

Kuru: A Review of a Rare Human Prion Disease

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Abstract

The kuru outbreak persisted for nearly one hundred years. It first appeared around 1901–1902, became a widespread epidemic in the middle of the 1950s and eventually disappeared in the 1990s. It is acknowledged as first known case of a group of neurological conditions called prion diseases, or ‘transmissible spongiform encephalopathies (TSEs)’. Scientific knowledge of Kuru has advanced due to developments in studies on the genetics as well as biological mechanisms of TSEs, while findings from the kuru epidemic itself have played a crucial role in understanding how variant Creutzfeldt-Jakob disease continues to spread throughout Europe. This review's main goal is to draw attention to and clarify these reciprocal contributions. The highly restricted marriage customs of the affected communities, combined with their geographic and social isolation, would have made the spread of a newly arisen genetic mutation extremely slow. Such a mutation could only have become widespread if it had existed in the original ancestors of a founding population from which the core groups later affected by kuru descended, prior to the development of near-complete marital isolation among hamlets. Although environmental influences and the potential roles of infectious agents, toxins, or nutritional deficiencies—either independently or interacting with genetic susceptibility—have not been entirely ruled out, current research has focused mainly on biochemical studies.

In particular, investigations into intermediary metabolism among individuals with kuru and unaffected members of the same population, some of whom later developed the disease, form the central approach. These biochemical studies are expected to deepen understanding of the causes and disease mechanisms of kuru, regardless of whether its origin is purely genetic or involves additional contributing factors.

Keywords: Kuru, prion, disease, rare.

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INTRODUCTION

The 1950s and 1960s saw an epidemic of Kuru, a rare and deadly brain condition. Kuru meaning "to tremble in/with fear" or "to shiver." Kuru is one of the illnesses referred to as human prion disease. The sickness was caused by the Fore people's ceremonial cannibalism, wherein the brain and other dead tissues of deceased family members were cooked and consumed by family members. It is a sickness that affects both humans and animals. ‘Bovine Spongiform Encephalopathy (BSE), also known as "mad cow disease," is an example of an animal prion illness. Creutzfeldt-Jacob disease (CJD), Gerstmann-Straussler-Scheinker disease are examples of human prion diseases. "Spongiform encephalopathy"

(SE) is occasionally used to describe the known prion illnesses, all of which are deadly. They get their name from the fact that they often leave holes in the brain. Sheep and goats suffer from a common form of "scrapie," which renders them immobile. They are referred to as "scrapies" because they occasionally experience severe itching that causes them to scrape off their wool or hair. Muscle twitching, lack of coordination, uncontrollable movements, euphoria, difficulty swallowing, slurred speech, dementia, difficulty walking, involuntary motion behavioral mood changes, and difficulties eating are some of the symptoms of this condition. It can have an impact on both people and animals. Malnutrition may result from

the latter. Although there is currently no known cure for Kuru, symptoms can be somewhat reduced with treatment. Within a year of incubation, it is typically lethal. Kuru is mostly restricted to the Fore individuals as well as those they intermarried with. Clinical features of Kuru include cerebellar ataxia, tremors, movement disorders, mental impairment and emotional lability. These prions have a very long incubation period among the hosts for about some months to even several years causing accumulation and growing into the nerve cells, inflicting harm to them and ultimately leading to neurodegeneration. The brain contains the aberrant protein type known as prion, which is far more resistant to enzyme degradation. D. Carleton Gajdusek, an American doctor, proved that the illness was contagious. Kuru cannot be controlled or cured except by preventing ritualistic cannibalism.

Other than treating the symptoms, there are currently no cures or therapies for any of the other transmissible spongiform encephalopathy (TSE) diseases. Kuru, like other TSEs, has a lengthy incubation period. Because Kuru primarily affects the cerebellum, that is in charge of coordination, it could take years or even decades for an infected person to exhibit symptoms. Typically, the first signs were tremors, slurred speech, and an unsteady walk. In contrast to the majority of other TSEs, mood swings were common and dementia was either limited or nonexistent. People eventually lost the ability to stand or eat, but six to twelve months after the onset of symptoms, they passed away in a stupor or comatose state.

The onset of the disease seemed random and was considered to be genetic for a while. Prion's remarkable resilience to traditional sterilizing techniques and its potent ability to adhere metal and plastic surfaces without losing its infectiousness are two of its most notable characteristics.⁴ In the past, the disease was caused by autoinoculation or ingestion of infected brain material. The Fore people practiced ritualistic cannibalism, whereby they made and eaten their deceased relatives' tissues, including their brains, as a sign of respect for their departed loved ones. Specificity was defined in Fore people what and which parts of the body should be consumed by whom^[1-5].

HISTORY OF KURU

In 1957–1959, Australian scientist W.T. Brown was the first to identify Kuru disease in members of the 'Fore tribe in Papua New Guinea's Eastern Highlands region'. Michael Alpers and Daniel Carleton Gajdusek conducted excellent studies on this illness. Australian physician Michael Alpers spent over half a century studying this illness. According to reports, a Fore girl named "Kigea" passed away in the middle of 1960 from Kuru sickness. During the girl's postmortem, Dr. Alper collected a sample of the damaged brain tissue. It was reported that the collected sample was taken to Gajdusek in USA and was transferred into two

Chimpanzees where transmission of the disease was to be checked.

Two years later, it was discovered that "Daisy," one of the chimpanzees, had started exhibiting signs of Kuru disease. This prion disease is able to pass from a single species to a different one through auto-inoculation and ingestion of the diseased brain material, as evidenced by the successful transfer of the afflicted brain tissue to a chimpanzee. There was no proof that the illness could be passed from mother to child or that it could be spread through milk or close social interaction^[1,2].

ETHNOGRAPHY AND GEOGRAPHIC BACKGROUND

"Kuru" means to tremble, usually due to a cold or fever. "The natives of almost all of the Fore hamlets have stated that kuru has been present for a 'long time', but they soon modify to mean that in the recent years, it has become an increasingly severe problem and that in the early youth of our oldest informants there was no Kuru at all".⁶ According to the fore report, Kuru first showed up in the northwest Keiagana hamlet of Uwami in 1900, and then in the North fore in 1920. Infectious agents diffused across the community and caused an epidemic when they were recycled through the consumption of deceased family members. The illness is also called "laughing sickness" because of the pathologic outbursts of laughter that are one of its symptoms. It is now generally acknowledged that ceremonial cannibalism was the primary means by which the Fore tribe of Papua New Guinea disseminated kuru.

Kuru was act of witchcraft or sorcery among the tribe of fore people. Kuru might have started with a single person who lived in a remote area of the nation before gradually spreading to the entire populace, according to study done on the subject. Because they were typically assigned to wash or bathe the deceased who might have had cuts and sores, women as well as children were more susceptible to kuru.

