Kuru in the 21st century—an acquired human prion disease with very long incubation periods

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Summary

Background Kuru provides the principal experience of epidemic human prion disease. Its incidence has steadily fallen after the abrupt cessation of its route of transmission (endocannibalism) in Papua New Guinea in the 1950s. The onset of variant Creutzfeldt-Jakob disease (vCJD), and the unknown prevalence of infection after the extensive dietary exposure to bovine spongiform encephalopathy (BSE) prions in the UK, has led to renewed interest in kuru. We investigated possible incubation periods, pathogenesis, and genetic susceptibility factors in kuru patients in Papua New Guinea.

Methods We strengthened active kuru surveillance in 1996 with an expanded field team to investigate all suspected patients. Detailed histories of residence and exposure to mortuary feasts were obtained together with serial neurological examination, if possible.

Findings We identified 11 patients with kuru from July, 1996, to June, 2004, all living in the South Fore. All patients were born before the cessation of cannibalism in 1956. The minimum estimated incubation periods ranged from 34 to 41 years. However, likely incubation periods in men ranged from 39 to 56 years and could have been up to 7 years longer. PRNP analysis showed that most patients with kuru were heterozygous at polymorphic codon 129, a genotype associated with extended incubation periods and resistance to prion disease.

Interpretation Incubation periods of infection with human prions can exceed 50 years. In human infection with BSE prions, species-barrier effects, which are characteristic of cross-species transmission, would be expected to further increase the mean and range of incubation periods, compared with recycling of prions within species. These data should inform attempts to model variant CJD epidemiology.

Kuru is one of a group of closely related neurodegenerative conditions that affect both human beings and animals, known as the transmissible spongiform encephalopathies or prion diseases. Prion diseases are associated with the accumulation in the brain of an abnormal, partly protease-resistant, isoform of a host-encoded glycoprotein known as prion protein (PrP). According to the protein-only hypothesis, an abnormal PrP isoform is the main, and possibly the only, constituent of the transmissible agent or prion. The large-scale epidemic of bovine spongiform encephalopathy (BSE) in the UK led to fears of a serious threat to public health. Since 1996, cases of a novel human prion disease, variant Creutzfeldt-Jakob disease (vCJD), have been identified in the UK, and strain typing has confirmed that both vCJD and BSE are caused by the same prion strain. Dietary exposure of the UK population to BSE prions has been widespread; the total cattle epidemic is thought to have affected 2 million cows. Cattle BSE has also been reported in most EU states, Israel, Switzerland, Canada, the USA, and Japan. So far, about 160 vCJD patients have been identified in the UK, with cases also reported in France, Italy, Ireland, the Netherlands, Canada, Japan, and the USA. Predictions of the eventual size of a vCJD epidemic have varied widely, although some recent estimates, based on current cases of vCJD, suggest that the total epidemic may be relatively small. However, key uncertainties, notably with respect to major genetic effects on the incubation period, suggest the need for caution. Importantly, such models cannot estimate the number of infected individuals, which remains unknown, and concerns of secondary transmission have heightened. These uncertainties, especially with the possibility of very long incubation periods of BSE in people, have renewed interest in kuru, which remains the only example of a major human epidemic. Kuru reached epidemic proportions in a defined population of the Eastern Highlands of Papua New Guinea. Local oral history, taken when the disease was first studied by western medicine in the 1950s, dated the onset of the first cases to the 1920s. Kuru mainly affected the people of the Fore linguistic group and also their neighbours with whom they intermarried. The disease predominantly affected women and children (of both sexes), with only 2% of cases in adult men; kuru also became the most common cause of death in women in affected villages. Kuru is a cerebellar syndrome with a characteristic and relentless progression through defined clinical stages, and is invariably fatal. Cognition is fairly preserved, and the disease is highly distinctive and is usually recognised easily by both the patients and their local community. These communities practised the consumption ritual of dead relatives as a mark of respect and mourning. Boys older than 6–8 years participated little in mortuary rituals, and the age of initiation of the consumption ritual was therefore an important indicator of the age of the patients. The large-scale epidemic of bovine spongiform encephalopathy (BSE) in the UK led to fears of a serious threat to public health. Since 1996, cases of a novel human prion disease, variant Creutzfeldt-Jakob disease (vCJD), have been identified in the UK, and strain typing has confirmed that both vCJD and BSE are caused by the same prion strain. Dietary exposure of the UK population to BSE prions has been widespread; the total cattle epidemic is thought to have affected 2 million cows. 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feasting, which could explain the differential age and sex incidence. From the age of the youngest affected patient, the shortest incubation period is estimated to be 5 years, although this time could be shorter, since time of infection is usually unknown.

