# Transmissible Spongiform Encephalopathies in Humans: Kuru, Creutzfeldt-Jakob Disease and Gerstmann-Sträussler-Scheinker Disease

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## INTRODUCTION

The separation of transmissible spongiform encephalopathies into veterinary and human categories is fundamentally artificial, as they all result from the same pathological process, involving the transformation of a normal host-encoded protein into amyloid fibrils that accumulate in, and eventually destroy, the brain.

Nevertheless, the human diseases are in some respects at least superficially different from the veterinary diseases, which have been described by Kimberlin in another article of this symposium (1). The following discussion will cover the three human varieties of spongiform encephalopathy: kuru, Creutzfeldt-Jakob disease (CJD), and Gerstmann-Sträussler-Scheinker disease (GSSD).

### KURU

Although it was the last of the three diseases to be described, kuru was the first to be transmitted. The story is by now well known of how in 1957 Gajdusek and Zigas observed the disease while trekking amongst the Fore people in the highland rain forests of Papua New Guinea (2); after years of unsuccessful experiments using laboratory rodents, Gajdusk *et al* finally succeeded in transmitting the disease to a chimpanzee in 1965 (3).

Kuru is also the native word for shivering, and well describes the most striking sign of the disease, a fine tremor of the head, trunk, and limbs, that is associated with the insidious onset of ataxia. Both the ataxia and tremor become more pronounced as the disease progresses, and are joined by other signs of cerebellar pathology, and by behavioral abnormalities, often in the form of inappropriate mood changes and hilarity. Intellectual deterioration, if it occurs at all, is usually minimal and supervenes only in the terminal state, several months after the onset of illness (Table I).

There is reason to believe that kuru first appeared among the Fore in the early years of this century, gradually increasing in frequency until by the middle 1950's it had reached epidemic proportions. Its predominant occurrence in children of both sexes and young adult women was for many years thought most likely to reflect either a sex-linked genetic abnormality, or an endocrine disorder.

The eventual solution proved to be much more prosaic. It was well known that ritual cannibalism was practiced among the Fore, and might be linked to the spread of disease. What was not appreciated, probably because of a natural reticence to reveal the details of a ritual that had been declared illegal, was the fact that adult men generally ate the meat, leaving the remaining parts of the body, including the brain, to the women and children.

We later learned that the disease could be experimentally transmitted by the oral route (4), and that virus was present in high titer in brain tissue, but almost never in muscle (5). The conjunction of these experimental observations with the details of ritual consumption fully explained the age and sex distribution of disease, and represents the closest human analogy to the epidemiology of scrapie in sheep, for which placental ingestion appears to be the major, and perhaps sole, source of viral spread (6).

Pathologically, kuru is characterized by a mild to moderate degree of neuronal vacuolation, an intense astrocytic gliosis, corticospinal and/or spinocerebellar tract degeneration, and, in at least half the studied cases, the presence of numerous amyloid plaques that tend to be most common in the cerebellum, but can also be widely distributed in the cerebrum. This pathological picture caused Klatzo to note its similarity to CJD (7), and the subsequent experimental transmission of kuru was quickly followed by an equally successful attempt with CJD in 1968 (8). Human spongiform encephalopathy was thus expanded from a small speck in the middle of New Guinea to a disease of world-wide distribution.

### CREUTZFELDT-JAKOB DISEASE

Clinically, CJD is typically a dementing disease, albeit usually associated with cerebellar and other neurological abnormalities, that terminates fatally in most cases within three to six months of onset. Instead of the kuru type of shivering tremor, patients with CJD usually exhibit myoclonic jerking, associated with a very characteristic electroencephalographic pattern of periodic triphasic slow wave spikes. Pathologically, the most striking alteration in the brain is a diffuse spongiform change; plaques, although seen in the occasional patient, are distinctly unusual.

The major difference between CJD and kuru probably lies in their epidemiological patterns. Instead of the highly focused and geographically constricted epidemic of kuru, CJD occurs in an almost completely disperse pattern of sporadic cases at an

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**TABLE I. Comparison of epidemiological, clinical, biological, and pathological features typically found in the three varieties of human spongiform encephalopathy**

| Characteristic | Kuru | Creutzfeldt-Jakob disease | Gerstmann-Sträussler Scheinker disease |
|---|---|---|---|
| Epidemiological pattern | epidemic | sporadic, familial, iatrogenic | familial, ?sporadic |
| Clinical features | | | |
| Age at onset | 5-35 yr | 50-75 yr | 35-50 yr |
| Duration | 6-9 mo | 2-8 mo | 2-8 yr |
| Early signs | cerebellar (ataxia, tremor) | dementia, cerebellar, visual | spinocerebellar (ataxia) |
| Later signs | behavioral changes | myoclonus, pyramidal, extra-pyramidal | dementia, pyramidal, amyotrophy |
| Abnormal biological tests | none | periodic EEG activity | PrP gene mutation |
| Neuropathology | | | |
| Spongiform change | +++ | ++++ | + |
| Astrogliosis | ++++ | +++ | ++ |
| Neuronal loss | + | + | + |
| Plaques | +++ | ± | ++++ |
| Myelin tract degeneration | ++ | 0 | ++ |

annual incidence of only about one case per million people, distributed equally among men and women, with a peak incidence in the 50 to 75 year age group. Approximately 5-10% of cases occur in families in an autosomal dominant pattern of inheritance.

