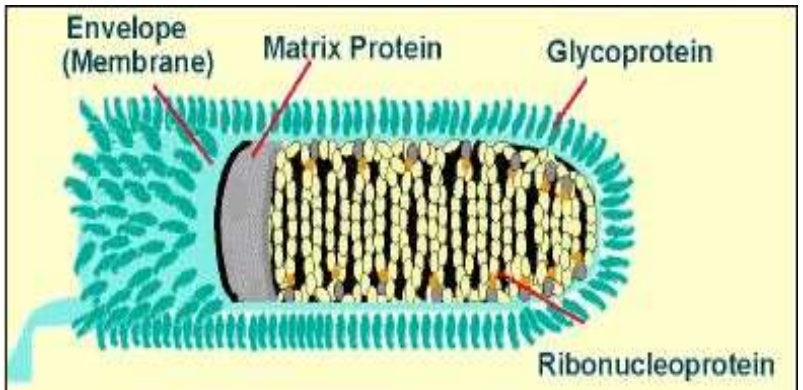
- Rabies is a preventable viral disease of mammals most often transmitted through the bite of a rabid animal
- Rabies is a rapidly progressive, acute infectious disease of the CNS in humans and animals.



Etiologic agent of Rabies

Main properties:

- Belongs to Rhabodoviruses family
- Single stranded negative sense RNA
- Has its own RNA-dependent RNA polymerase
- Surrounded by a bullet shaped capsid and a lipoprotein envelop
- Single antigenic type
- It has a broad range of hosts, all mammals basically but also birds, reptiles.



Rabies virions are bullet-shaped with 10-nm spike-like glycoprotein peplomers covering the surface. The ribonucleoprotein is composed of RNA encased in nucleoprotein -(), phosphorylated or phosphoprotein -, and polymerase -.

Virulence

- Depends on severity of bite
- If treatment is given and when
- Once the disease manifests in CNS: ultimate death

Factors do not constitute exposure

- Petting
- Handling an animal
- Contact with blood
- Contact with urine or feces

Types of exposure to Rabies virus

1. Bite :

- ✓ Any penetration of the skin by teeth constitutes a bite exposure.

2. Non-bite

- ✓ Exposure to large amounts of aerosolized rabies virus.
- ✓ The contamination of open wounds and mucous membranes.

3. Human-to-human transmission:

Human-to-human transmission has occurred among eight recipients of transplanted corneas.

Pathogenesis

1. **The incubation period:**
   - ✓ Usually 20–90 days
   - ✓ In rare cases is as short as a few days or is >1 year
   - ✓ Why there is a variation in the incubation periods?
2. **The mechanism of reaching the CNS:**
   - A. In neurons: rabies virus spreads toward the CNS via retrograde fast axonal transport to the spinal cord or brainstem at a rate up to ~250 mm/d
   - B. In muscles: the virus is known to bind to nicotinic acetylcholine receptors on postsynaptic membranes at neuromuscular junctions
   - C. Once the virus enters the CNS, it rapidly disseminates to other regions of the CNS via fast axonal transport along neuroanatomic connections

Pathogenesis

D. After CNS infection becomes established, there is centrifugal spread along sensory and autonomic nerves to other tissues, including the salivary glands, heart, adrenal glands, and skin.

E. Pathologic studies show mild inflammatory changes in the CNS in rabies, with mononuclear inflammatory infiltration in the leptomeninges, perivascular regions, and parenchyma.