Genetic susceptibility is important in both the sporadic and acquired forms of human prion disease; human PrP has a common polymorphism, with either methionine or valine present at residue 129. About 38% of Europeans are homozygous for the more frequent methionine allele, 51% are heterozygous, and 11% homozygous for valine. Most sporadic CJD occurs in individuals homozygous for this polymorphism. This susceptibility factor is also relevant in the acquired forms of CJD, most strikingly in vCJD; all clinical cases studied so far have been homozygous for codon 129 methionine of the PrP gene PRNP. The PRNP codon 129 genotype has shown a pronounced effect on kuru incubation periods and susceptibility, and most elderly survivors of the kuru epidemic are heterozygotes. The clear survival advantage for codon 129 heterozygotes provides a powerful basis for selection pressure in the Fore. However, an analysis of worldwide haplotype diversity and allele frequency of coding and non-coding polymorphisms of PRNP suggests that balancing selection at this locus (in which there is more variation than expected because of heterozygote advantage) is much older and more geographically widespread. Evidence for balancing selection has been shown in only a few human genes. With biochemical and physical evidence of cannibalism on five continents, one explanation is that cannibalism resulted in several prion disease epidemics in human prehistory, thus imposing selection pressure on prion genes.

Kuru was extensively studied at its peak in the late 1950s and early 1960s and monitoring was continued through the Papua New Guinea Institute of Medical Research. We strengthened active kuru surveillance in 1996 and aimed to study all patients with kuru until the end of the epidemic. Here, we aimed to determine the maximum period possible for incubation in human prion infection and to investigate genetic factors in recent patients with kuru. The abrupt interruption of transmission of kuru, after the effective prohibition of cannibalism by Australian authorities in the mid-1950s, allows a unique opportunity to investigate the incubation period of infection as a key variable in human prion disease. Our findings of detailed clinical features and mortuary feast practices will be reported elsewhere.

Methods

Research ethics

Our study was approved by the Papua New Guinea Medical Research Advisory Committee and by the local research ethics committees of St Mary’s Hospital and National Hospital for Neurology and Neurosurgery, in London, UK. The full participation in the project from the communities, which was critical with respect to the ethics and operation of the study, was established and maintained through discussions with village leaders, communities, families, and individuals, and the field studies followed the principles and practice of the Papua New Guinea Institute of Medical Research.

Kuru surveillance and clinical studies

A field base and laboratory was established in Waisa in the South Fore. A team of local kuru reporters communicated details of any suspected case to the field base. 50 suspect cases investigated during this period proved not to have kuru. The field team consisted of staff from the UK Medical Research Council (MRC), the Papua New Guinea Institute of Medical Research, and local communities, who undertook regular field patrols throughout the kuru-affected areas.

Table 1: Estimation of kuru incubation periods in 11 patients identified in current study

