Ethical issues in human prion diseases

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Prion diseases or transmissible spongiform encephalopathies are a group of closely related transmissible neurodegenerative conditions of humans and animals, all of which are incurable. In recent years, they have captured public attention with the emergence of the bovine spongiform encephalopathy (BSE) epidemic in Europe, and more recently with the appearance of variant CJD (vCJD) in humans, a novel form of Creutzfeldt-Jakob disease (CJD) that is linked to dietary exposure to BSE. In this chapter, we outline ethical questions posed by research, diagnostic procedures and therapy in the field of prion diseases.

Epidemiology and clinical features of human prion diseases

Human prion diseases are unique in that they manifest as sporadic, genetic and transmissible diseases. They have been traditionally classified into Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI) and kuru; these, however, should be viewed as clinicopathological phenotypes rather than individual disease entities. The majority of cases of human prion disease occur sporadically as Creutzfeldt-Jakob disease (sCJD), at a rate of roughly 1 per 10^6 of the population across the world, with equal incidence in men and women. sCJD is a rapidly progressive, multifocal dementia, usually with myoclonus with peak onset between 60–65 years. The clinical progression is typically weeks long, progressing to akinetic mutism and death often in 2–3 months. The aetiology of sCJD is unknown, but hypotheses include somatic mutation of the prion gene (referred to as PRNP), and the spontaneous conversion of PrP\(^c\) into PrP\(^\text{Sc}\), which is believed to be the essential or only component of the prion, as a rare stochastic event. There is a common coding polymorphism at codon 129 of PRNP encoding either methionine or valine. Homozygosity at this position predisposes to the development of sporadic and iatrogenic CJD, and all vCJD cases to date are homozygous for methionine at this codon. Other polymorphisms predisposing to sCJD are located at or near the PRNP locus.

Approximately 15% of human prion diseases are familial, with an autosomal dominant mode of inheritance. Familial human prion...
diseases are associated with one of more than 30 different missense or insertion mutations in the coding sequence of \textit{PRNP}\textsuperscript{7–10}. \textit{PRNP} analysis can be used for presymptomatic genetic testing in affected families\textsuperscript{11}. Kindreds with inherited prion disease have been described with phenotypes of sCJD, GSS, and also of other neurodegenerative diseases\textsuperscript{12}. GSS commonly presents as a chronic cerebellar ataxia with pyramidal features, dementia occurs much later in the clinical course, which is longer than that seen in sCJD. Fatal familial insomnia (FFI) is characterised by progressive untreatable insomnia, dysautonomia and dementia, selective thalamic degeneration and is most commonly associated with a missense mutation at codon 178 of \textit{PRNP}\textsuperscript{13,14}.

Although the human prion diseases are experimentally transmissible to animals, acquired forms in humans have, until recently, been confined to rare and unusual situations. For example, kuru, a progressive cerebellar ataxia accompanied by dementia in the later stages and death, is attributed to cannibalism among the Fore tribe in Papua New Guinea\textsuperscript{15}. Iatrogenic CJD has occurred as a result of exposure to prion-contaminated growth hormone or gonadotropin derived from pituitary glands of human cadavers, dura mater grafts\textsuperscript{16,17}, corneal transplants, or to surgical instruments.

The appearance of CJD cases in teenagers and young adults in the UK during the mid-1990s prompted considerable concern that they might have acquired the illness as a result of exposure to BSE\textsuperscript{18}. The early clinical presentation of vCJD resembles kuru more than sCJD and consists of behavioural and psychiatric disturbances, peripheral sensory disturbance and cerebellar ataxia\textsuperscript{19}. The duration of disease is longer in vCJD, with mean patient survival times of about 13 months, compared with about 4 months for sCJD. Moreover, whereas sCJD has a peak onset age between 60–65 years, the median age of onset of vCJD is 26 years\textsuperscript{19}. Up until March 2003, 129 cases of probable and pathologically confirmed vCJD have been reported in predominantly teenagers and young adults in the UK, and 11 cases world-wide\textsuperscript{20}. Molecular strain typing, which focuses on the biochemical properties of PrP\textsuperscript{Sc} from the brains of BSE-infected cattle and patients with CJD, has demonstrated that vCJD is different from sCJD but similar to BSE\textsuperscript{11,12}. Moreover, the incubation times and profiles of neuropathological lesions caused by vCJD and BSE prions in inbred lines of mice are indistinguishable\textsuperscript{3}. These data argue that BSE and vCJD prions are the same strain. All reported cases of vCJD have been homozygous for methionine at the polymorphic codon 129, a genotype shared by ~40% of the British Caucasian population\textsuperscript{21}. Polymorphisms in the \textit{PRNP} gene are likely not the sole genetic influence on disease susceptibility and incubation time. Studies with inbred lines of mice show that large differences in incubation time occur even with the same amino acid sequence of the
prion protein, suggesting that other genes may contribute to the observed variation\textsuperscript{22}. Therefore, the patients identified to date with vCJD may represent those individuals most genetically susceptible to the disease. Iatrogenic secondary transmission of vCJD prions from asymptomatic carriers is of considerable concern in the UK. As there is no non-invasive diagnostic test for preclinical carriers of vCJD, estimates of the frequency of asymptomatic carriers relies on screening of surgical lymphoreticular tissue\textsuperscript{23,24}.