The only cases for which the mechanism of disease transmission is apparent are those rare instances of iatrogenic infection by direct bodily penetration of contaminated instruments or tissues, most recently highlighted by the outbreak of CJD in recipients of growth hormone extracted from autopsied pituitary glands (9). In this regard, there is at least one clear parallel between kuru and CJD: epidemiological study of the dwindling number of kuru patients has documented incubation periods of 20-30 years between the last participation in ritual cannibalism and the onset of disease (10); similar study of hormone recipients shows a range of incubation periods between the last dose of hormone and the onset of symptoms that also extends up to 20 years (11) (Fig. 1). Thus, while direct intracerebral inoculation of virus causes disease in humans and chimpanzees in two years or less, the intake of virus by inefficient peripheral routes is followed by decades-long intervals between infection and clinical disease.

Even with these long incubation periods, kuru was such a distinctive illness that diagnosis was never a problem. The same cannot be said of CJD. Before the bedrock criterion of transmissibility was established, the rubric of CJD contained a heterogeneous assortment of cerebral degenerative diseases; indeed, Creutzfeldt's original case (12), and three of the five cases later reported by Jakob (13) do not, according to our present definition, qualify as cases of Creutzfeldt-Jakob disease (14). It was only by analysis of a large core of transmitted cases that we were able to peel away the confusing husk of other diseases, and refine our appreciation of the clinical and pathological features of CJD to the point that today, in all but the most atypical cases, diagnostic verification by animal inoculation is a redundant exercise.

## GERSTMANN-STRÄUSSLER-SCHEINKER DISEASE

First described in an Austrian family in 1936 (15), GSSD has subsequently been reported to occur in about a dozen other unrelated families, as well as in sporadic form. The disease shows a substantial clinical and pathological overlap with kuru and CJD, but certain features tend to be distinctive. First, is the fact that the majority of cases are familial. Second, the disease usually affects an age group between 35 and 55 years, and its duration may range from two to ten years. Third, spinocerebellar signs usually precede the appearance of significant dementia. And fourth, the pathology is dominated by the presence of various types of plaques in the cerebral and cerebellar cortex, especially multicentric plaques in the cerebellar cortex, but also includes spinocerebellar tract degeneration and a variable (usually modest) degree of spongiform change in the cerebral cortex and subcortical nuclei.

This description of GSSD is based on a literature that, like the earlier literature of CJD, may be contaminated by case reports of similar but unrelated neurological disorders. Gerstmann-Sträussler-Scheinker disease can transmit a disease to experimentally inoculated animals that is indistinguishable from CJD, but its rarity has hindered definition by the criterion of transmissibility. Thus, the recent discovery of an identical point mutation in affected members of several different, unrelated GSSD families (16,17) is a welcome adjunct to diagnosis, and the definition of GSSD may now be poised for the same kind of revision that transmissibility achieved for CJD, at a fraction of the cost.

The mutation occurs in a gene on chromosome 20 encoding an amyloidogenic protein (PrP) that is critically implicated in the pathogenesis of all of the spongiform encephalopathies. This mutation is clearly not the root cause of GSSD, since it is not found in any other spongiform encephalopathy, and all are transmissible; however, it undoubtedly influences the clinical and pathological expression of disease enough to permit its separation from kuru and CJD as a third variety of human transmissible spongiform encephalopathy.

## THE CAUSATIVE AGENTS

In light of the fact that these encephalopathies are transmissible, it is logical to ask whether they are also contagious, in the sense of naturally occurring spread among humans, and whether the infectious agent has been identified. The answer to both questions is a qualified no.