<table>
<thead>
<tr>
<th>Sex</th>
<th>Year of birth</th>
<th>Onset</th>
<th>Age at onset (years)</th>
<th>Age at death (years)</th>
<th>PRNP 129 genotype</th>
<th>Minimum incubation period (years)*</th>
<th>Likely incubation period (years)?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKW</td>
<td>F</td>
<td>1946</td>
<td>August, 1995</td>
<td>49</td>
<td>50</td>
<td>Heterozygous</td>
<td>35</td>
</tr>
<tr>
<td>YAK</td>
<td>M</td>
<td>1948</td>
<td>November, 1994</td>
<td>46</td>
<td>48</td>
<td>Heterozygous</td>
<td>34</td>
</tr>
<tr>
<td>MWK</td>
<td>M</td>
<td>1933</td>
<td>April, 1996</td>
<td>61</td>
<td>64</td>
<td>Methionine homozygous</td>
<td>36</td>
</tr>
<tr>
<td>AKA</td>
<td>M</td>
<td>1949</td>
<td>November, 1996</td>
<td>47</td>
<td>49</td>
<td>Heterozygous</td>
<td>36</td>
</tr>
<tr>
<td>AYA</td>
<td>M</td>
<td>1936</td>
<td>November, 1998</td>
<td>62</td>
<td>63</td>
<td>n/a</td>
<td>38</td>
</tr>
<tr>
<td>TAM</td>
<td>F</td>
<td>1945</td>
<td>March, 1999</td>
<td>54</td>
<td>55</td>
<td>Valine homozygous</td>
<td>39</td>
</tr>
<tr>
<td>AYY</td>
<td>M</td>
<td>1940</td>
<td>June, 1998</td>
<td>58</td>
<td>60</td>
<td>Heterozygous</td>
<td>38</td>
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<tr>
<td>WKO</td>
<td>M</td>
<td>1943</td>
<td>January, 1999</td>
<td>56</td>
<td>57</td>
<td>Heterozygous</td>
<td>39</td>
</tr>
<tr>
<td>MAA</td>
<td>F</td>
<td>1944</td>
<td>April, 1999</td>
<td>55</td>
<td>57</td>
<td>Heterozygous</td>
<td>39</td>
</tr>
<tr>
<td>INO</td>
<td>F</td>
<td>1942</td>
<td>January, 2000</td>
<td>58</td>
<td>59</td>
<td>Heterozygous</td>
<td>40</td>
</tr>
<tr>
<td>KAW</td>
<td>M</td>
<td>1943</td>
<td>October, 2001</td>
<td>58</td>
<td>60</td>
<td>Heterozygous</td>
<td>41</td>
</tr>
</tbody>
</table>

Patients’ initials are based on name and coded. *Calculated conservatively as the number of years between 1960 and onset of kuru (assuming latest possible exposure at mortuary feast in 1959). This period would be an underestimate (in some cases of many years) of the actual incubation period (measured from the date that infection was actually acquired). The maximum incubation period possible (in the event of neonatal infection) would be the same as age at onset. †Since male individuals were unlikely to be infected after age 6–8 years, the likely minimum incubation period can be calculated as the number of years from age 7 years to disease onset, which is also a conservative estimate, since actual infection could have taken place (up to 7 years) earlier. F=female. M=male. n/a=not available.

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**Results**

The total number of cases of kuru from 1957 to 2004 exceeded 2700, with more than 200 dying every year in the late 1950s. This number fell to about six a year in the early 1990s and between one and two a year during the study; since July, 1996, we identified 11 kuru patients up to the end of June, 2004.

Table 1 shows the ages at onset of all 11 patients in the study. Age might not be accurately known or reported by individuals in these communities, but can be reliably and accurately estimated by reference to family relationships and clearly defined recent historical events. Figures 1 and 2 show the area and populations historically affected by kuru. All patients identified in the current study were from the South Fore, now that kuru has disappeared from the North Fore and adjacent linguistic groups (figure 2).

On the basis of a conjunction of experimental, epidemiological, and human behavioural evidence, we can assume that all transmission through the traditional mortuary practice had ceased by 1960. The practice had been important to the Fore people as a way of respecting their dead relatives, but it was rigorously forbidden by Australian Government officers in one of their first acts of administrative control after making contact with the people, when the Okapa patrol post was established in 1954. Public consumption of dead relatives ceased almost immediately and compliance was ensured by the police force responsible for the subdistrict. By 1956, endocannibalism was effectively gone. Surreptitious eating of dead relatives had been reported in remote communities for some years afterwards, but by the end of the 1950s the practice had ended. Epidemiological surveillance for kuru began in 1957 and has been continued ever since. Because of the wide geographical extent of the families participating in a feast, secret feasting with entire 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 onset could have been underestimated by a few years.

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Therefore, for practical purposes, we can assume that all transmission through the traditional mortuary practices had ceased by 1960. Therefore, we could define the minimum incubation period as the time between 1960 and the date of onset of kuru (table 1). For patients born in earlier decades, the actual incubation could be much longer; however, since the infecting event can never be known, all individuals alive during the period when consumption of dead relatives’ bodies was universally practised must be regarded as being at risk.

**Role of the funding source**

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.
Figure 2: Individual patients with kuru recorded during the 5 years immediately after cessation of endocannibalism (1957–61), after 20 years (1977–81), and in the current study (1996–2004).

