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KURU THE LAUGHING DEATH-A REVIEW

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ABSTRACT

Kuru was the first human transmissible spongiform encephalopathy (TSE) or prion disease identified, occurring in the fore linguistic group of Papua New Guinea. Kuru was a uniformly fatal cerebellar atoxic syndrome, usually followed by choreiform and athetoid movements. Kuru imposed a strong balancing selection on the fore population, with individuals homozygous for the 129 met allele of the gene (PRNP) encoding for prion protein (PRP) being the most susceptible. The decline in the incidence of kuru in the fore has been attributed to the exhaustion of the susceptible genotype and ultimately by discontinuation of exposure via cannibalism .Neuropathologically Kuru-affected brains were characterized by widespread degeneration of neurons, astroglial and microloglial proliferation, and the presence of amyloid plaques. These early findings have been confirmed and by recent immune histochemical studies for the detection of the TSE-specific PRNP.

INTRODUCTION:

Kuru is a rare and fatal nervous system disease. Its highest prevalence occurred during the 1950's and 1960's among the fore people in the highlands of Papua New Guinea.The disorder was described in 1957 by the Australian doctor Zigasom and American researcher Carleton Gajdusek. One of the symptoms of kuru is tremors. Also it got a name "laughing death" as some of patients was noticed to have a strange smile. The fore people contracted the disease by performing cannibalism on corpses during funeral rituals. **The name Kuru means "to shiver (or) trembling in fear"** [1]. The symptoms of the disease includes muscle twitching and loss of coordination other symptoms include difficulty walking, involuntary movements behavioral and mood changes, dementia and difficulty eating. The later may cause malnutrition. Kuru has no known cure. It's usually fatal within one year of contraction. The identification and study of kuru helped along scientific research in a number of ways. It was the first neurodegenerative disease resulting from an infectious agent. It led to the creation of new class of disease including Creutzfeldt-Jakob disease, Gerstmann-straussler-scheinker disease and fatal familial insomnia. Today the study of kuru still impacts research on neurodegenerative diseases. Another name of kuru disease-laughing sickness [2].

Symptoms: Body tremors, random outbursts of laughter, gradual loss of coordination, headache, Joint pains.

Complications: Infection and pneumonia during the terminal stage.

Usual onset: Often takes years (or) even decades for symptoms to appear after exposure.
Specialty: Neuropathology [3].
Duration: 11-14 months life expectancy after onset of symptoms.
Incubation period: 10-12 years. Kuru is a form of transmissible spongiform encephalopathy (TSE) caused by the transmission of abnormally folded proteins (prions), which leads to symptoms such as tremors and loss of co-ordination from neurodegeneration [4].
Risk factors: Cannibalism.
Diagnostic method: Autopsy.
Differential diagnosis: Creutzfeldt-Jakob disease, memory problem, behavior changes, vision problem, poor muscle co-ordination.
Prevention: Avoid practices of cannibalism.
Treatment: None.
Prognosis: Always fatal.
Frequency: 2,700(1957-2014).
Deaths: Approximately 2,700[5].
Pathophysiology:
They are divided into three stages: As shown in Figure 1

1. Ambulant stage.
2. Sedentary stage.
3. Terminal stage.

In the first (ambulant) stage, the infected individual may exhibit unsteady stance and gait, decreased muscle control, tremors, difficulty pronouncing words and tremors tibation.

- This stage is named the ambulant because the individual is still able to walk around despite symptoms [6].
- In the second (sedentary) stage the infected individual is incapable of walking without support and suffers atoxia and severe tremors.
- Furthermore, individual shows signs of emotional instability and depression, yet exhibits uncontrolled and sporadic laughter. Despite the other neurological symptoms, tendon reflexes are still intact at this stage of the disease [7].
- In the third and final (terminal) stage, the infected individuals existing symptoms, like ataxia progress to the point where it is no longer possible to sit up without support. New symptoms also emerge the individual develops "dysphasia", which can lead to severe malnutrition, and may also become incontinent, loss the ability or will to speak and become unresponsive to their surroundings despite maintaining consciousness.
- Towards the end of the terminal stage, patients often develop chronic ulcerated wounds that can be easily infected.
- An infected person usually dies within three months to two years after the first terminal stage symptoms often because of pneumonia or other secondary infection.

