

## A Review on Kuru: Fatal Neurodegenerative Disease

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### **Abstract:**

*Kuru, a very rare fatal neurodegenerative disease. It mainly affects the cerebellar region of the brain. It is caused by infectious proteins called prions. These prions are a deviant form of harmless protein. Kuru is a transmissible spongiform encephalopathy, prion disease. It is a human prion disease. The symptoms include tremors, loss of coordination, depression, muscle spasms and behavioural changes and ultimately lead to death. The incubation period of this disease varies from person to person and it could be as short as 5years and could be as long as 50 years. It is most prevalently seen in Papua New Guinea where a ritual of cannibalism is practiced, where most of the elderly women and children are affected as they are the one to whom human brain is given to consume during cannibalism. The neuropathological changes are observed on brain tissue during biopsy or after death. There is no treatment for this disease only supportive therapy is given. Moreover, this disease is almost vanished as there are no cases reported in recent years. The practice of cannibalism ritual was also banned by Australian government in 1960s.*

**Keywords:** kuru, neurodegenerative disease, prions, transmissible spongiform encephalopathy, tremors, cannibalism, biopsy.

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### **I. Introduction:**

**SYNONYM:**LAUGHING DISEASE.

The term “KURU” is the foreword, which means shiver/tremor. KURU is a very rare disease which belongs to class of infectious diseases called transmissible spongiform encephalopathy’s (TSE’S), also known as prion protein diseases, as these diseases are caused prions. Prions are deviant forms of harmless proteins which are normally found in the brain. These prions are much smaller than viruses and differ from viruses, bacteria and all living cells because they don’t contain any genetic material.

### **HISTORY:**

The first recognised case of kuru belongs to the tribe of fore of the villages called Wise isolated highlands of Papua New Guinea, then officially an Australian territory. Gores had been left untouched by the outside world until the 1930s and were unstudied until 1950s. When patrol officers and anthropologists are exploring this region, they noticed and reported many ill women and children. By observing the symptoms of tremors, uncontrollable laughing and incoordination, they referred it as psychosomatic illness. The fore believed kuru to be a curse and blamed the sorcery foe this condition.

In 1957, WincentZigas, a district medical officer of the fore tribe region of Papua New Guinea introduced the problem of kuru to Dr. Carlton Gajdusek. He then published the first medical description of this unique neurological disease, as “laughing sickness” as some patients displayed sustained spasm of facial muscles, as a symptom.

In 1961, a medical student from Adelaide Michael Alpers teamed up with Dr. Gajdusek and observed patients affected with kuru, starting from the initial stage to final stages, until the death of the patients but could not find anything that is useful. After baffled by kuru, they learned about a Neuro degenerative disease common to sheep that had been observed over 200 years, referred to Scrapie disease. They found the similarities between both kuru and scrappy as both show same clinical manifestations and microscopic sponge like appearance, with thousands of tiny holes appearing throughout the brain. Based on this information, they decided to know whether kuru could be passed on to primates by conducting an experiment. In that experiment they performed an autopsy on the person who is suffering with Kuru (initial stage) and incubated the pathogenic material in a Chimpanzee and after which Dr. Alpers extracted the sample of that death patient brain, and injected it into a Chimpanzee, Daisey.

Meanwhile, they would not find any new case after 1960 and concluded that the reason is enforced bans the practice of cannibalism by the Govt. They also observed that the women and children are mostly affected as they are the one who consumed brain of human during this cannibalism ritual.

After two years, they proved that this Neurodegenerative brain disease was both infectious and transmissible, with inherent potential to cross barriers if species as well as having a remarkable long incubation period of average 10-13 years and in most cases (90%) incubation period could be up to 21-27 years and the maximum incubation period is 50 years.

According to oral testimony by Fore, Kuru had begun to appear at midst beginning in 1910's. In 1970, Dr. Alpers proposed that Kuru started when prion-contaminated tissues of a person with Creutzfeldt-Jakob disease were eaten. CJD-a rare but well documented occurrence in any human population.

Stanley prionerdiscarded the previously used "unconventional virus" (said to be the cause Kuru disease given by Dr. Gajdusek) and instead coined the term "prion", in 1982. He referred that previous undescribed form of infection (Kuru) is due to protein misfiling, also known as Proteopathy.

#### **DEFINITION AND ETIOLOGY:**

Kuru, a transmissible spongiform encephalopathy(TSE),is a disease of the nervous system that causes physiological and neurological effects which ultimately lead to death.

It is characterized by progressive cerebellar ataxia, loss of coordination and control over muscle movements.

It is the first Neurodegenerative disease resulting from an infectious agent, PRIONS which are found in contaminated human brain tissue.