Patients plotted by village of residence. Black squares indicate towns.

After the age of 6–8 years, boys were taken from their mothers and brought up in the men’s house. From this point on, they were exposed only to the same risk as adult men, who participated little in feasts and did not eat the brain, by far the most infectious organ in kuru. This practice can explain why adult men in 1957–58 and from what we now know about the incubation period, most would have been from transmissions in their childhood. Therefore, we can estimate that the likely incubation period of the male patients identified in this study began at about age 7 years, lasting up to the age of onset (table 1). These projections are less robust than the minimum estimates, but nevertheless are potentially real and should not be ignored in any consideration of the incubation period of human prion diseases.

DNA was available for genetic analysis from ten of 11 patients with kuru (table 2). Eight patients were heterozygous at the polymorphic residue 129 of PRNP. In 140 unrelated healthy individuals from the South Fore, allele frequencies at the PRNP residue 129 were 48% methionine and 52% valine. Although most of the kuru cases with long incubation periods were heterozygous (as expected), this distribution did not differ from the current frequencies of the control population ($\chi^2$ test, $p=0.85$). For other genetic loci implicated in human prion disease susceptibility ($PRND$, $APOE$, $HLA$, table 2), these alleles for kuru patients with long incubation periods also were not significantly different from the healthy population in the South Fore.

### Discussion

The early clinical, epidemiological, and anthropological study of kuru; the recognition of its neuropathological, and then causal parallels to ovine scrapie; and then crucially, the experimental transmission of the disease...
to primates,\textsuperscript{21} originated the concept of the human transmissible spongiform encephalopathies, which was followed in turn by the eventual unifying concept of the mammalian prion diseases. However, in addition to the central historical importance of kuru, study of the end-stage of this epidemic offers a unique opportunity to study the variables of a near-complete epidemic of human prion disease. In particular, recognition of the incubation periods possible after natural prion infection in people is important in providing an insight (from actual case histories rather than from mathematical models) into the probable span of the vCJD epidemic in the UK. Although estimation of kuru incubation periods early in the epidemic was difficult, and the timing of the actual infecting event for an individual can rarely be determined, the abrupt and permanent interruption of the source of infection, endocannibalism, in the late 1950s, has progressively allowed recognition of an enormous span of possible incubation periods, at its shortest extreme bracketed by the rare onset of disease in children as young as 5 years and extending up to (and perhaps beyond) the incubations covering more than half a century, as we describe here.

In our field studies, we have interviewed many individuals who participated in traditional mortuary feasting or who described the participation of family members from the preceding generation. These detailed descriptions will be published elsewhere but have reaffirmed the oral histories of endocannibalism in the Fore recorded previously\textsuperscript{22–24} and that this practice ceased abruptly at the time of Australian administrative control over the kuru areas. Although isolated events might have occurred for a few years after this prohibition, we are confident that new exposures of individuals to kuru at mortuary feasts would not have occurred after 1960. Not only have no cases of kuru been recorded in people born after 1959 (and only nine were recorded in those born after 1956); but also all the 11 last recorded cases of kuru that we report here were born before 1950. If any source of infection remained, whether from surreptitious cannibalism, possible ground contamination with human prions at sites where food was prepared, or other lateral routes, we would expect individuals born after this period to have kuru—especially since children are thought to have had shorter incubation periods than adults. However, no such cases have been observed.

Additionally, although a fraction of hamster-adapted scrapie prions have been shown to survive in soil for at least 3 years,\textsuperscript{25} the mortuary feast practices (during which the entire body would be consumed) were undertaken so that any substantial contamination of soil would not have occurred, and traditional bamboo knives and leaf plates were burned after the feast. Furthermore, no clusters of kuru cases, as seen earlier in the epidemic,\textsuperscript{26} have been recorded for many years. We have also reviewed the assertion that maternal transmission of kuru did not occur, and saw no evidence for maternal transmission from kuru archives, interviews of colleagues who have practised medicine in the Fore, or local oral history. Again, any possible vertical route of kuru transmission would have resulted in the presence of kuru in children born after 1960, especially since kuru was common in women of childbearing age; no such cases have occurred.