Kuru causes brain and nervous system changes similar to Creutzfeldt-Jakob disease [8].

MATERIAL AND METHODS:

(a) Research ethics

The clinical and laboratory studies were approved by the Medical Research Advisory Committee of the Government of Papua New Guinea and by the local research ethics committees of St Mary's Hospital and the Institute of Neurology and National Hospital for Neurology and Neurosurgery in London. Critically important from both the ethical and operational aspects was the full participation in the project of the communities involved. This was established and maintained through discussions with village leaders, communities, families and individuals. The field studies followed the principles and practice of the PNGIMR, in collaboration with which this study was performed [9].

(b) Kuru surveillance and clinical studies

A field base and basic laboratory for sample processing and storage was established in the village of

Waisa in the South Fore. A team of local kuru reporters communicated to the field base the details of any person suspected of suffering from kuru [10]. The large majority of these suspect cases would not be confirmed as kuru on subsequent investigation by the field team or the visiting Medical Research Council (MRC) Unit medical staff; 50 suspect cases investigated during this period proved not to have kuru. The field team comprised MRC, PNGIMR and local staff, and undertook regular field patrols throughout the kuru-affected area, which includes the North and South Fore, Keiagana, Kanite and Gimi linguistic groups [11].

(c) Tonsil biopsy- With informed consent from the patient and his family, tonsil biopsy was performed at Goroka General Hospital by one of us (A.F.), with assistance from local medical staff using disposable instruments, as previously described [12]. A portion of the tonsil tissue was fixed in 10% formal saline and the rest shipped frozen on dry ice to London for analysis. PrP immunohistochemistry was performed using anti-PrP monoclonal antibody ICSM 35 (D-Gen Ltd, London) and Western blot analysis for PrPSc performed as previously described [13].

(d) Molecular genetic studies

The methodology used was as previously described. In brief, genomic DNA was extracted from venous blood and the complete coding sequence of the prion protein gene (*PRNP*) determined by the direct sequencing of the polymerase chain reaction (PCR)-amplified open reading frame[14].Restriction endonuclease digestion of PCR amplicons was used to analyse the apolipoprotein E gene (*APOE*) and the prion-protein-like protein gene (*PRND*). The ABI SDS 7000 sequence detection system was used for the allelic discrimination of *PRNP* codon 129 and *PRNP* haplotypes. HLA-DQB1 alleles were determined by the automated fluorescent sequencing of PCR amplicons using the Amersham Mega BACE DNA analysis system [15].

RESULTS: Since July 1996 to the end of June 2004, we identified 11 kuru patients. The sex, age of onset and duration of disease of all patients are given in table 1. Age is not usually accurately known in these communities but can be reliably estimated by reference to family relationship and historical events. The area and linguistic groups historically affected by kuru are illustrated in figure 2[16]. Figure 3 locates all the villages that have had a history of kuru and shows the shape and extent of the kuru region. All patients identified in the current study were from the south fore, kuru now having disappeared from the north fore and other linguistic groups to the north. The 11 patients were from 10 villages, as there were two patients from Kamira, which since 1957 has had more patients than any other village[17]. "As, males are unlikely to have become infected after the age of 6-8 years, a conservative estimate of the likely minimum incubation period can be calculated as the number of years from age '7' to disease onset[18]. Of the 11 patients four were female and seven male. The age of onset ranged from 46 to 63 years. The ages at death included two in their 40s, five in their 50s and four in their 60s. These distributions are strikingly different from those found when kuru was first analysed 60% of the cases in adult women, with the remainder mostly in children and adolescents of both sexes. In 1957–1958, the proportion of cases in adult males was 2%; this percentage gradually rose as the disease died out in children and adolescents, but the numbers of adult male deaths from kuru were never high. The demography of the South Fore in 1962 shows that in a population of 7224, 6% of males and 4% of females were aged 50 years or more. These percentages are low but consistent with the life expectancy of a traditional society; the difference is one example of the effect that kuru had on the Fore demography (by comparison, the corresponding figures for the 2001 population of the UK are 31 and 35%).