Zigas and Gajdusek observed that the Yar people had temporarily displaced the Fore people from Kasarai, and they had lived there for around ten years, but Kuru cases continued to be happening. Lindenbaum noted that the early accounts of their experience with the novel illness were extremely detailed. Kuru is currently thought to have started in one individual due to alteration that produced a pathogenic, infectious disease in the brain, similar to how sporadic Creutzfeldt-Jakob disease happened. Kuru was shown to be prevalent in epidemic proportions during the initial research, which was conducted in 1957. During the first five years, from 1957 to 1961, there were about 1000 deaths. The research of Kuru took over fifty years to complete while epidemiological surveillance tracked the outbreak's progression. The number of Kuru-related deaths has decreased to 2% over the past five years from its height period, suggesting that the pandemic must be coming to an end. The transmutation process used in local

mortuaries was the means by which the prion agent for Kuru was spread. The epidemic decreased once ceremonial cannibalism was outlawed in the 1950s.

The Kuru region, which is separated into South and North Fore, is located in the eastern central highlands of Papua New Guinea. With a population of 5 million, Papua New Guinea is home to a total of about 850 different linguistic groupings, or one-seventh of all languages spoken worldwide. The Kuru region, which is roughly 65 km by 40 km, was home to about 40,000 people in the late 1950s. In every community where it spread, it turned into a hyper endemic disease. Symptoms were initially considered to mirror the cassowary's quills, which also reminded them of the casuarina tree's swinging fronds in their Fore region. They consequently administered casuarina bark, a homeopathic treatment, to the afflicted, which did not seem to provide any help. Due to the affected women's excess laughter, many also known to the illness as "negi nagi," a Fore phrase meaning silly or dumb person. They made jokes and had sex with the ill women in the beginning, just like they did in those who experienced brief mental illness. Kuru is always lethal. This illness killed over 2700 people between 1957 and 2004.

KURU ETIOLOGY: FINDING A NEW CLASS OF PATHOGENS

Proteinaceous infectious particles are abbreviated as prions. The solitary molecules of 250 amino acids are called prions. These are the aberrant forms of proteins that are typically seen in cells. They are able to transform the typical shapes they come across into aberrant ones, which increases the quantity or population of aberrant protein forms in the brain. The illness brought on by prions cannot be cured by antibiotics. They do not fit the description of a prokaryotic or eukaryotic organism. Only the protein PrP^{Sc} (bad form), which is a mutation of PrP^C (normal form), is present. PrP^{Sc} resists digestion in all its forms. Prions are not easy to decompose biologically. Clinically, cases of Kuru presented purely with cerebellar syndrome. In 1965, D. Carleton Gajdusek inoculated 3 brain tissues from kuru patients; spread the disease to chimpanzees two years prior, and then to Sooty Mangabey monkeys, marmosets, gibbons, and Rhesus monkeys.

There were essentially three different causes of Kuru: exposure to environmental particles (either by food or by unintentional exposure during medical as well as surgical procedures); they may be autosomal dominant inherited conditions; or they may arise sporadically. Food, air, water for drinking, bodily fluids, and even neurosurgery transmission and attachment are all ways that pathogens can spread. Algae, mycobacteria, bacteria, fungi, viroids, bacteriophages, viruses, helminthes, protozoa, and prions are only a few of the various kinds.

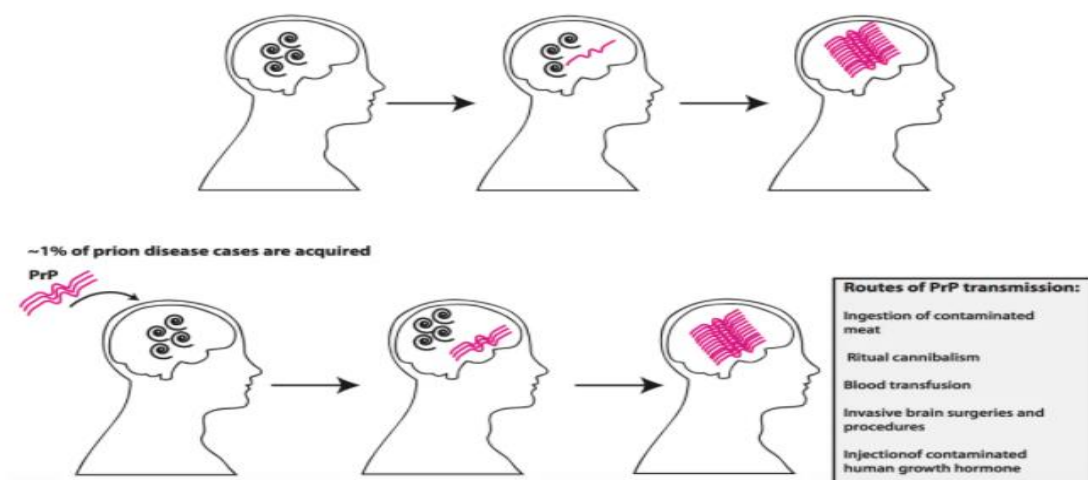


Fig 1: Transmission of prion disease

This figure illustrates how prion disease spreads. Most human cases of prion disease develop on their own. However, a small minority (~1%) of diseases can spread from person to person in a number of ways. [Fig 1]

However, only a small number are directly linked to Kuru illnesses. Prion is an infectious particle that causes diseases including scrapie, Creutzfeldt-Jakob disease (CJD), and bovine spongiform encephalopathy (BSE). It is made up of an aberrant isoform of the prion protein (PrP^{Sc}). The cellular prion protein (PrP^C), that is expressed by host cells, is crucial for regular processes like anti-oxidative stress.

PrP^C is the source of PrP^{Sc}, which is created through conformational conversion. Prion is a well-known and resilient virus that is challenging to render inactive using standard sterilizing techniques. Therefore, using the right techniques to inactivate prions is crucial to preventing iatrogenic disorders caused by prions. Prion is highly resistant to all types of sterilization methods, such as autoclaving (121 C, 20 min), γ -ray irradiation, and alcohol therapy, which are used to disinfect,

prevent sepsis, or sterilize bacteria and viruses. This is a basic overview of prions and how to deactivate them.² Following an infection, host cells, particularly neurons, express cellular PrP (PrPC), which might have a part in controlling circadian cycles, calcium as well as copper homeostasis, learning, signaling, anti-oxidative stress, and spatial memory, as well as synapse formation. PrPSc is the result of these changes. Protease-resistant PrPSc deposits are created when PrPSc builds up in the brain. The buildup results in vacuolation, astroglycysis, and loss of brain cells, which ultimately produces spongiform and fatalities.