F. Degenerative neuronal changes usually are **not prominent**, and there is **little evidence of neuronal death**.

Pathogenesis

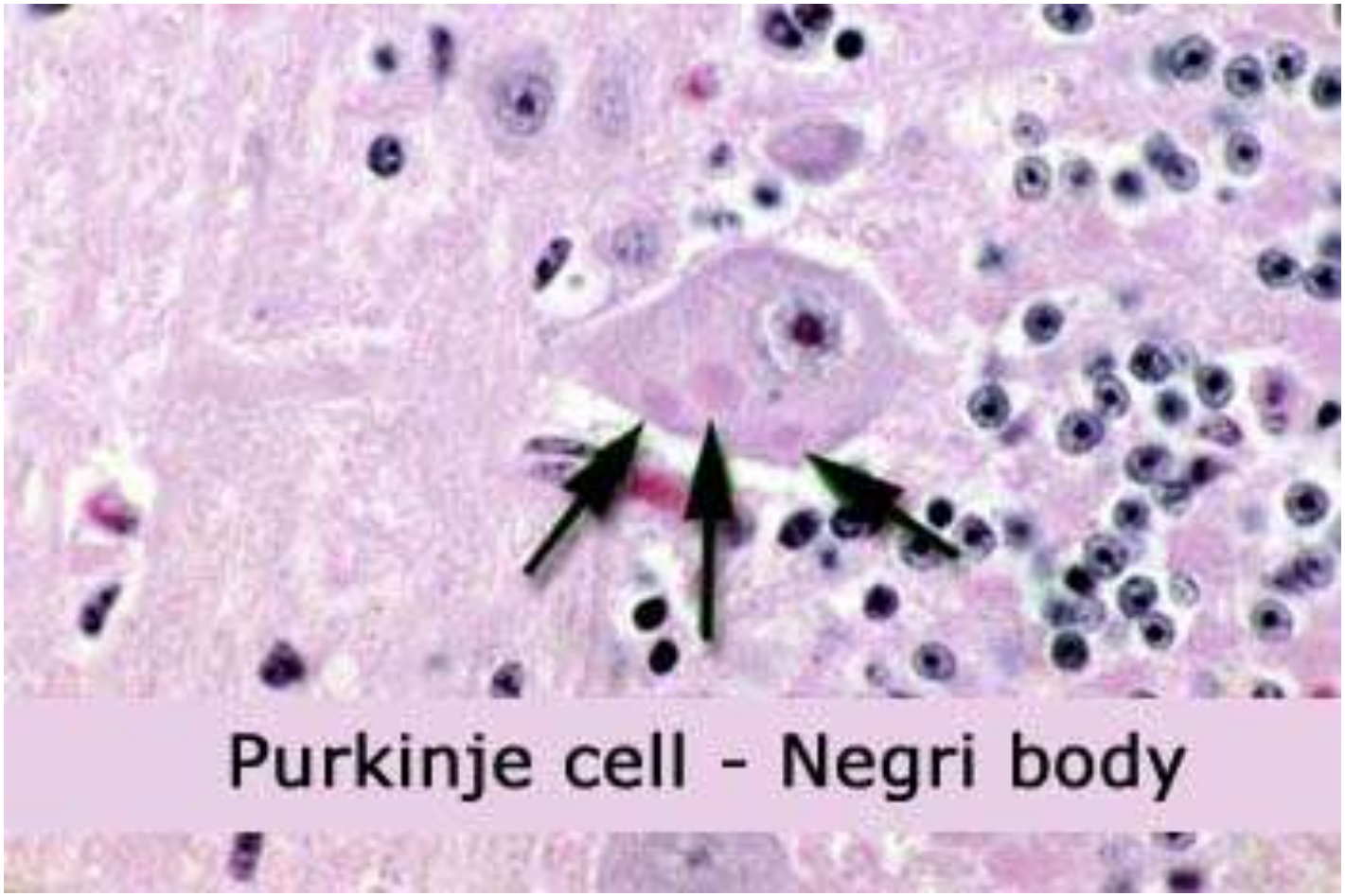
G. The pathologic changes are surprisingly mild in light of the clinical severity and fatal outcome of the disease.

H. The most characteristic pathologic finding in rabies is the *Negri body*.

I. Negri bodies are not observed in all cases of rabies.

J. The lack of prominent degenerative neuronal changes has led to the concept that neuronal dysfunction—rather than neuronal death—is responsible for clinical disease in rabies.