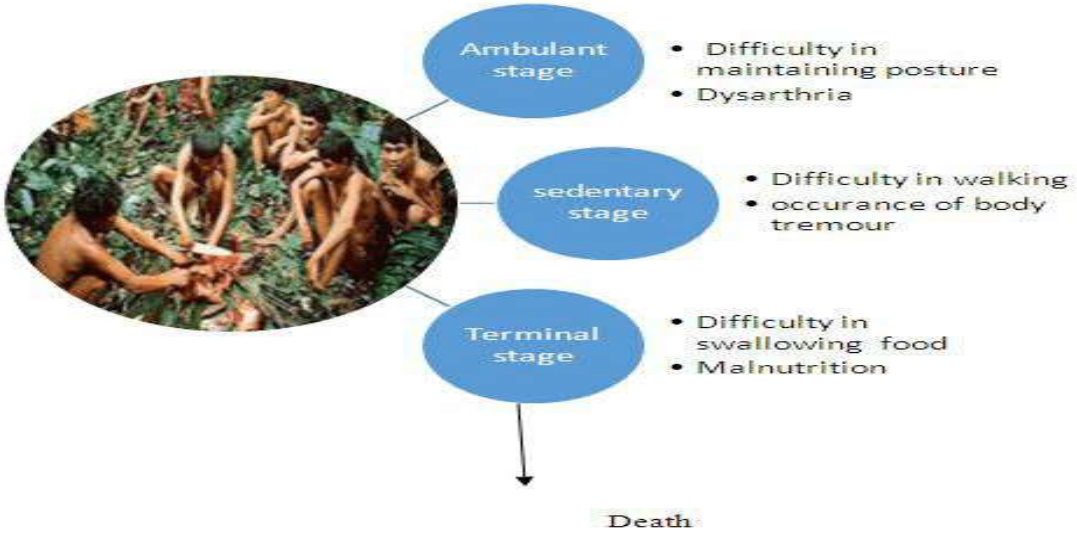

Figure 1: Stages of Kuru.

Figure 2: The area and linguistic groups historically affected by Kuru in the Eastern Highlands Province of Papua New Guinea.

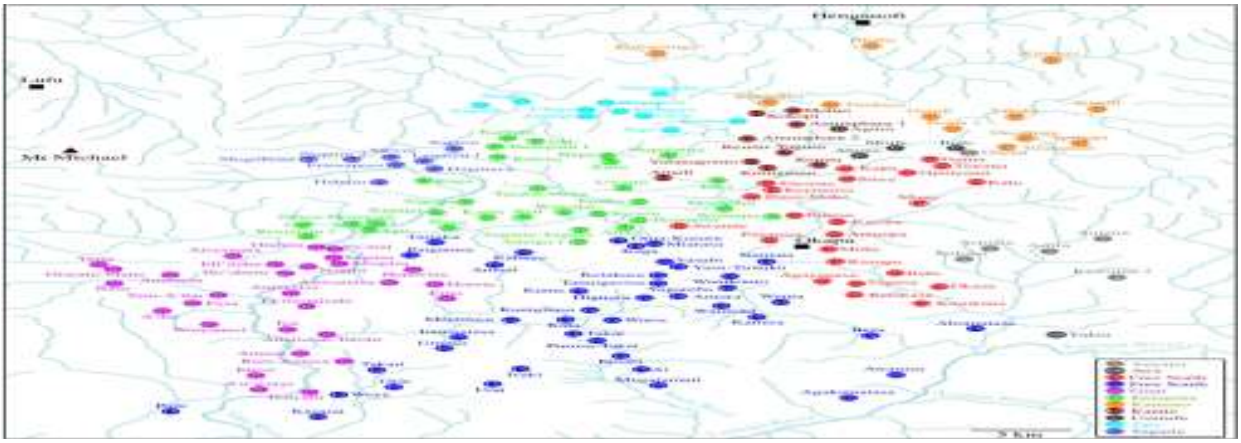

Figure 3: Map showing the location of all villages that have had a history of kuru. Of the 172 villages names on the map, 155 appear in the database if patients recorded since kuru survillance began in 1957; however, only 145 of these villages have had confirmed.