GENETICS OF KURU

In the 20th century, scientists found that a protein known as Prion Protein might cause any disease, which is most frequently responsible for neurodegenerative illnesses, disorders, and other diseases. A protein known as the PrP is carried by PRNP on human chromosomal number 20. The PrPC is a typical protein with an alpha-helical shape that is also involved in human healing. However, PrPC's alpha helices turn it into PrPSc as well as beta sheets within the transforming receptacle known as the Molten Globule due to the production of amino acids and polypeptides.

When prions fold incorrectly, the normal protein takes on an aberrant shape. Beta-sheets that are closely

packed together create an aggregate. By producing holes in the tissue and ultimately leading to cell death, altered structure, stability, and accumulation within infected tissue interfere with normal cell functioning and cause tissue damage. The PrP gene, which is located on chromosomal number 20, produces the prion. There is only one intron separating the two exons in this gene. 'The two RNAs merge to form a single mRNA after Exon I and Exon II transcription. The PrP protein is translated from the open reading frame (ORF) or protein coding region found in this mRNA. The normal cellular prion protein, 10PrPC, is converted into the aberrant protein isoform, PrPSc. Those homozygous to the 129Met allele of the gene (PRNP) producing prion protein (PrP) were most vulnerable to Kuru's potent balancing selection on the Fore tribe population. Two Kuru cases were first identified as 129 Met Met. According to the studies, Kuru posed a threat to the population of 129Val Val and 129Met Val. Younger' persons were more likely to have the 129Met Met genotype, whereas older people were more likely to have the 129Val Val 129 Met Val. There were no 129 Met Met homozygotes in those who survived the outbreak. It has been suggested that the vulnerable genotype's weariness and, ultimately, the cessation of exposure via cannibalism are the reasons for the drop in Kuru incidence in the Fore[3].

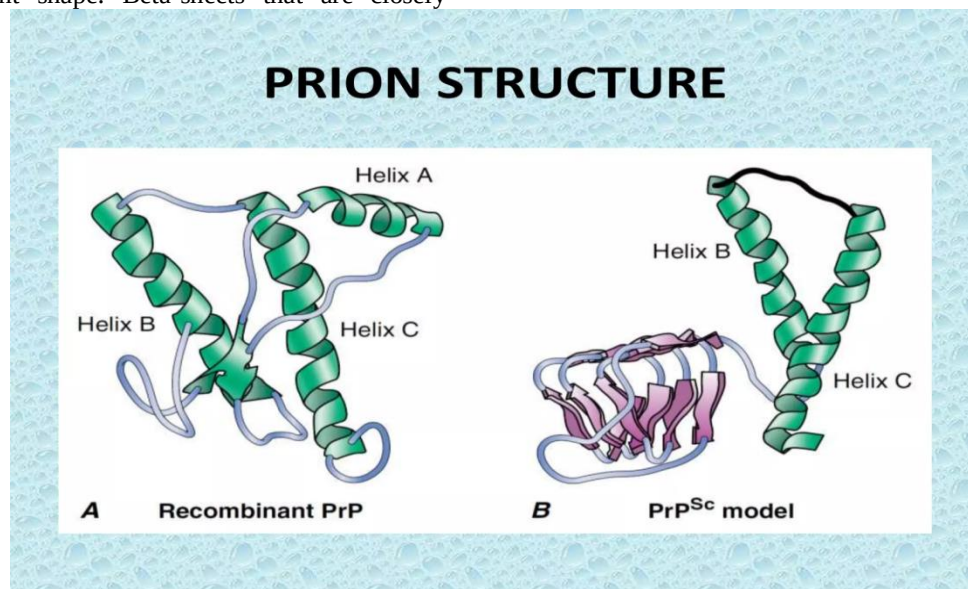


Fig 2: Pathophysiology of Kuru

Pathophysiology of kuru is discussed in figure 2. The PrPC is encoded by the PRNP gene. Although it does not cause the disease on its own, the methionine/valine (Met/Val) variant at position 129 significantly affects the phenotype that results from the other PRNP mutations, as well as the susceptibility defense against Kuru and iatrogenic as well as sporadic forms of CJD. According to the background populations, the genotype frequencies range from '0.32Met/Met/0.43Met/Val/0.24Val/Val in New Guineans to 0.37/0.51/0.12 in

British and 0.92/0.08/0' in Japanese. Gibbons, marmosets, rhesus monkeys, as well as sooty mangabey monkeys are among the non-human primates on the list. The duration of incubation ranged from 11 to 39 months. Researchers from the Medical Research Council found a naturally occurring prion protein variant that exhibits significant resistance to kuru in the Papua New Guinean population in 2009. The study began in 1996, and the researchers evaluated over 3000 members of the Eastern Highland population that was

affected and nearby. The study came to the conclusion that the prion protein G127 was different.

The missense mutation that causes the G127 polymorphism is limited to very geographically specific areas where the Kuru pandemic was most prevalent. The PrnP variation was discovered only recently, according to Simon Mead and his colleagues, who were primarily English physicians. Therefore prion protein G127 variant enhances immunity to a very large extent.

PHYSICAL PARAMETERS OF KURU

Clinically the course was divided into 3 stages:

- 1) EARLY STAGE (I) / AMBULANT
- 2) INTERMEDIATE STAGE (II) / SEDENTARY
- 3) LATE STAGE (III) / TERMINAL*

Clinically, cases of kuru presented with a pure cerebellar syndrome. Kuru laik i-kamp nau, or "kuru is about to begin," is an ill-defined prodromal period characterized by headache and limb aches, mainly in the joints; elbows and wrists were affected initially, followed by knees and ankles; sometimes, interphalangeal joints were afflicted first, accompanied with weight loss and abdominal pain. Even several months passed during the prodromal phase. The "ambulant stage" that follows the prodromal phase concludes When the sick is unable to move without the help of the "family," the search for a witchcraft sorcerer also begins. The emergence of symptoms associated with gait instability characterizes this ambulatory stage., which the patient self-diagnosed without initially seeing them. Twelve After about a month, such symptoms progressed to ataxia and astasis. In the third stage, the patient dies from severe malnutrition, becomes bedridden as well as incontinent, and has dysphasia and primitive reflexes. A supportive attitude has to be enforced. "The patient at the beginning of the third stage typically spent the day supported within the arms with a close relative." Extra ocular motions were slow, jerky, and a little stiff. Cerebellar ataxia, tremor, mental illness, movement abnormalities, emotional liability, along with frontal release signals (snout, suck, root, and grip reflexes) are among Kuru's clinical characteristics. Gajdusek received a Nobel Prize in 1976 for passing kuru on to chimpanzees. Primates that are not on the list include gibbons, sooty mangabey monkeys, marmosets, and rhesus monkeys. The physical parameters of kuru were observed in animals through the experimental transmission the prions to various animals, therefore results obtained were as follows:

In 1973, a comprehensive account of experimental kuru was published, based on observations made in 41 chimpanzees. There were three phases to the clinical course, and the incubation period ranged

from 11 to 39 months. 23 months was the average incubation period for the first passage, 12 months for the second, 13 months for the third, and the same for the fourth.