**Ethical issues in genetic testing for inherited human prion diseases**

**Predictive testing for inherited prion disease**

As discussed above, it is now possible to test for inherited mutations and polymorphisms in disease-associated genes. This raises ethical issues regarding genetic testing and, in particular, for predictive (or presymptomatic) testing for people at risk of untreatable inherited dementias such as prion diseases. Because these are autosomal dominant disorders, only one mutant allele (heterozygous state) is required to elicit the disease and, therefore, offspring have a 50% chance of inheriting the disorder. Genetic testing is able to identify which of those individuals with a family history of prion disease will develop the condition at some time in the future. With autosomal dominant disorders such as prion diseases that have near 100% penetrance (the proportion of heterozygotes for a dominant gene that will express the disease), the presence of the mutant gene gives a clear indication that the individual will develop the condition, although the age of onset and the severity of the disease will vary between individuals and cannot be accurately predicted, even within the same family. Where it is possible to treat the condition for which an individual is at risk, or where some intervention can usefully delay onset or diminish the symptoms (e.g. Von Hippel-Lindau disease, where yearly screening is required to detect the presence of CNS and renal tumours), early diagnosis would clearly be beneficial and, with the relevant consent and appropriate counselling, presymptomatic testing is relatively unproblematic. More controversial is testing for conditions where there is no useful medical intervention. Predictive genetic testing for incurable conditions such as prion disease is offered using the internationally agreed Huntington’s disease protocol\textsuperscript{25}. Huntington’s disease is an autosomal dominant, fully penetrant neurodegenerative disorder and most research on predictive testing for untreatable dementias has been done with Huntington’s
disease patients. The Huntington’s disease genetic counselling protocol recommends a ‘cooling off’ period of at least 1 month between the initial visit and the blood sample being taken. This is to allow the person time to consider all possible benefits and harms – both personally and for others close to them. It is sometimes assumed that if there is no useful medical intervention, then there is no benefit to the individual in seeking the genetic test. However, non-medical factors need to be taken into account, such as relief of uncertainty and planning for the future. Some people would simply prefer not to know what fate holds in store for them, even if they know they are at risk, while others welcome the opportunity to plan for the future, particularly when planning a family. Interestingly, experience with Huntington’s disease patients suggests that once detailed information and counselling have been provided, most people choose not to proceed with testing. Prior to the gene mutation in Huntington’s disease being discovered in 1993, 80% of those with a family history of the disease expressed a desire to know their genetic status, but since the test has been available the take-up rate has been only 10–20%. What is absolutely clear from the extensive research that has been carried out in this area is the importance of providing accurate information, pre- and post-test counselling and support, and for mechanisms to be in place to ensure adequate safeguards against discrimination and breaches of confidentiality. An informed, competent adult should be free to make his or her own decision; but in certain circumstances, such as when the patient is pregnant or depressed, then testing should be delayed. It is generally agreed in the UK that it is unethical to perform presymptomatic testing on children below the age of 18 years for adult onset, incurable neurodegenerative conditions.

Prenatal testing for incurable adult-onset dementia

A prospective parent, who knows she may have inherited the gene for a dementia such as prion disease, can choose prenatal diagnosis in the first trimester. This is carried out by direct mutation analysis of a sample of fetal DNA, taken at about 10 weeks’ gestation by chorionic villus sampling. This test is performed with the expectation that the pregnancy will be terminated if a fetus is found to have the genetic mutation. Only a minority of those at risk of Huntington’s disease use prenatal diagnosis to prevent transmission of the disease; there is one published case of prenatal testing for GSS and there have been no requests for prenatal testing for familial prion diseases at the National Prion Clinic in London (John Collinge, personal communication). This may be due, in part, to lack of knowledge of the tests that are available among people at risk. Also, the decision to take up prenatal testing for an adult-onset disorder,
with the expectation of termination of an affected pregnancy, is never easy. A problem arises if, after positive prenatal testing, the mother wishes to continue the pregnancy, because the child obviously had no choice in the decision to be tested and may wish not to have been tested when it is old enough to make an informed decision. Perhaps the child with a known, inauspicious prognosis will be disadvantaged by the prejudices of parents and others, who know the child will develop the disease in the future. Fortunately, such situations are scarce, because those who for religious or moral reasons reject termination of a pregnancy will not subject themselves to prenatal diagnosis.