The major perturbation of the demography by kuru was in the male: female ratio of the population: 1.64 in the South Fore in 1962 (in the UK it is 0.95). Despite the relatively small proportion of older people in the population, in the 7-year period of 1957–1963, out of 1254 deaths from kuru, 203 were in females aged 40 years or more including 54 in their 50s and 19 in their 60s. In striking contrast, there were only two male deaths from kuru in this age group. Since both of these deaths occurred in 1962, all males who died of kuru before 1962 were aged less than 40 years (unpublished data from the kuru epidemiological database) [19].

Table 1: Illness duration, PRNP genotype and estimation of incubation period in II recent kuru patients.

SEX	YEAR OF BIRTH	ONSET	AGE AT ONSET	DEATH	AGE OF DEATH	DURATION OF ILLNESS (MONTH)	PRNP GENOTYPE	LIKELY INCUBATION PERIOD (YEARS)
Male	1948	November 1994	46	December 1996	48	25	MV	39
Female	1946	August 1995	49	December 1996	50	16	MV	__
Male	1933	April 1996	63	April 1997	64	12	MV	56
Male	1949	November 1996	47	July 1998	49	20	MV	40
Male	1940	June 1998	58	April 2000	60	22	MV	51
Male	1936	November 1998	62	November 1999	63	12	N.a	55
Male	1943	January 1999	56	June 2000	57	17	MV	49
Female	1945	March 1999	55	January 2000	55	10	VV	__
Female	1944	April 1999	55	January 2001	57	21	MV	__
Female	1942	January 2000	58	May 2001	59	16	MV	__
Male	1943	October 2001	58	April 2003	60	18	MV	51
Male	1949	November 2003	52	May 2014	52	14	MV	__
Female	1949	November 2003	53	November 2014	53	16	MV	__

(M: methionine; V: valine; N.a: not available)

The duration of the disease from the onset of kuru to death varied in the 11 patients from 10 to 25 months. The mean was 17 months and standard deviation (SD) 5 months. This is consistent with earlier findings and the established range of 3–23 months found in 1962–1963, except that there were no cases of short duration. The mean is consequently higher than the 12.5 months (SD 5 months) previously found; however, since that study included all ages and showed that duration tended to lengthen with age, the present finding in patients with a mean age of onset of 55 years is not exceptional.

Wing of a flower or house, although such cognitive testing may be of limited validity in a Fore individual of this age. He was able to complete a three-stage

command and name the local representative and missionary at a nearby larger village. He was able to copy simple hand movements and a salute. There was marked perseveration. Affect appeared normal with appropriate laughter. There was no astereognosis; he was able to correctly name coins, a pen and various vegetables by hand with eyes closed. There was bilateral pout reflex, but palmomental and grasp reflexes were absent. He had a brisk jaw jerk. He was examined in bright light in the village and pupils were small but symmetrical. There was an equivocal light response but definite response to accommodation. Eye movements were full, but pursuit jerky. There was no nystagmus or diplopia and visual fields were intact to confrontation. There was reduced left trigeminal sensation to touch and pinprick and reduced left corneal response. There was no facial weakness, and hearing, palatal movement and tongue movements were normal. Limbs were generally thin with fasciculation of medial thighs bilaterally. There was no wasting of the small muscles of the hand. There was no myoclonus, rest or postural tremor. There was no dystonic posturing but there was marked clawing of the toes while standing. There was extra pyramidal increase in tone in both arms, left greater than right. Limb power was normal with the exception of mild weakness (4/5) in finger abduction. The clinical features of contemporary kuru patients are exemplified by the following case histories[20].