- Early stage (I)
- Intermediate stage (II)
- Later stage (III)

- The Early stage (I)

(a) The early behavioral changes are known as the prodromal stage, during which animals frequently become "extremely dirty," submissive, and lazy. The smaller chimpanzees were able to taunt and steal food from the vicious as well as aggressive animals because they became quiet and stopped competing with their regular cage mates. Outbursts of angry screaming frequently broke up periods of morose lethargy.

(b) The animals weren't leaving their cages "to run or to climb," they were slow because fell with forced movements, and their movements were "like-in slow-motion cinema" during this period of mild infirmities.

- The Intermediate stage (II)

The challenges a chimp faces when rising from a supine position—its gait is ataxic, but it is still possible to sit—were identified as the start of this stage. Chimpanzees have a quadrupedal stride, or "knuckle walking," in which they place their hands onto the ground with their knuckles rather than their palms. Stage II of human kuru is characterized by truncal titubation, which mostly affects the body's nerves or affects the body's trunk. Flexion contractures develop and muscle tone increases (muscles, tendons stiffen and produce deformity). Babinski indications were only infrequently seen, but severe tremor is accompanied with choreiform actions, vision problems, lateral nystagmus (a vision ailment in which the eyes produce repetitive and uncontrollable movements), and intermittent left strabismus.

- The late stage (III)

The animals develop decubitus ulcers, or bedsores, and are unable to sit or get out of a supine position on their own. They consume inedible items. A violent, coarse trembling among every limbs develops together with a significant startled reaction of flexion of the all extremities.

KURU AND CANNIBALISM

The regulations governing the ingestion of human flesh appeared to support the link between Kuru and cannibalism, as they were more consistent with the epidemiological data. The Fore publicly discussed their ceremonial habit of eating their deceased relatives, which is known as ritualistic cannibalism. The government or mission banned cannibalism in the 1960s. A genetic or hormonal theory appeared to offer a solution when Kuru was initially described as existing in specific families as well as hamlets, but only in the

Fore and nearby individuals who they intermarried, and exhibiting a preference for young kids as well as adults women. It was believed to be a hereditary or genetic condition caused by a single autosomal gene. In contrast to the Fore pattern, exo-cannibalism involved eating foes rather than deceased family members.

In order to connect the Fore with those who weren't eating the dead, a government road was built through the area by the end of the 1950s. However, not every dead individual was consumed.

Those who died from leprosy, dysentery, or even yaws weren't consumed, but Kuru sufferers received good care, particularly if their bodies had not been malnourished. Every bodily part was consumed, with the exception of the gallbladder, that was found to be excessively bitter. Living in homes with their moms, significant Fore children consumed the food that their mothers provided. Consumption guidelines were strict and predetermined. Body parts were distributed based on gender and kinship rights. For instance, a deceased person's daughters-in-law typically asked for the head. To cook brain tissue and wild green vegetables, the daughters-in-law exchanged bamboo tubes with the other ladies.

Young children were not allowed to attend the ritual and were never fed meat. The Fore continue to hold the view that the malevolent sorcerers are the source of Kuru, a theory of illness causation that includes considers age, gender, clinical signs, and the history of epidemics. At the age of twelve, 13 initiated youngsters left the domain of femininity, immaturity, and cannibalism to move into the men's home. As a result, compared to their sisters who stayed with their mothers, male children were less exposed to the kuru agent. According to the epidemiology in kuru during the 1960s, Kuru victims received good treatment, particularly if their bodies weren't starved, but those who perished from leprosy, dysentery, as well as yaws were not eaten. It was proposed that changes in kuru prevalence could be linked to minor variations in eating patterns across the region.

Since many mothers had kuru while they were pregnant, giving birth, or nursing, and no such infants were getting the disease, a corollary for this explanatory reasoning was that kuru was not vertically transferred from mother to kid. This argument serves as an excellent example of how both statistical and logical proof may be used in epidemiology. Additionally, the Fore was able to identify persons who had died from kuru while those who had consumed the corpses, allowing for an account of how the disease manifested in certain hamlets 4–20 years after consuming infected

tissues. This knowledge led to an anthropological research to learn more about the cannibalism practice.

Early in the 1950s, Lutheran missionaries from the North Fore became the first to forbid the practice. The government had a role as well. Armed patrol officers showed their strength by buying a local pig as well as shooting it from a distance. They instructed people to cease fighting, to remove the barricades surrounding hamlets, and to relocate their homes to open spaces so they could be enumerated for a census, in addition to outlawing cannibalism (enforcing an Australian law). According to the first government patrol over the late 1940s, cannibalism was also common throughout a large portion of the area. The guidelines for eating human flesh appeared to support the link between kuru and cannibalism, as they were more consistent with the epidemiological data.

"Everyone in the area understood that Kuru was infectious especially due to cannibalism, including missionaries to bush pilots," Gajdusek said on multiple occasions, but chose to use lab tests to identify a "classical" or "slow" virus rather than pursuing this discovery as a research issue.

According to a recent analysis of their funeral customs, the Fore believed that by consuming their departed relatives, they were ensuring that their spirits would enter the afterlife and reincarnate as ancestors. Originally associated with population genetics, anthropological research on cannibalism now finds a place in molecular genetics. In the context of the Fore usage of endocannibalism, Kuru is currently thought to have exerted a considerable selective stress upon the human PrP gene.

PATHOPHYSIOLOGY

The PRNP gene is a protein gene that codes for the prion proteins (PrP). PrP^C are typically folded proteins that are rich in alpha helices and go through full proteolysis, which is the body's regular process for breaking down proteins. The condition is caused by a misfolded protein called the PrP^{Sc} isoform, which is high in beta sheets as well as resistant to enzyme breakdown. There is no proteolysis of the PrP^{Sc} isoform. As a result, the PrP^{Sc} aggregates and encourages more PrP^C to become PrP^{Sc}. The pathogenesis, a disrupted physiological process linked to prion disease, is the outcome of a chain reaction. [Fig 3]