How we respond to the first question depends upon our definition of the word "natural". If, like certain

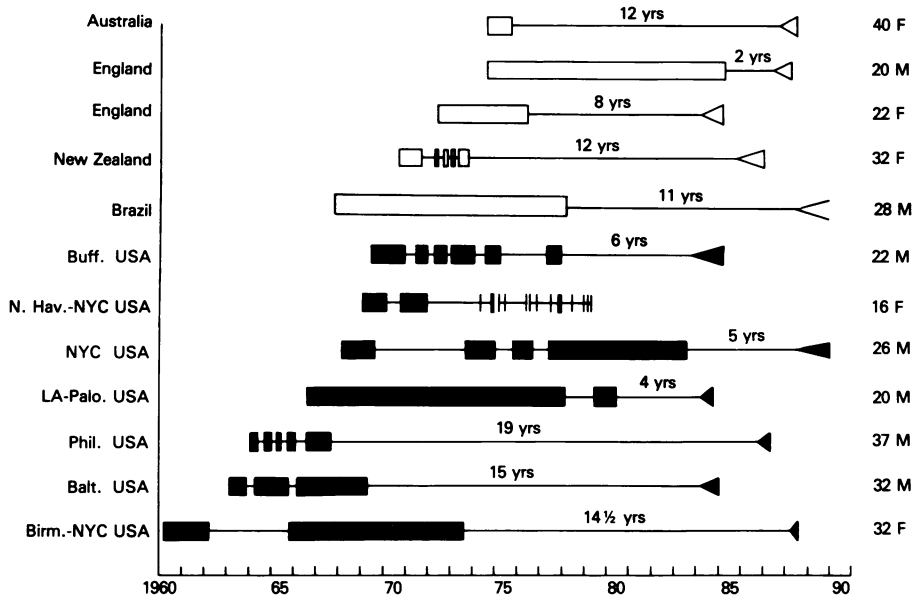


**Fig. 1. Graphic representation of the time course of hormone treatment and subsequent death from CJD of 11 patients who received human growth hormone, and one patient who received human gonadotropin (Australian case at top of figure). Rectangles represent treatment periods, triangles represent the onset and duration of CJD, and times between last treatment and onset of disease (minimum incubation periods) are shown in years. The patient with no triangle died from an unrelated cause during the preclinical incubation period of CJD.**

religious groups, we consider the practice of transfusing blood products to be unnatural, then serum hepatitis is not a naturally occurring disease. If we believe the sexual practices of the gay community to be unnatural, then AIDS is not a naturally transmitted disease. And if we view the practice of ritual cannibalism among the Fore to be unnatural, then kuru is not a naturally transmitted disease.

Creutzfeldt-Jakob disease presents quite a different problem. It has always been a rare, and in the main, sporadic disease, and has defeated every attempt to identify a mechanism by which it might spread, with the exception of a handful of iatrogenic cases (11,18). Gerstmann-Sträussler-Scheinker disease is even more puzzling, since it is virtually restricted to a few widely scattered families around the world. We know that none of these diseases is vertically transmitted (19), and the opportunities for horizontal transmission of CJD and GSSD range from small to nonexistent. We are thus obliged to admit that it is highly unlikely that any of the human spongiform encephalopathies are naturally transmitted.

What is the nature of this transmissible but not normally contagious agent? This is what we used to call, before the advent of creeping inflation, the $64 question, and there is still no consensus about the answer. Most of the work to characterize the transmissible agent has been carried out in experimental models of scrapie, but the results of these studies are equally applicable to the human disease agents.

The scrapie-associated fibril (SAF) dicovered in 1981 by Merz *et al* (20) in extracts of infected rodent brains was subsequently found with essentially the same morphology in the human encephalopathies (21), and the host-encoded amyloid protein of which it is in part or wholly composed varies only slightly in different species (22).

There is little doubt that the extracted fibril contains the infectious agent. There remains a question, however, about whether this morphological package exists *in vivo*, and whether its constituent protein is the infective unit. A running argument continues over the existence of a putative but as yet undetected foreign nucleic acid that promotes conversion of the normal host protein into an amyloid configuration, or, if such a nucleic acid does not exist, by what alternative mechanism the amyloid molecule might reproduce itself (23).

The latter possibility, although inconsistent with the central dogma of molecular biology, and with certain aspects of the genetics and pathogenesis of the spongiform encephalopathies, nevertheless benefits hugely from having a real molecule to study, instead of a phantom to seek. The most recent ingredient to be thrown into the stewpot of ideas about the nature of the infectious agent is the concept of a seed molecule that functions as the nucleating agent in a process of organic crystallization (24,25). The identity of this seed molecule (infectious agent) is still a matter of pure speculation, but once initiated, the process would be self-sustaining, producing ever increasing quantities of itself that would eventually aggregate into paracrystalline arrays of amyloid.

However the story may end, it is appropriate to reemphasize that long before the names kuru, Creutzfeldt, and Gerstmann had become part of the neurologist's vocabulary, field and research veterinarians had not only described the natural history, clinical signs, and pathological picture of scrapie, they had shown it to be transmissible (26), genetically influenced (27), and adaptable to the laboratory mouse (28), in which a vast quantity of fundamental information was obtained. And it was a veterinarian who first saw a connection between this already well studied animal disease and kuru, the prototype human disease (29). In a very real sense, then, the whole field of human spongiform encephalpathies owes its origins to the tenacity and perspicacity of the veterinary profession.

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