Analysis of tonsil biopsy

It is of considerable interest as to whether kuru, transmitted by dietary prion exposure, is associated with tonsillar prion infection, as seen in vCJD, which is also thought to be transmitted by dietary exposure, but not in other forms of human prion disease. Tonsil biopsy tissue was examined by PrP immunohistochemistry using anti-PrP monoclonal antibody ICSM 35 and no abnormal staining of follicular centre's or other areas was seen, in sharp contrast to vCJD tonsil. Western blot analysis did not demonstrate PrPSc and remained negative following high-sensitivity analysis involving NaPTA precipitation from tissue homogenate to concentrate any PrPSc present[21].

Incubation period estimation

They are, however, presented and discussed here in the context of the local mortuary practices and epidemiological and clinical findings. The transmission of the infectious prion of kuru occurred through the endocannibalism (transumption) of dead relatives at mortuary feasts held in their honour; our understanding of this is based on a conjunction of experimental, epidemiological and human behavioral evidence. The practice was important to the people as a way of respecting their dead, but it was rigorously proscribed by the Australian government officers in one of their first acts of administrative control after making contact with the people. The Okapa Patrol Post was established in 1954. Public consumption of the dead ceased almost immediately and compliance was ensured by the police force responsible for the sub district. By 1956, endocannibalism was suppressed. There were reports of surreptitious eating of the dead in remote hamlets for some years afterwards, but by 1960 the practice had effectively ended; though after this time a few dead bodies may have been exhumed and partially eaten by older women determined to maintain their proper respect for the dead, this would not have had any epidemiological significance since such women would have had multiple previous exposures. Epidemiological surveillance for kuru began in 1957 and has been continued ever since. Owing to the wide geographical extent of the families involved in a feast, secret feasting with whole families taking part would not have gone undetected. The communities of the North Fore, who had been the first of the Fore people to lose their traditional practices in the wake of Australian administrative control, ended their mortuary feasting at the beginning of the decade or earlier; kuru is no longer present in this area. The latest year of birth recorded for any kuru patient is 1959. From this combination of evidence, we can conclude that transmission through the traditional mortuary practices had ceased by 1960. This enables us to obtain a measure of minimum incubation period as the time between 1960 and the date of onset of kuru. The range of minimum incubation period in the 11 patients was 34–41years.

In males, after the age of 6–8 years, boys were taken from their mother and brought up in the men's house. From then on, they were exposed only to the same risk as adult males, who participated little in feasts and did not eat the brain, by far the most infectious organ in kuru. This can explain why in 1957–1958 adult males contributed only 2 percent to the total number of kuru cases and, from what we now know about the incubation period, most of these adult male cases would have been from transmissions in their childhood. This also explains why all males dying of kuru before 1962 were aged less than 40 years: those older would have been aged 6–8 years before 1930, when the epidemic was still slowly building up and their childhood risk of exposure to infection consequently small (females, by contrast, were exposed at all ages throughout the epidemic). From the male ages of exposure, we can estimate the likely minimum incubation period of the males in the recent group of patients described here as extending from the year in which they turned 7 to the year of onset (and it could possibly be up to 7 years longer). The range of likely incubation period in the seven males in 39–56 years. Compared with the UK population, the people of the kuru region, even now, have a relatively low life expectancy; hence, many long incubation cases of kuru would have died of some other cause and would not have been detected. The proportion of such cases relative to those of shorter incubation period will therefore be underestimated in the study described here. Nevertheless, what we have been able to demonstrate is the fact that incubation periods of this length do occur in human prion diseases[22].