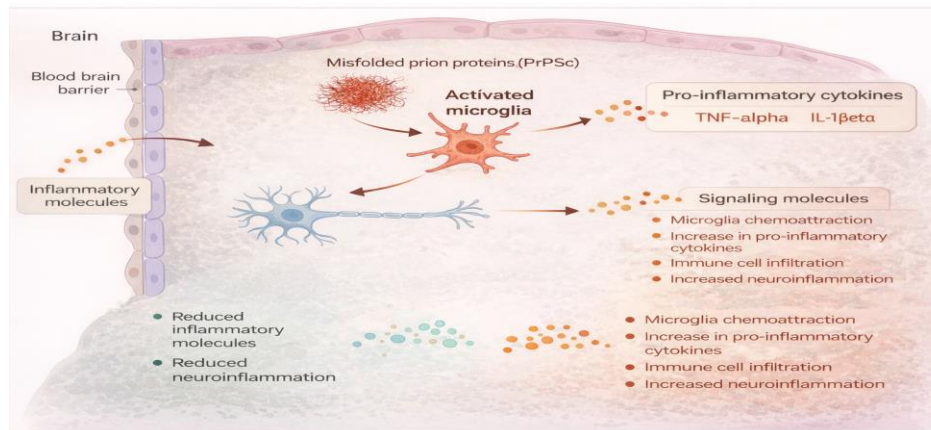


Fig 3: Pathogenesis of Kuru

Since prion is a protein that occurs naturally, there are no immunologic and inflammatory responses to it. Because the misfolded PrPSc protein is identical to the normal PrPc protein, B and T cells most likely recognize it as a self-protein. Short incubation times and early death were risks for those who were homozygous for the prion protein gene's (PRNP gene) codon 129 methionine allele. Those that were heterozygous at this location, on the other hand, had an extended period of incubation and a delayed mortality, making them comparatively resistant to the illness. Conversely, heterozygosity at codon 127 offers a potentially robust and total resistance to kuru.

The ability to produce beta sheets, which combine peptides to form amyloid fibrils, is induced by the irreversible conformational change in PrP27-30. In the neural system, PrP 27-30 builds up and results in (i) astrocyte gliosis (an increase in astrocyte counts), (ii) the creation of many vacuoles of the cerebellar cortex, and (iii) a reduction of dendritic spines within neurons[5].

The substantia gelatinosa in the spinal cord was primarily impacted, as in iatrogenic CJD cases after peripheral inoculation, according to an immunohistochemical analysis that shows the misfolded PrPSc existed not only in kuru plaques but additionally in synaptic and perineuronal locations. Compared to immunocytochemistry using 3F4 anti-PrP antibodies, immunocytochemistry with 12F10 antibodies showed a higher signal.

PrPTSE is likely present (and capable of spreading the disease) in all bodily fluids and tissues during the incubation especially active clinical phases with prion disease, particularly in the brain, nerves, including skeletal muscles. Only within the brain does pathology arise. In the neurons, intracytoplasmic vacuoles first emerge. The name "spongiform encephalopathy" refers to the spongy look of the cortical neuropil as the condition worsens, and vacuolization intensifies.

In more advanced cases, there is brain atrophy, gliosis, and neuronal loss. Usually, severe cases result in cerebellar atrophy. Granular neurons are more severely lost than Purkinje cells, in contrast to the majority of

cerebellar degenerations. Such inflammation does not exist. The cerebrospinal fluid is in normal condition. The underlying disease affects the neuronal body, although the alterations are limited to the gray matter. PrPTSE is precipitated as amyloid plaques in certain prion disorders.

HISTOPATHOLOGY

Amyloid plaques, sometimes referred to as "kuru plaques," are found in the brain histology of kuru victims. In decreasing order, these plaques are widely distributed across the cerebral cortex, thalamus, cerebellum, and basal ganglia. Schiff, Alcian blue, and Congo red stain are periodic acids that are used to stain these amyloid plaques. The brain appears to be free of lesions. The brain autopsy revealed no evidence of inflammation or perivascular cuffing. Nonetheless, microscopic examination of the brain reveals astrocyte proliferation and changes brought on by neuronal injury. Prion protein increase in brain tissues can also be seen using anti-PrP immunocytochemistry[5].

THE CONNECTION OF ALZHEIMER DISEASE AND LAUGHING DEATH

Today, researchers link the aggregations of the misfolded proteins to a growing number various illnesses such as amyotrophic lateral sclerosis (ALS), Huntington's disease, Parkinson's disease, and type 2 diabetes. The brains of AD patients are rich with beta amyloid protein. As Kuru, BSE, TSE, and variant CJD demonstrates that the misfolded proteins are transmissible since they can spread between individuals and even cross species boundaries. Additionally, vCJD has unintentionally spread during brain medical and surgical operations, including: (i) poorly sanitized neurosurgical devices; (ii) blood transfusions; and (iii) dura mater and corneal transplantation. To rule out any potential risk, more epidemiological and experimental study is necessary as there is no proof that Alzheimer's disease is contagious in humans. Complete disinfection of the surgical instruments as well as other medical equipment should continue to be prudent in the interim.

The brains of Alzheimer disease patients are rich in a protein called the beta-amyloid ($A\beta$) as plaques, soluble proteins, fibrils and so on. The brain clears some, but not all, $A\beta$ deposits can be cleared. Most of the $A\beta$ contains 40 or 42 amino acids ($A\beta_{40}$ and $A\beta_{42}$). The two forms differ in various ways, such as $A\beta_{40}$ is much more abundant in the brain than $A\beta_{42}$. However, $A\beta_{42}$ is much more toxic than $A\beta_{40}$. Furthermore, $A\beta_{40}$ forms the small dimers (two monomers) and tetramers that are four monomers and, when injected into mouse brains, they show long straight fibrils [6]. 3000 individuals from the surrounding and impacted area were examined by MRC Prion Unit Director and lead author Professor John Collinge and his group. Of these, 709 had

participated in the funeral rites, 152 of whom later passed away from kuru. They discovered that a unique variation in the prion protein gene known as G127V was present in individuals from the Purosa valley region, wherein Kuru disease was most common. High or total protection for the disease seems to be provided by this gene mutation. Kuru, similar to vCJD, is believed to have an incubation period of many years or even decades. Signs and symptoms of the progressive neurological deterioration caused by the disease includes, tremors, unsteadiness, disordered movements, mood disorders, and in some cases it leads to dementia. Six to twelve months after the onset of symptoms, death takes place. Kuru has no known cure. Link between kuru and Alzheimer's disease is shown in figure 4.

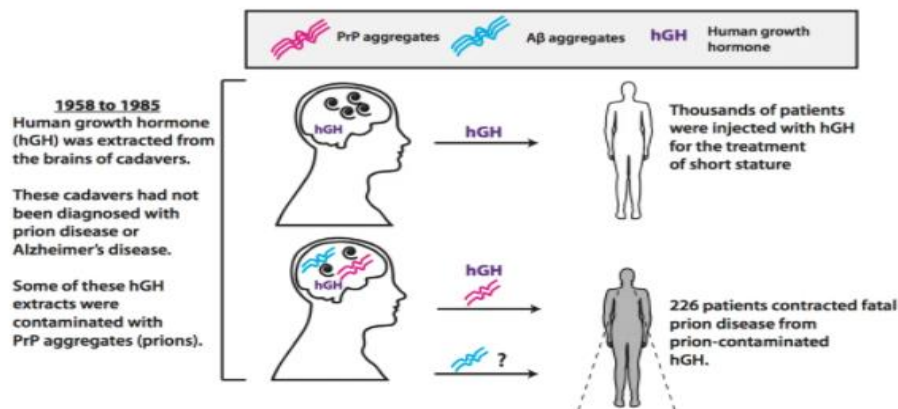


Fig 4: Link between kuru and Alzheimer's disease

The researchers came to the conclusion that the little amyloid beta clumps seen in cadaver-extracted human growth hormone (hGH) were what caused the large amyloid beta aggregates in these patients. The misfolding as well as aggregation of normal proteins in the brains of Kuru patients is probably caused by these corpse clumps. These results may be the first evidence of amyloid beta transmission between humans, demonstrating the spread of Alzheimer's disease [7].