With respect to extrapolation of incubation periods of BSE prion infection in people, we should recognise that the kuru epidemic arose from intraspecies recycling of infectious prions. However, transmission of prions between different mammalian species is associated with a species barrier, which is better described as a transmission barrier, because of the importance of within-species prion strain type, in addition to species-specific differences in its determination.\textsuperscript{27} The biological effects of such a barrier are: extended mean incubation period; increased spread of incubation periods in individual animals; and reduced attack rate (in which only a fraction of inoculated animals will succumb), by comparison with the 100% mortality generally associated with within-species inoculation with high-titre infectivity. Incubation periods approaching the natural lifespan of the inoculated species are often seen in such primary cross-species transmissions of prions. Second and subsequent passage of prions within the new species is always associated with adaptation involving a considerable shortening of the mean and spread of incubation periods and high or total lethality to high-titre inocula. Thus, estimation of the range of possible incubation periods in human BSE infection needs superimposition of the effect of a transmission barrier onto these findings of natural human incubation periods.

The mean incubation period for kuru has been estimated to be around 12 years,\textsuperscript{2} with a similar estimate in iatrogenic CJD associated with the use of human-cadaver-derived pituitary growth hormone.\textsuperscript{28} As shown here, maximum incubation periods in kuru can exceed 50 years. The transmission barrier of BSE between cattle and human beings is unknown and cannot be directly measured. However, the cattle-to-mouse barrier for BSE has been well characterised experimentally by comparative endpoint titration. BSE prions transmit readily to laboratory mice, including after oral dosing.\textsuperscript{29} The murine LD\textsubscript{50} (lethal dose causing 50% mortality) in C57Bl/6 mice is about 500-fold higher than that in cattle;\textsuperscript{30} this barrier also results in a three-fold to four-fold increase in mean incubation period.\textsuperscript{31} Mean incubation periods of human BSE infection of 30 years or more should therefore be regarded as possible, if not probable,\textsuperscript{31} with the longest incubation periods approaching (and perhaps exceeding) the typical human lifespan. The shortest incubation periods in kuru were estimated from the age of the youngest patients—suggesting that the shortest incubation period was
4–5 years. Similarly in vCJD, although the total clinical caseload so far has been small, the youngest onsets of vCJD have been at age 12 years or above, providing an early estimate of a minimum incubation period.

Furthermore, prion disease in mice follows a well-defined course with a highly distinctive and repeatable incubation time for a specific prion strain in a defined inbred mouse line. In addition to the PrP gene, a few additional genetic loci with a major effect on incubation period have been mapped.\textsuperscript{3,11,12} Human homologues of such loci could be important in human susceptibility to prion disease, both after accidental human prion exposure and after exposure to the BSE agent. By definition, patients identified so far with vCJD are those with the shortest incubation periods for BSE. These patients could have received an especially high dose of BSE prions. However, no unusual history of dietary, occupational, or other exposure to BSE has been reported from case-control studies. Because of the powerful genetic effects on incubation period in laboratory animals, vCJD patients identified could represent a distinct genetic subpopulation with unusually short incubation periods to BSE prions, with vCJD so far occurring predominantly in those individuals with short incubation time alleles at these multiple genetic loci, in addition to having the homozygous PRNP genotype of codon 129methionine. Therefore, a human BSE epidemic may be multiphasic, and recent estimations of the size of the vCJD epidemic based on uniform genetic susceptibility could be substantial underestimations.\textsuperscript{3,11,12} Genes implicated in species-barrier effects, which would further increase both the mean and range of human BSE incubation periods, are also probably relevant. In this context, a human epidemic will be difficult to accurately model until such modifier loci are identified and their gene frequencies in the population can be measured.\textsuperscript{3}

Heterozygosity at PRNP codon 129 is a major determinant of susceptibility to and incubation time of human prion diseases.\textsuperscript{3,7,8,10} As expected, most of these recent kuru cases with extended incubation periods (eight of ten) were heterozygotes. We have reported previously that most elderly survivors of exposure to traditional mortuary feasts are heterozygous.\textsuperscript{7} Although the study included a small number of patients with kuru with long incubation periods, we saw no evidence of association with PRNP haplotype,\textsuperscript{39} HLA-DQ7,\textsuperscript{10} APOE,\textsuperscript{14} or PRND alleles.\textsuperscript{11}

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References