Genetic analysis

Results of genetic analysis in these patients have been reported elsewhere and are summarized here and compared with those in the healthy South Fore population. DNA was available for analysis in 10 out of 11 kuru patients and 8 out of 10 were heterozygous at polymorphic residue 129 of *PRNP*. Allele frequencies at *PRNP* 129 in 140 unrelated healthy South Fore were 129M (methionine; 48%) and 129V (valine; 52%). Although the majority of the long incubation kuru cases were heterozygous, as expected from the known protective effect of this polymorphism, this distribution was not statistically different from the current normal population frequencies (X2-test, p=0.22). However, a comparison of clinical duration of illness against codon 129 genotype is interesting in that the two homozygous patients have the shortest durations (10 and 12 months) when compared with the eight heterozygote's. The clinical durations for the two homozygous patients (10 and 12 months) fall 4.2 and 5.2 SD. below the mean clinical duration for heterozygous patients (mean 20.4 months and SD 2.0 months). Although formal statistical tests are not appropriate with only two observations, these data support a modifying effect of codon 129 genotype. The *PRNP* B haplotype has been associated with susceptibility to sporadic CJD in the UK and *PRNP* haplotyping was carried out in these patients and in the normal Fore population. Nine single nucleotide polymorphisms within 25kb of *PRNP* codon 129, identified in the European population, may be used to predict *PRNP* haplotypes. Two common haplotypes are found in the South Fore: 129M is associated with haplotype F (haplotype frequency 40%) and 129V with haplotype A (haplotype frequency 52%). Haplotype B, known to be a common variant in Europe and overrepresented in sporadic CJD patients, was found at a 3 per cent frequency in the South Fore. Albeit from the analysis of a small sample size, the distribution of *PRNP* haplotypes in the long incubation kuru patients was not significantly different from that in the healthy South Fore population (X2-test, p=0.85).

As we have previously reported, allele frequencies at the *PRND* codon 174 polymorphism, *APOE* and HLA-DQB1 in these long incubation kuru patients were not significantly different from those in the current healthy South Fore population, although, clearly, the number of patients analysed was small [23].

SYMPTOMS OF KURU:

The major common symptom of kuru is the neurological disorders such as Parkinson's disease or stroke may resemble kuru symptoms [24]. These include:

Difficulty in walking shown in Figure 4
Headache
Runny nose
Poor co-ordination
Difficulty in swallowing
Slurred speech
Mood and behavioral changes
Dementia
Muscle twitching and tremors
Inability to grasp objects
Random, compulsive laughing or cryin
Joint pain in legs
Impulsive movements of the head
Cough
Fever

Figure 4: Image of Kuru patient.

CAUSES OF KURU:

Kuru belongs to a class of disease called transmissible spongiform encephalopathesis (TSE) also called as prion diseases.

- It primarily affects the cerebellum the part of your brain responsible for coordination and balance.
- Unlike most infections (or) infectious agents kuru is not caused by bacteria, virus or fungus. Infectious, abnormal proteins known as prions cause kuru.
- Prions are not living organisms and do not reproduce.
- They are inanimate, misshapen proteins that multiply in the brain and form clumps, hindering brain processes.
- Creutzfeldt-Jakob, Gerstmann-Straussler-Scheinker disease and fatal familial insomnia are other degenerative disease caused by prions.
- These spongiform diseases as well as kuru create sponge like holes in your brain and are fatal.
- You can contract the disease by eating an infected brain or coming into contact with open wounds or sores of someone infected with it.
- Kuru developed primarily in the fore people of New Guinea when they ate the brains of dead relatives during funeral rites.
- Women and children were mainly infected because they were the primary participants in these rites.
- The New Guinea government has discouraged the practice of cannibalism.
- Kuru has long incubation period and cases still appear, but they are rare [25].

DIAGNOSIS:

- Neurological examination:

Prescriber perform neurological examination to diagnose kuru.

This is comprehensive medical exam including:

Medical history

Neurological function

Blood tests, such as thyroid, folic acid levels

Liver and kidney function tests

Electro diagnostic tests:

- A test such as electroencephalogram (ECG) is used to examine the

electrical activity of brain shown in Figure 5.

- Brain scans such as MRI can be performed, but they may not be helpful in making a definitive diagnosis [26].