According to Professor John Collinge, this research has implications for Kuru victims and those suffering from dementia. "Kuru comes from the same disease family as that of CJD, so the discovery of this powerful resistance factor opens up new areas for research taking us closer to understanding, treating and hopefully preventing a range of prion diseases" [4].

DETECTION AND INACTIVATION OF PRIONS

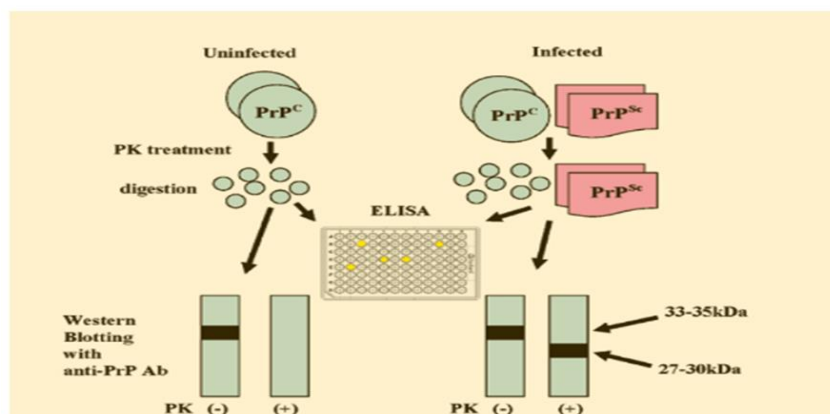


Fig 5: Activation and deactivation of prions

Following an infection, the host cells' expression of cellular PrP (PrPC), particularly in neurons, may play a role in the regulation for anti-oxidative stress, circadian cycles, memory, spatial learning, calcium along with copper homeostasis signaling, as well as synapse formation. Protease-resistant PrP deposits are created when PrPSc builds up in the brain. PrPSc buildup results in astrogliosis, vacuolation, loss of neuronal cells, spongiform, and ultimately death. The primary distinction between the prion as well as other diseases is that, unlike all other pathogens, the prion lacks nucleic acid. As a result, it cannot be rendered inactive by any type of traditional sterilizing process, such as autoclaving (121 °C, 20 min), being exposed to UV light, or even being exposed to γ -ray radiation. Treatments using alcohol, such as 70% ethanol, work well against microorganisms, including enveloped viruses, while they do not do much for prions. It is advised to utilize an autoclave set to extreme temperatures (134 °C, 18 min), SDS (30%, 100 °C, 10 min), NaOH (1 N, 20 °C, 1 h), and NaOCl (20000 ppm, 20 °C, 1 min) in order to inactivate these prions. The prions should be inactivated by autoclaving at 134 °C, gas plasma sterilization with vaporized hydrogen peroxide etc.

Lastly, we concentrate on gas plasma sterilization, a method that partially inactivates prions. After solid, liquid, and gas, the fourth state of matter is gas plasma. By eliminating the electrons, a highly excited mixture of charged electrons is formed, which is known as gas plasma

Complications

Kuru patients experience significant cerebellar and extrapyramidal symptoms and signs as their diseases worsen. At the point of death, the patients become immobile and moribund. Once the victim reaches the third stage of the illness, family members play a major role in providing care. Patients frequently suffer from malnutrition, aspiration pneumonia, which kills Kuru victims, and decubitus ulcers, which are pressure ulcers or bedsores with secondary infections.

DIAGNOSIS OF KURU

In the past, brain samples from individuals in their severe stages of the disease or frequently after death during autopsy were used to diagnose prion disease, which was a highly challenging process. It was discovered in January 1999 that tonsil samples may be used in an immunofluorescence test to identify the accumulating prion protein in the tonsils. Other methods for diagnosing kuru included the following:

- Kuru is diagnosed via a neurological examination. The neurological function, medical history, and blood tests, such as folic acid, thyroid, and the functioning of the kidneys and liver tests (KFT), are all included in this thorough examination.
- Your brain's electrical activity was examined using electrodiagnostic tests including electroencephalograms (EEGs). Although brain scans like magnetic resonance imaging

(MRI) may be carried out, they might not be useful in reaching a conclusive diagnosis.

- Fatigue, sleeplessness, sadness, weight loss, discomfort, and headaches are the most common clinical symptoms that can be physically assessed.
- Histopathological analysis of a brain that has been biopsied or autopsied can reveal amyloid plaques; no lesions, perivascular cuffing, or other inflammatory symptoms were found.
- The electrophoretic patterns which identify the various prion strains are revealed by Western blotting of PrPSc. The core of PrPSc that is resistant to proteases is PrP 27-30.

MRI

DWI and FLAIR sequences reveal abnormalities in brain volume, strong signal abnormalities at least two cortical areas (temporal, parietal-occipital), or in the putamen and caudate nucleus. Signals within the posterior thalamus (pulvinar) are more intense in patients with vCJD. CSF: There is no pleocytosis, or an unusually high number of lymphocytes within the cerebrospinal fluid, and the content of protein and glucose in the fluid is normal. Total tau and >protein 14-3-3 are the most helpful indicators of CJD found in cerebrospinal fluid. The 30kD protein 14-3-3 controls the manufacture of neurotransmitters and is involved in signal transduction, cell division, and proliferation. Tau is also high in Alzheimer's disease, while protein 14-3-3 is elevated in people with encephalitis, cerebral infarction, as well as other disorders.

Elevated 14-3-3 as well as total tau are compatible with a diagnosis of prion disease, despite the nonspecificity of these tests. These proteins' detection offers much-needed premortem diagnostic testing for vCJD. They are especially helpful when more common neurological conditions such as HIV encephalitis, stroke, Alzheimer's disease, etc. have been ruled out and the differential diagnosis has been narrowed.

(RT-QuIC) Real-time quaking-induced conversions in CSF and brain biopsies is a sensitive and accurate method for detecting prion diseases. Biopsy of the brain: A microscopic analysis of the brain tissue demonstrating the distinctive spongy alteration in the brain can provide a conclusive diagnosis.