This disease is found among people of New Guinea who practiced a form of ritual called CANNIBALISM. This practice, however, stopped in 1960, but cases of kuru were reported even after banning this ritual, as the incubation period of kuru is remarkably long.

Kuru belongs to a class of infectious diseases called transmissible spongiform encephalopathy (TSE), also known as prion diseases. The hallmark of TSE diseases is the presence of misshapen protein molecules that clump together and accumulate in brain tissue.

#### **PRIONS AND PRION PROTEIN DISEASES:**

The term prion was coined to mean as proteinaceous infectious particle by Prusiner, 1982.

In 1983, Prusiner discovered the proteins from which prions were made and called them as PRION PROTIENS (PrP).

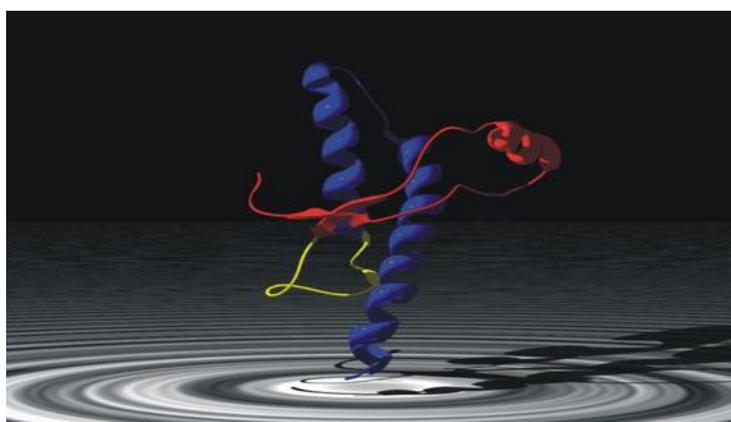
The PrPs are the proteins that everyone has on their bodies. The gene in the DNA, on chromosome 20, gives instructions regarding the making of PrPs.

Prion protein is a normal cellular constituent that in certain circumstances may undergo post-translational conformational change such that it acquires a high Beta-sheet content, which becomes insoluble and accumulate in brain tissue. These bits of misfiled proteins have the ability to spread by making other normal proteins misfiled.

#### **STRUCTURE OF PRIONS:**

The prion protein is a relatively small glycoprotein that is tethered to the outer leaflet of the plasma membrane. It has a globular structure and a partially disordered region that acts as a binding site for copper ions.

It is a monomeric, detergent soluble protein. It plays a major role in a devastating class of neurodegenerative diseases known as TSE's /prion diseases.



**Fig.1 PRION PROTEIN (NORMAL)**

### **PRION PROTEIN DISEASES:**

Prion diseases are a group of neurodegenerative disorders that affect both humans and animals.

These diseases are usually caused by deposition of abnormally folded prions in the brain. These are very rare, but an extremely fatal type of diseases.

In these diseases the misfolded PrP binds to healthy PrP, as a result of which the healthiest proteins also fold abnormally. These misfolded PrP begins to accumulate and form clumps within the brain, leading to damage and killing of nerve cells. This damage to brain leads to the formation of tiny holes in brain tissue, which appears as sponge under a microscope, because of this condition the prion diseases also referred as "SPONGIFORM ENCEPHALOPATHIES".

Different ways of developing prion diseases include:

1. **ACQUIRED PRION DISEASES:** Developed due to Exposure to abnormal PrPs from an outside source, may be through contaminated food/medical equipment.
2. **INHERENT PRION DISEASES:** Mutations in the gene that codes for PrP leads to production of misfolded PrP.
3. **SPORADIC PRION DISEASES:** In this type, there is no known cause for the development of misfolded PrP.

### **TYPES OF PRION DISEASES:**

#### **HUMAN PRION DISEASES:**

1. **CREUTZFELDT-JAKOB DISEASE (CJD)**
2. **VARIANT CREUTZFELDT-JAKOB DISEASE**
3. **FATAL FAMILIAL INSOMNIA (FFI)**
4. **GERSTMANN-STRAUSSLER-SCHENKER SYNDROME**
5. **KURU.**

#### **ANIMAL PRION DISEASES:**

1. **BOVINE SPONGIFORM ENCEPHALOPATHY (BSE)**
2. **CHRONIC WASTING DISEASE (CWD)**
3. **SCRAPIE**
4. **FELINE SPONGIFORM ENCEPHALOPATHY (FSE)**
5. **TRANSMISSIBLE MILK ENCEPHALOPATHY (TME)**
6. **UNGULATE SPONGIFORM ENCEPHALOPATHY.**

### **TRANSMISSION:**

Kuru disease is transmitted by eating an infected brain/coming in contact with open wounds or sores of someone infected with it.