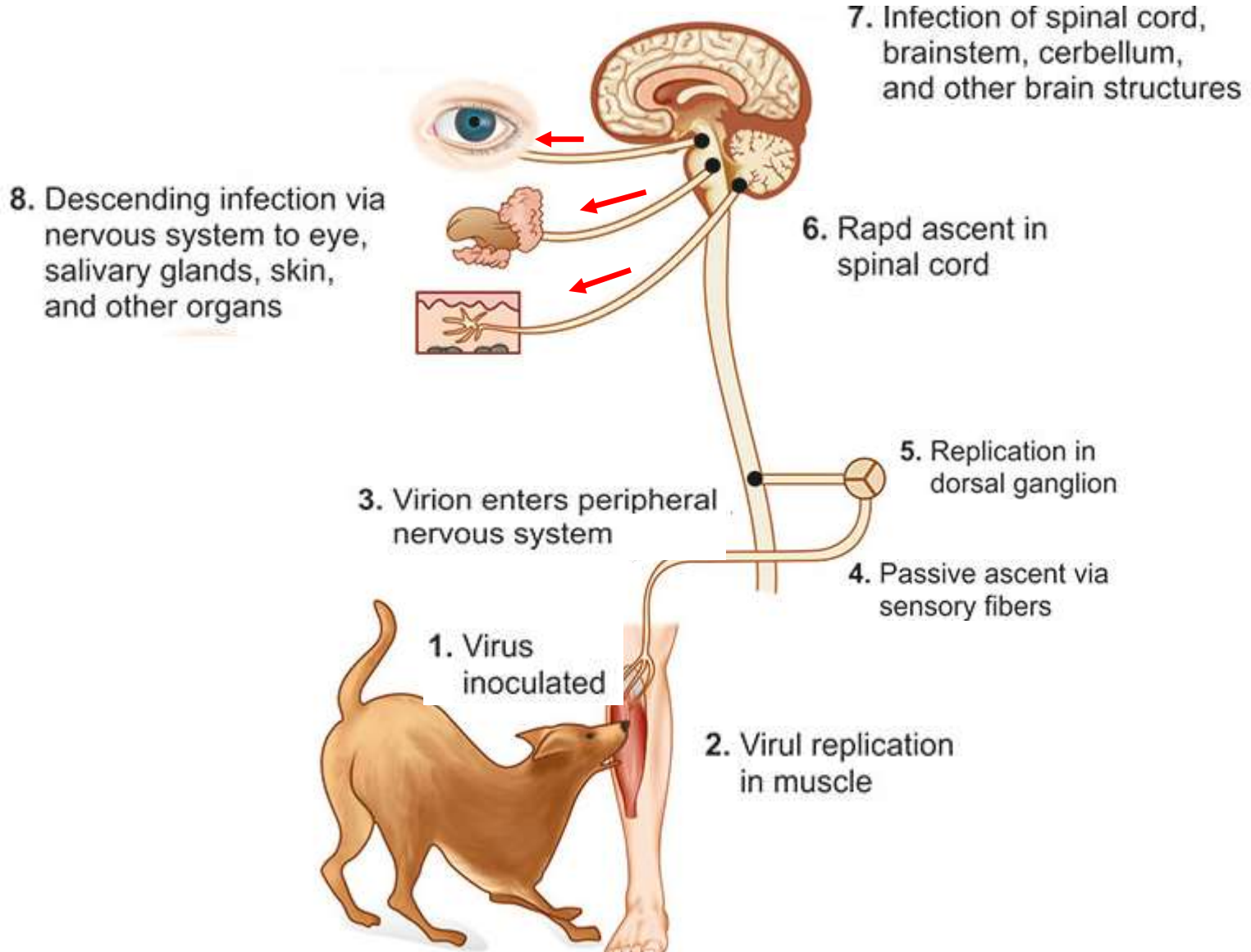
K. The basis for behavioral changes, including the aggressive behavior of rabid animals, is not well understood.