The electrophoretic patterns that distinguish various prion strains are revealed by Western blotting the brain tissue extracts following digestion with proteinase K. These investigations aided in identifying the PrPSc strain in BSEs and CJD.

Dual tissue grinders were used to prepare the brain's frontal cortex and peripheral tissues as 10%w/v homogenates with Dulbecco's sterile phosphate buffered saline lacking Ca²⁺ and Mg²⁺ ions. Brain homogenate was analyzed using high sensitivity improved chemiluminescence as well as immunoblotting using the anti-PrP monoclonal

antibody 3F4 either prior to or during proteinase K digestion. DNA sequencing: DNA collected from the brain, blood, and other tissues can be sequenced to identify mutations of the codon 129 polymorphism that effects CJD and the PRNP gene that causes vCJD.

CURING THE INCURABLE: KURU

There is currently no known cure or treatment for this neurological illness, Kuru, but symptomatic treatment could give relief to the patient to a much extent. Some of the recent studies say, to cure KURU but they have no such evidence anywhere.

When Kuru initially arose, the Fore people believed that the symptoms were similar to those of the quills of the cassowary, which also evoked the waving fronds of the casuarina tree. They consequently gave the victims casuarina bark, a homeopathic treatment that did not really help.

People with Kuru eventually go into a state of coma and they usually die between 6 to 12 months after symptoms of kuru begin.

The prion illnesses do not have such a treatment. However, the victims could receive supportive care. As soon as the disease is diagnosed, patients should be urged to draft advanced directives (such as preferred end-of-life care). It is strongly advised that family members of individuals with a familial prion illness receive genetic counseling.⁷

Using common chemical cleaning methods such as autoclaving using water at 134 degrees C, NaOH 1N, and NaOCl 20,000 ppm, the infectivity was decreased by $>5.6 \log_{10}$ lethal doses; autoclaving without immersion was only marginally more successful (4–4.5 log reduction) than the former. Some beneficial effects were demonstrated by steam autoclaving at 132°C for one hour and immersing in either a 10% sodium hypochlorite solution or sodium hydroxide 1N for one hour.

Chemicals that would bind from and to stabilize the PrPc conformation can be hypothesized. The ones that disrupt the PrPSc conformation may work simultaneously. Numerous vaccinations for Alzheimer's amyloid plaques are undergoing clinical testing; they may be helpful in treating the neurodegenerative illness as well as Alzheimer's to some degree. The following are some of the chemicals, reagents, drugs used to treat the kuru patient not completely but symptomatically.

- The reagent which shows affinity for the amyloid proteins is CONGO RED.
- For example, amphotericin has been shown to postpone prion illness in hamsters, but it has very little effect on people.
- Humanized anti-PrP monoclonal antibodies, quinacrine, and pentosan polyphosphate can be administered as passive vaccinations in the early stages of disease to prevent prion neuroinvasion.

- Acridines and phenothiazines were found to prevent the production of PrPSc in the cells in culture.
- Quinacrine trails shows that it slows the rate of progress of neuroinvasion.
- Anti PrP Antibodies, Pentosan Polysulphate and Porphyrin derivatives are been tried as well.
- The modified Quinacrine are effective than the original Quinacrine used. (Alpers MP)^[8].

Sporadic CJD as well as other prion disorders were considered "degenerative" diseases prior to the discovery of prions. They were classed as infectious diseases once it was found that they could spread from people to humans as well as animals to humans. They were also referred to as "slow virus diseases" at one stage. As a result, they clearly differ from viral and bacterial infections. It was noted that the prion's chemistry and structure differed from those of bacteria and viruses, and that it lacked nucleic acid. They cause direct destruction to the neurons and do not trigger any immunological or inflammatory responses.

The family types of prion illnesses can be considered inherited metabolic disorders, much like Huntington's disease as well as familial Alzheimer's disease. The intermittent and transmitted types of prion are hard to understand. When an abnormal protein enters the body, passes across the blood-brain barrier (BBB), and modifies the folding pattern of its normal counterparts within neurons, it sounds like science fiction. This sets off a series of events that eventually cause the brain to fail.

Star Trek's Borg are an extraterrestrial mechanical-anthropoid species have been likened to prions because of their unrelenting assimilation of other species. This research on prion disorders has earned two Nobel Awards. Stanley Prusiner won the prize to the prion hypothesis in 1997, and Carleton Gajdusek won it in 1976 for using chimpanzees to demonstrate their transmissibility^[9].

Past researchers on Kuru

• Alpers. P. Michael (2008)

Kuru is a spongiform encephalopathy that can be deadly. When it was originally studied in 1957, it was discovered to be found in epidemic areas, with about a thousand deaths during the first five years, or between 1957 and 1961. For over 50 years, epidemiological monitoring has been used to track the spread of the disease. The number of Kuru-related deaths has decreased over the past 50 years from its peak, suggesting that the pandemic is coming to an end. The native funeral practice of transmutation served as the Kuru prion agent's mode of transmission. The epidemic decreased once this practice was outlawed in the 1950s.^[10]

• Lindenbaum S. (2008)

It was necessary to combine information from medical and anthropological studies in order to comprehend Kuru and address the issues surrounding its etiology and

transmission. The origins and dissemination of Kuru, the local endocannibalism in mortuary practices, the societal implications of Kuru, women's lives and childrearing practices, the Fore's kinship system as well as their willingness to include outsiders in it, the myths, folklore, and past history of the Fore and other people, sorcery as a potent social phenomenon and a means of explaining the causes of disease, and ideas of how to treat disease were all clarified by anthropological studies[11].

- **Sakudo Akikazu (2015)**

Protein is an infectious particle composed of an abnormal version of the prion protein (PrP^{Sc}), which causes prion diseases like scrapie, Creutzfeldt-Jacob disease (CJD), and bovine spongiform encephalopathy (BSE). PrP^{Sc} is essential for normal functions like reducing oxidative stress. PrP^{Sc} is produced by conformational conversion and is derived from PrP^C. The well-known resistant pathogen prion is difficult to render inactive with conventional sterilizing methods. Alcohol treatment, autoclaving (121 °C, 20 min), and gamma ray irradiation are methods of disinfection that do not work against prions; antiseptics, which sterilizes bacteria and viruses, does not work against prions[12].

- **Liberski. P. Pawel *et al* (2019)**

Kuru, which was found in the Fore linguistic group of Papua New Guinea, was the first human case of transmissible spongiform encephalopathy (TSE) or prion disease, a deadly cerebellar ataxic syndrome that typically manifests as athetoid and choreiform movements. Individuals homozygous for the 129 Met allele in the gene (PRNP) encoding for prion protein (PrP) were the most vulnerable to Kuru's strong balancing selection on the Fore population. The exhaustion of the vulnerable genotype and, eventually, the cessation of exposure through cannibalism have been cited as the reasons for the drop in Kuru incidence in the Fore[13].