Pre-implantation genetic diagnosis (PGD) is an evolving technique that provides a practical alternative to prenatal testing and termination of pregnancy and has been used in over 1000 cases (recently reviewed by Braude et al.28 and Robertson29). Samples for genetic testing are obtained by extracting a single cell from a 3-day embryo generated by in vitro fertilisation. Only embryos that are shown to be free of the genetic disorder are implanted into the uterus to establish pregnancy. This procedure is available for many genetic disorders, but the number of specialist centres offering PGD is still small. However, the rapid advances in molecular genetics are likely to stimulate further use of PGD, and will encourage substantial change in the way that parents carrying a deleterious gene can avoid the birth of a genetically doomed child28.

Ethical issues surrounding selective termination of pregnancy and PGD in general include discrimination against the disabled in society. Some people have predicted that an emphasis on prenatal diagnosis and selective termination will lead to less tolerance of ‘difference’ and ‘less than perfect’ individuals, and in this way is discriminatory. There is the argument invoking the ‘slippery slope’ that leads to eugenics, variously described as aimed at the breeding of individuals with the optimum genetic make-up or at improving the human gene pool, whatever optimum or improved may mean. However, in our view, the ethical counter-arguments, in particular the principles of parental responsibility and obligations, are over-riding. These principles hold that it is wrong to bring children into the world if there is good reason to think that their lives will be fraught with suffering. It has been argued26 that ‘the duty of care that parents have to their children extends to the duty to provide them with such genetic protections that are available, just as they have the duty to vaccinate babies against prevalent dangers such as polio’. We believe that abstract ethical issues should not prevent or deter the use of pre-implantation or prenatal testing followed by avoidance or termination of pregnancy, where this is within the law, and is the choice of the pregnant woman after she has carefully considered the issues and her own circumstances.

A full and detailed discussion on all the ethical issues involved in genetic testing for incurable inherited dementias is outwith the scope of this review.
Population genetic screening for codon 129 status

As discussed above, vCJD has to date been associated only with codon 129 methionine homozygotes. From clinical experience with kuru, one might expect that, after a longer incubation period, codon 129 valine homozygotes, and even later heterozygotes may become affected, unless progression to clinical disease exceeds the life-time of the patient. Epidemiological studies analysing birth cohort and gender have been performed on UK dietary exposure in 1980–1996 to the BSE infectious agent through the consumption of mechanically recovered meat (MRM) and bovine head meat contained in burgers, sausages, and other meat products. Statistics suggest significant exposure to infected material during 1980–1989 particularly in the 1940–1969 birth cohort with an average of 3.7 million male consumers of burgers, 2.6 million of sausages and 8.5 million of other meat products per 7-day period. Population screening in the UK for codon 129 status would yield information on the predisposition to the development of vCJD following exposure to BSE-contaminated meat. However, there are a number of ethical issues raised by genetic screening of populations, or groups of adults and children, in whom there is no family history of genetic disorder. The criteria for the introduction of a genetic screening programme are that: (i) the problem must be important; (ii) a suitable screening test should be available with a precise level of sensitivity, specificity and positive predictive value; (iii) the results must provide useful information (e.g. permit early diagnosis followed by treatment of the condition); (iv) the benefits outweigh the risks; and (v) adequate provision must be made for information, counselling and confidentiality. In the context of screening for a genetic predisposition to vCJD in the UK population, not all of these criteria would be met; therefore, such screening is not acceptable. In Switzerland, a diagnostic company offered a privately funded test for codon 129 status; apart from being pretty useless, there is here the danger of inducing a false sense of security because, as discussed above, it is possible that carriers of any codon 129 polymorphism will be susceptible to vCJD, albeit with longer incubation times.