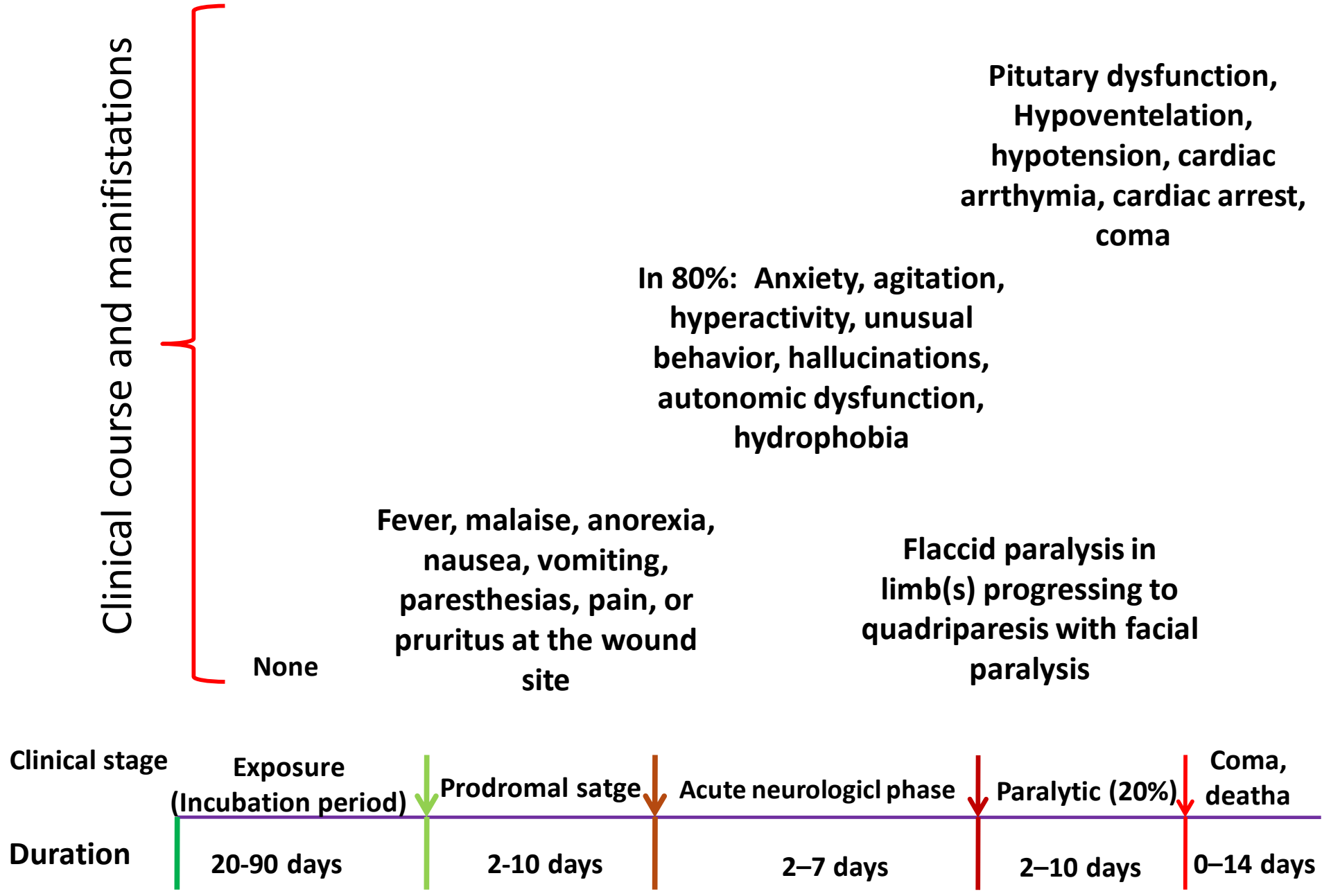


Negri bodies: are eosinophilic cytoplasmic inclusions in brain neurons that are composed of rabies virus proteins and viral RNA

Pathogenesis

Rout of infection




Clinical course and manifistations
Pitutary dysfunction, Hypoventelation, hypotension, cardiac arrthymia, cardiac arrest, coma
In 80%: Anxiety, agitation, hyperactivity, unusual behavior, hallucinations, autonomic dysfunction, hydrophobia
Fever, malaise, anorexia, nausea, vomiting, paresthesias, pain, or pruritus at the wound site
Flaccid paralysis in limb(s) progressing to quadriparesis with facial paralysis
None
Clinical stage
Exposure (Incubation period)
Prodromal satge
Acute neurologicl phase
Paralytic (20%)
Coma, deatha
Duration
20-90 days
2-10 days
2–7 days
2–10 days
0–14 days