### **CLINICAL MANIFESTATIONS:**

The kuru is a disease, which mainly affects cerebellum part of the brain, which is responsible for coordination and balance. Symptoms of Kuru include - Difficulty walking, Poor coordination, Difficulty swallowing, Slurred speech, Moodiness and Behavioural changes, Dementia, Muscle twitching and Tremors, Inability to grasp objects, Random compulsive Laughing/crying.

As this disease has long and variable incubation periods, these symptoms make take years to develop.

**STAGES OF KURU:** The cause of all these symptoms is due to dysfunction of the cerebellar region of the brain.

1. **PRECLINICAL/ASYMPTOMATIC PHASE (INCUBATION PERIOD):** It could be average of about 10-15 years, it can be as short as 5 years and it can do as long as 50 years / more after initial exposure.
2. **THE AMBULANT (FIRST) STAGE:** This is the first stage where patient experience unsteadiness of stance, gait, voice, hands and eyes; deterioration of speech; tremor; shivering; loss of coordination and dysarthria (slurring speech).
3. **THE SEDENTARY (SECOND) STAGE:** In this stage, the patient cannot walk without support; more severe tremors and ataxia, shock-like muscle jerks, outbursts of laughter, emotional liability, depression and mental slowing.
4. **THE TERMINAL (FINAL) STAGE:** Patient cannot sit up without support; more severe ataxia, tremor, dysarthria; urinary and faecal incontinence, dysphagia and deep ulcerations appear.

### **PATHOPHYSIOLOGY:**

The prion is a naturally occurring protein found in the CNS and elsewhere. Prion diseases are associated with an accumulation of a disease-related isoform of host encoded PrP through a post translational process involving conformational change and aggregation.

According to the protein-only hypothesis, an abnormal PrP isoform is the principle, a constituent of the transmissible agent/prion. A common coding polymorphism located at codon 129 of the PrP gene (PRNP), where

either Methionine(M) or Valine (V) amino acids may be encoded, which is the strong susceptibility factor for human prion diseases. The codon 129 heterozygosity protects against the development of iatrogenic and sporadic CJD and Kuru.

A Protease-resistant glycol protein, designated PrP, was isolated as a result of work done by Prusiner and his co-workers in 1982 by progressive enrichment of brain homogenates for infection. The main feature of this protein was post translational conversion of the host-encoded cellular Prion protein(PrP<sup>C</sup>) to an abnormal isoform, termed as PrP<sup>Sc</sup>, that consists of "small proteinaceous infectious particles that resist inactivation by procedures which modify nucleic acids," i.e., radiation, heat or enzymatic degradation.

The mechanism for prion propagation involves the largely alpha-helical isoform (PrP<sup>C</sup>) refolding into a beta-sheet isoform (beta-PrP). Beta-PrP is prone to aggregation in physiological salt concentrations. The process of recruitment of beta-PrP monomers are essentially thermodynamic irreversible and driven by intermolecular interactions. Immunologic or Inflammatory response to this infection is absent, as prions are naturally occurring proteins.



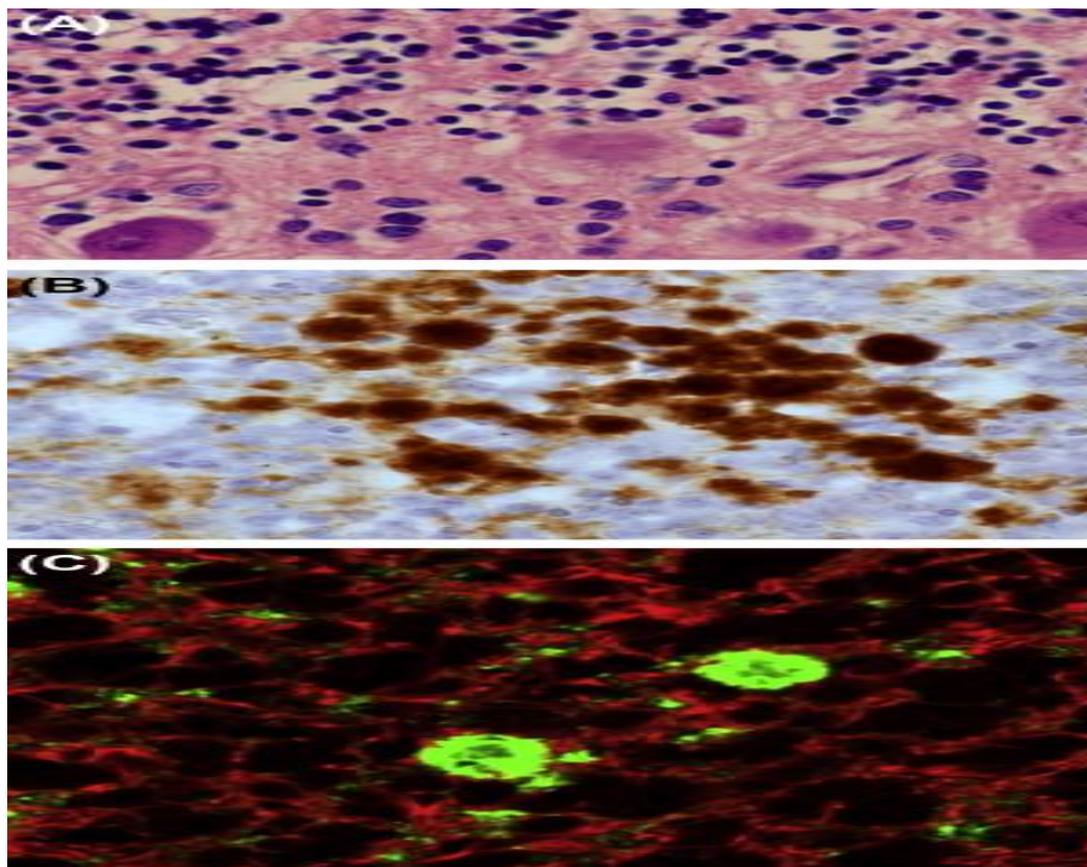
**Fig.2 NORMAL PRION PROTEIN AND PRION PROTEIN AFTER POST TRANSLATIONAL CONFORMATIONS.**