TREATMENT:

There is no successful treatment for kuru.

- Prions that cause kuru can't be easily destroyed.
- Brains contaminated with prions remain infectious even when preserved in formaldehyde for years.
- People with kuru require assistance to stand and move and eventually lose the ability to swallow and eat because of symptoms.
- As there is no cure for it, people infected with it may lapse into a common within 6 to 12 months after experiencing initial symptoms.
- The disease is fatal and its best to prevent it by avoiding exposure [27].

PREVENTION: Kuru is exceptionally rare. It's only contracted by ingesting infected within brain tissue (or) coming into contract with soars infected with kuru prions.

- Governments and societies sought to prevent the disease in the mid-20th century by discouraging the social practice of cannibalism.
- According to **NINDS**. The disease has almost completely vanished.
- The incubation period of kuru- the time between initial infection and the appearance of symptoms-can be as long as 30 years.
- Cases have been reported long after the practice of cannibalism has ceased.

Today, kuru is rarely diagnosed. Symptoms similar to those of kuru more likely indicate another serious neurological disorder (or) spongiform disease [28].

AUTOPSY: An autopsy case of Creutzfeldt-Jakob disease with kuru-like neuropathological changes which revealed clinically extra pyramidal, pyramidal and psychic symptoms are reported [29]. On microscopic examination, status spongiosus, neuronal degeneration, proliferation of hypertrophic astrocytes and numerous plaques were observed in the cerebrum and cerebellum accompanied with widespread demyelinization. These plaques which suggested kuru plaques measuring 10 to 60 micron were strongly PAS positive and had a dense central core surrounded by a hole of fine radially arranged fibrils. As for the relationship between Creutzfeldt-Jakob disease and kuru, the significance of these morphological changes is discussed [30].

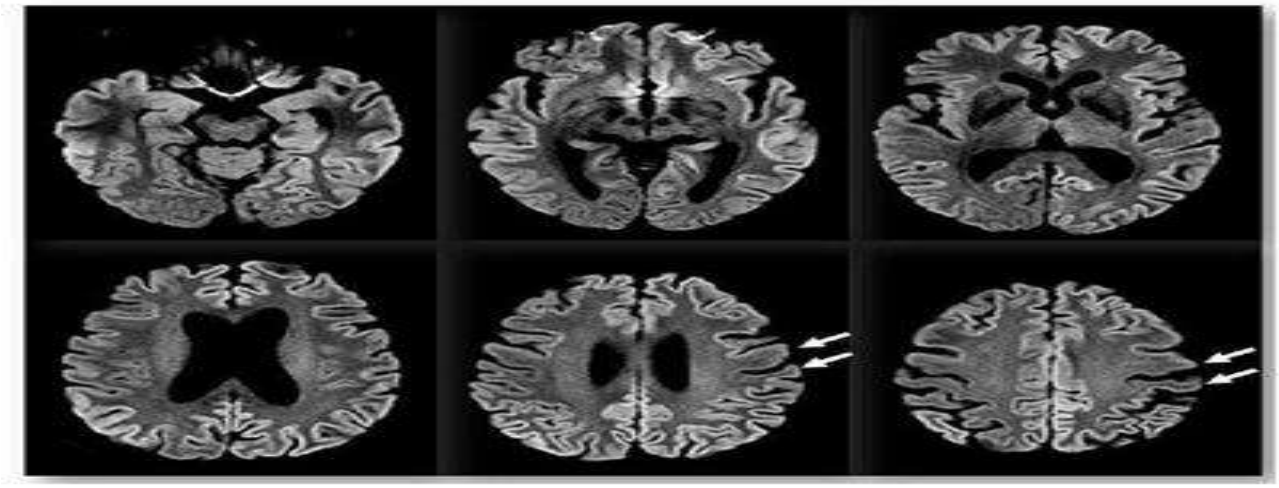

Figure 5: Magnetic Resonance imagining in the diagnosis of Creutzfeldt-Jakob disease.

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