Rabies

Two clinical patterns:

dumb (paralytic) and Furious (encephalitis)

- Non-specific symptoms:

Fever, headache, bite site pain numbness and pain

Dry throat, cough, insomnia

1. Dumb:

- symmetrical ascending paralysis
- 1/3 of cases
- May develops into encephalitis in 2-3 weeks > coma and death

Rabies

2. Furious:

- Encephalitis (delirium, convulsions, coma and death)
- Hydro and aerophobia
- In 2/3 cases
- Death usually in 1 week

- Prognosis:

✓ Once symptoms occur: fatal in 3-10 days

Laboratory investigations of Rabies

- Most routine laboratory tests in rabies yield normal results or show nonspecific abnormalities.
- Complete blood counts are usually normal.
- Examination of CSF often reveals mild mononuclear cell pleocytosis with a mildly elevated protein level.
- Severe pleocytosis (>1000 white cells/µL) is unusual and should prompt a search for an alternative diagnosis.
- CT head scans are usually normal in rabies.
- MRI brain scans may show signal abnormalities in the brainstem or other gray-matter areas, but these findings are variable and nonspecific.
- EEG show only nonspecific abnormalities.

Laboratory investigations of Rabies

- Specimens include
  - ✓Serum
  - ✓CSF
  - ✓Fresh saliva
  - ✓Brain tissue (rarely obtained before death).

» RT-PCR amplification: This technique can detect virus in fresh saliva samples, CSF, and skin and brain tissues.

» Direct fluorescent antibody: skin biopsies and brain tissue

Prognosis

- Prognosis Rabies is an almost uniformly fatal disease but is almost always preventable with appropriate postexposure therapy during the early incubation period.
- Most patients with rabies die within several days of illness, despite aggressive care in a critical care uni

Control and Prevention

Pre-exposure vaccination

Pre-exposure vaccination should be offered to:

1. Persons in high-risk groups, such as:
   - ✓ Veterinarians and all at risk with frequent contact with the rabies virus or potentially rabid bats, raccoons, skunks, cats, dogs, or other species at risk for having rabies.

Pre-exposure vaccination schedule:

	Route	Regimen
Vaccine	Intramuscular (IM) Intradermal (ID)	1 ml on days 0, 7, 28 0.1 ml on days 0, 7, 28
Bosster	Intramuscular (IM) Intradermal (ID)	1 ml every 2 years 0.1 ml every 2 years

Control and Prevention

Post-exposure prophylaxis guide

Vaccination Status	Treatmen	Regimen
Not previously vaccinated	Wound cleansing	The wound needs to be thoroughly scrubbed with soap and water, or, if available, iodine solution, 40-70% alcohol, cetrimide 0.1% or a similar compound, or the virucidal agent povidone, all under local anaesthesia if possible. The rabies virus is killed by sunlight, drying, soap, and the other agents mentioned.
	RIG*	Administer 20 IU/kg body weight. If anatomically feasible, the full dose should be infiltrated around the wound(s) and any remaining volume should be administered IM at an anatomical site distant from the vaccination site. Also, RIG should not be administered in the same syringe as the vaccine. Because RIG may partially suppress the active production of antibodies, no more than the recommended dose should be given
	Rabies vaccine	Administer 1 ml IM or 0.1 ml ID in the deltoid area on days 0, 3, 7, 14 and 30. A booster dose on day 90 is optional.
Previously vaccinated	Wound cleansing	The same
	RIG	RIG should not be administered
	Rabies vaccine	If vaccinated within one year: 1 ml IM or 0.1 ml ID on day 0. If vaccinated more than one year prior: 1 ml IM or 0.1 ml ID on days 0, 3, and

Immediately wash the wound with soap and running water for at least 15 minutes.

Disinfect the wound with alcohol or an iodine solution. (If possible)

Immediately consult a doctor or go to the nearest health facility.

Illustrations by Mary Faye Maruguinas