- **Ironside J *et al* (2017)**

"The human prion diseases comprise Creutzfeldt-Jacob disease, variably protease-sensitive prionopathy, Gerstmann-Sträussler-Scheinker disease, fatal familial insomnia, and kuru. Each is a uniformly fatal rare neurodegenerative disease in which conformational changes in the prion protein are thought to be the central pathophysiologic event. The intensive study of these diseases continues to inform on neurodegenerative mechanisms and the role of protein misfolding in more common neurodegenerative diseases such as Parkinson disease and Alzheimer disease[14].

- **Agata Gajos *et al* (2019)**

D. Carleton Gajdusek (1923–2008) infected chimpanzees with Kuru, the first human prion disease. An outline of this ground-breaking discovery's anthropological background, epidemiology, clinical presentation, neuropathology, molecular genetics, as well as history is given here. Using electron and confocal imaging, Kuru amyloid plaques found in a paraffin-embedded block of an old Kuru case called Kupaenota are described. Kuru's discovery opened up new avenues for human medicine and had a crucial role

in the future spread of both bovine spongiform encephalopathy (BSE) and Creutzfeldt-Jacob disease[15].

- **John Collinge *et al* (2007)**

Kuru, the primary example of pandemic human prion disease, has attracted increased attention due to the broad exposure of the UK population with bovine spongiform encephalopathy prions and the possible implications for public health. In order to better understand the peripheral pathogenesis of oral acquired prion disease in humans, Kuru research in Papua New Guinea was extended to examine the range of incubation periods that may occur in human prion infection, characterize genetic predisposition and resistance factors, and look into maternal and other potential natural routes of transmission. Even if the Kuru outbreak is practically over, there are still valuable lessons to be learned[16].

- **Jerome Whitfield *et al* (2008)**

Although Kuru's neuropathology is well understood, little is known about how the disease-related prion protein is distributed in peripheral tissues. The examination of the brain as well as peripheral tissues from an Kuru patient who passed away in 2003 is described here. The neuropathological results were contrasted with those of variant Creutzfeldt-Jacob disease (vCJD) and traditional (sporadic and iatrogenic) CJD. The patient's neuropathological results revealed all the characteristic alterations that characterize Kuru, including the presence of noticeable PrP plaques all over the brain. The absence of prion colonization in lymphoreticular tissue indicates that Kuru's peripheral pathophysiology is more akin to that of classical CJD than vCJD. These results now clearly imply that prion strain type alone, rather than infection method, determines the distinctive peripheral pathophysiology of vCJD [17].

- **Pawel P Liberski (2013)**

Kuru, the first transmissible spongiform encephalopathy from humans, was passed from D. Carleton Gajdusek (1923–2008) to chimpanzees. I provide a brief overview of the epidemiology, clinical picture, neuropathology, and molecular genetics of this groundbreaking discovery in this article. The later propagation of Creutzfeldt-Jacob disease as well as Gerstmann-Straussler-Scheinker disease, as well as the significance of bovine spongiform encephalopathy for human transmission, were all made possible by the discovery of Kuru, which also provided fresh insights into the field of human medicine. One of the most significant contributions to the biomedical sciences in the 20th century was the transmission of Kuru[18].

- **Luisetto M. *et al* (2018)**

We attempt to look into the immunologic function of central nervous systems by first observing the pathophysiology of KURU sickness. A thorough understanding of the pathology's transmission model can be used as a diagnostic or imaging tool to confirm the prion molecule's movement from the gastrointestinal tract to the brain (after cannibalistic behavior). In KURU, the prions can be thought of as a

kind of trace ant for tracking this process and the immune-brain connection. It is possible to gather intriguing data that will help develop novel pharmaceutical approaches for other degenerative brain diseases that involve the activation of the innate immune system[19].

- **Ilman Ahnaf et al (2021)**

Kuru is an uncommon neurodegenerative illness that mainly and efficiently impacts neuronal connections and the central nervous system. As a result, brain tissues and cells began to deteriorate and die. Spongiform encephalopathy results from microorganisms acting against the hazardous dead brain cells. Thus, the human brain's axon-dendron of neurons becomes obstructed. Kuru was discovered to be a complex and possibly pandemic-causing illness in the middle of the 19th century. Kuru is the first human-transmitted disease to be caused by a complex and misfolded protein, despite the fact that the majority of diseases are caused by various viruses, bacteria, fungi, etc. The human body also has a protein called Cellular Prion Protein, or PrPC, which is a normal and harmless protein[20].

- **Collinge et al (2008)**

Nowadays, Kuru is the most prevalent prion disease in people. Even though the incidence of kuru has gradually declined since the 1950s when its mode of transfer, endocannibalism, was stopped in Papua New Guinea, the emergence of variant Creutzfeldt-Jakob disease (vCJD), that is also thought to be spread by dietary prion exposure, gave it a new global significance. We investigated every suspected case of kuru between July 1996 and June 2004 and discovered 11 kuru patients. There were four girls and seven males, having a median age of 46–63 years at the onset of the disease, which stands in sharp contrast to the age distribution among sexes since Kuru was first investigated fifty years ago. Where feasible, we conducted genetic research and serial neurological examinations in addition to obtaining thorough histories of habitation and exposure to funeral feasts. Every patient was born a considerable amount of time before the mortuary practice of consuming ended, and in several cases, their estimated incubation periods were longer than fifty years. Kuru's primary clinical characteristics in the patients under study revealed the same progressive cerebellar condition as had been previously reported. In contrast to previous clinical descriptions, two patients exhibited significant cognitive impairment well before preterminal stages. The mean clinical duration of 17 months in these patients was comparable to that previously identified for the same age group, but it was longer than the Kuru general average. This could be related to the impact of both patient age and the PRNP codon 129 genotype. Crucially, at tonsil biopsy, a patient with kuru showed no signs of lymphoreticular colonization by prions, which is uniformly seen in vCJD[21].

CONCLUSION

It has been determined that Kuru was the first human TSE. The Fore people of Papua New Guinea use cannibalism, which allows it to enter the body through the mouth. Additionally, it indicates that chimpanzees may be the medium of transmission to humans, and recent research has linked them to prion-induced disorders like Alzheimer's, which is currently the subject of additional study. Since no vaccine or medication has been developed as of yet, the only way we can prevent this from happening is to treat Kuru victims symptomatically. We can also prevent cannibalism rituals and sterilize surgical instruments during medical procedures to lessen the severity of laughing disease.

LIST OF DECLARATIONS

Conflict of interests: The authors declare that the manuscript work was conducted in the absence of any commercial relationship that could be construed as a potential conflict of interest.

Authors contribution: Satinder Kakar, Ramandeep Singh and Amisha Maheshwari designed, written and validated the content. The final manuscript was read and approved by all authors.

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