#### **DIAGNOSIS:**

Prion diseases can be confirmed by taking samples of brain tissue during biopsy or after the death. The tests include:

- MRI scans of brain.
- Samples of fluid from the spinal cord.
- Electroencephalogram.
- Neurologic and visual examinations are used to evaluate for nerve damage and vision loss.

Neuropathology examination of kuru brains shows neuronal loss, Astrogliosis and accumulation of PrP<sup>Sc</sup>, all findings typical of prion disease. The pathological hallmark of kuru is the presence of PrP Amyloid plaques, predominately in cerebellar tissue. These plaques are usually eccentric, located in the granular layer of the cerebellum, and often associated with Microglial cells.



**Fig.3 AMYLOID PLAQUES OF KURU-NEUROPATHOLOGICAL EXAMINATION**

#### **PHARMACOLOGICAL THERAPY:**

There is no treatment for kuru, meanwhile this disease vanished because cannibalism is no longer practiced by the fore. Some type of supportive care is provided depending on the condition of the patient.

Supportive care in kuru includes:

**MEDICATIONS:** Some medications can be prescribed that help to treat symptoms.

- For reducing psychological symptoms: Antidepressants or Sedatives are prescribed.
- For pain relief: Opiates are recommended.
- For muscle spasms: Drugs like Sodium valproate and Clonazepam.

**ASSISTANCE:** As the disease advances, people need support for taking care of themselves and performing their daily activities.

**PROVIDING HYDRATION AND NUTRIENTS:** In advanced stages of this disease, IV fluids or a Feeding tube may be provided.

#### **COMPLICATIONS:**

Individuals with kuru progressively become vegetative and moribund. Most patients die of complications of neurological decline, such as wound infection, pneumonia/ malnutrition.

#### **ROLE OF CLINICAL PHARMACIST**

- Antidepressants are the drugs prescribed to reduce depression, which should be contraindicated in patients having glaucoma, epilepsy, ischemic heart disease and enlarged prostate.
- Monitoring the dose of clonazepam is necessary as it worsens the conditions like dysarthria, behavioural changes in patients.
- The CNS Side effects of sodium valproate which worsen the condition of the patient include ataxia, tremors and sedation. So, precaution should be taken while using this drug.
- A rare but serious complication-FULMINANT HEPATITIS is developed while using sodium valproate hence this drug is avoided in children below 3 years of age.
- Monitoring of hepatic function is essential if the patient is on valproate therapy; as elevation of liver enzymes may occur.

## II. Conclusion

KURU is a very rare human prion disease which is fatal. It is Neurodegenerative disease found in fore of New Guinea. The causative agent is a prion. This disease, prominently affects the cerebellar activities of the brain leads to symptoms such as ataxia and tremors and finally death. The diagnostic tests are performed on brain biopsy/after death, but definite test is not available for screening this disease. There is no definite treatment for this disease. This disease is not epidemic as it is seen in mostly new guinea and also **VANISHED AS THE PRACTICE OF CANNIBALISM IS BANNED.THEREIS NO NEW REPORTED CASES IN RECENT YEARS.**

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