Anonymous population screening for vCJD in the UK – the tonsil and appendix studies

As discussed, the pathophysiology of vCJD is different from that of other human prion diseases, particularly in that infectious prions may be
detected in peripheral lymphoreticular tissue, such as tonsil or appendix\textsuperscript{23,33}. The presence of PrP\textsuperscript{Sc} in tonsil tissue forms the basis of a diagnostic test\textsuperscript{23,33} that to date has 100\% specificity and sensitivity (Angus Kennedy, manuscript in preparation). In 1998, a report appeared about a patient who developed the first symptoms of vCJD in May 1996. Eight months earlier, he had had his appendix removed; this was subsequently analysed and found to be positive for PrP\textsuperscript{Sc} using immunohistochemical techniques\textsuperscript{34}. This first demonstration that vCJD can be detected before symptoms appear prompted a national UK screening study of archived tonsil and appendix samples, to look for clinically silent infection. The rationale was that such screening may provide a rough indication of the extent to which the UK population harbours the vCJD prion. A scheme similar to that used in Britain for HIV testing of donated blood was proposed, where unlinked, anonymous sampling makes it impossible to trace a donor. The largest published study to date reports on 8318 samples from people aged 10–50 years in the UK\textsuperscript{24}. Most samples were appendix and 70\% were from patients aged 20–29 years. One appendix sample showed accumulation of PrP\textsuperscript{Sc}, giving an estimated detectable prevalence of 120 per million among people aged 10–50 years during 1995–1999. This is the first estimate of the number of people who may be a potential source of vCJD in the UK. The study also reported that of 20 appendix samples removed at autopsy from vCJD patients, 19 showed accumulation of PrP\textsuperscript{Sc}.

A study funded by the UK Department of Health of vCJD prion prevalence in 2000 archived tonsil biopsies is soon to be published by Collinge’s group. It is now planned to undertake a large-scale prospective screening of fresh tissue from tonsillectomies to obtain precise data on prevalence. The use of fresh tissue would allow for more rapid Western blot analysis, and also for verification of positive samples by mouse transmission studies\textsuperscript{24}. Aside from the ethics of the anonymous screening programme itself, as discussed below, the fact that patients may harbour silent prion disease has another important implication. Because prions have great affinity for metal surfaces\textsuperscript{35} and because conventional sterilisation procedures do not completely abolish infectivity, surgical instruments used on these people could transmit the disease\textsuperscript{36}. This raises the ethical question as to what price society is prepared to pay in order to avoid a low, and as yet undefinable, risk level. In January 2001, the UK Department of Health recommended single-use disposable surgical instruments for all tonsillectomies; however, this recommendation was reversed in December 2001 following an increase in adverse incidents – typically increased bleeding but including one death, which represented an actual risk to patients compared with the theoretical risk of transmission of vCJD\textsuperscript{20}. 
Ethical issues raised by anonymous screening for prion disease

Anonymised screening is a research tool to inform policy and practice <...>, but it is not a tool to identify those at risk that could directly benefit from intervention\(^7\).

In the anticipated prospective UK screening study of tonsil tissue mentioned above, adequate information is provided to individuals to allow them to exercise their autonomy and choose whether or not to participate in the study, knowing they will not receive results or benefit from the research. There is a concern, with evidential support, that in relation to anonymised HIV testing in pregnancy, some women either did not receive adequate information or did not understand that they would not be told of a positive result\(^8\). Such information is of key importance in rendering such screening ethically acceptable, unless one accepts that individual autonomy may be abrogated to promote public good.

Many of the ethical issues relating to anonymous screening have been rehearsed in relation to HIV/AIDS. Anonymised screening of a population is used to obtain epidemiological data, for example, the tonsil and appendix studies described above. Anonymous screening is, however, ethically controversial and has not been universally accepted, even when it will increase information about the public health of the nation. The essential issue is that individuals are being tested for no benefit to themselves and, in the case of a treatable condition, without the advantage of treatment if the test is positive. It may, however, be in the public interest for such testing to be performed, to further scientific research and to inform health policy: ultimately, other individuals or generations may benefit. Thus, the debate about testing shows signs of the ethical dichotomy about the rights of society on the one hand, and the rights of the individual on the other.

It has been argued\(^7\) that anonymising data is a ‘procedural research tool which enables the studies to be done in a way that does not undermine consent or individual autonomy’. Pinching also points out that many of the flaws in such work are a result of poor implementation of the procedure rather than the procedure itself\(^7\). On the other hand, anonymised screening may be considered as ‘non-therapeutic research’. de Zalueta\(^8\) argues that anonymising data means that physicians undertaking such research break the Helsinki Declaration on non-therapeutic research by failing to ‘remain the protector of the life and health of that person on whom biomedical research is carried out’ (article 1), and also flouts article 4: “the interest of science and society should never take precedence over considerations related to the well-being of the subject” (World Medical Association, Helsinki Declaration on non-therapeutic...
research involving human subjects, 1996). The authors agree with this view in regard to anonymous screening for prion disease, because infected unidentifiable individuals will be denied treatment if, or when, it becomes available. Surely it is ethically more acceptable to perform studies where the patients are ‘conditionally anonymised’, which allows those individuals who prove to be incubating vCJD to be traced at a later date and treated.

Another grave ethical question concerns the rights of society to be protected against possible infection with prion disease emanating from a blood or organ donor, since these rights are opposed to the individual’s right to privacy, or autonomy. In the case of AIDS, autonomy was given highest priority, part of the argument being that infected individuals could protect their surroundings or that their partners could protect themselves by appropriate conduct\textsuperscript{39}. This possibility, however, does not obtain in the case of prion disease, where transmission is iatrogenic and beyond the control of the recipient.

**Experimentation on human subjects and randomised control therapy trials in human prion disease**

The difficulty in this area, compared to some others in medicine, is that potential recruits to a study have a terminal illness that may be progressing rapidly. Participating in a trial could reduce the time left during which they could receive beneficial symptomatic treatment, and taking a placebo drug may deny them the benefit of novel treatment. There are obvious parallels to AIDS trials and cancer research. The attempts to research therapy for HIV dealt with an articulate group of patients, many young and highly pro-active in the management of their disease. Some argued strongly against what was regarded as the ‘paternalism’ of controlled trials and the medical ethos that patients were not allowed to receive developing treatments except through such work. Such restriction of access to new therapies is justified on the grounds that patients could come to harm by self treatment or referral, and secondly that without such trials new treatments cannot be evaluated, potentially harming future patients\textsuperscript{40}. This is countered by groups who argue that controlled trials infringe on patient autonomy in decision-making, because they cannot freely consent to enter a trial if they have no other means of receiving a potentially life-prolonging or life-enhancing treatment\textsuperscript{41}.

Researchers in the field of prion-disease therapeutics will have to address the issue of whether to allow unrestricted access by patients to innovative therapy, or to try to restrict access to the more conservative path of randomised controlled trials. In the MRC-funded UK clinical trial of quinacrine therapy for prion disease, there will be no placebo group and all patients will be treated (Angus Kennedy, personal communication), because
it is felt that a randomised controlled trial would be unethical in such a rapidly lethal disease. In the study cited above, however, an objective measure such as analysis of serial tonsil biopsies will be implemented to act as a therapeutic biomarker (Angus Kennedy, personal communication).

**Experimental therapy for human prion diseases**

As discussed, vCJD is a highly distressing, rapidly progressive incurable disorder that predominantly affects young people, and very recently a legal case was brought by two families whose children JS and PA, aged 18 and 16 years, respectively, suffer from vCJD (DS v JS and an NHS Trust and The Secretary of State for Health, intervener; PA v JA and an NHS Trust and The Secretary of State for Health [2002] EWHC 2734 (Fam)). They applied to the court to permit intraventricular administration of pentosan polysulphate (PPS), a treatment previously given only to rodents and dogs. This drug clears prions in cell culture and prolongs incubation time in scrapie-infected mice, but it does not cross the blood-brain barrier, making it of questionable use in disease affecting the central nervous system. In late 2002, data were presented at two prion meetings suggesting that intraventricular administration of PPS to intracerebrally infected mice was effective at prolonging incubation time (Katsumi Doh-ura, personal communication). The dosing regimen of the drug, however, was critical, because higher doses resulted in fatal intracerebral haemorrhage. PPS is marketed in certain countries as a treatment for interstitial cystitis and as an anticoagulant, although its side-effects include haemorrhage and hypersensitivity reactions. The judge heard the evidence of Doh-ura, the Japanese researcher who had performed the animal studies, that of a neurosurgeon willing to administer the novel treatment and the opinion of a number of respected neurologists who expressed some reservations regarding this experimental treatment. Dame Butler-Schloss found that both young patients had ‘some enjoyment from life which is worth preserving’ and that the treatment, as it was supported by medical opinion would be in their ‘best interest’ (the legal criteria for doctors to treat those lacking capacity for personal decisions). Researchers could thus come under pressure from the courts to allow new treatments to be used, although from the ruling described above, such decisions would have to withstand the ‘Bolam’ test of being acceptable to a reasonable body of medical opinion. Of note, in addition to reliance on medical opinion, Dame Butler-Schloss also applied her own analysis to the research data in determining whether it was in the patients’ best interest to receive it. The ruling also upheld the application of the Human Rights Act in this area, citing Articles 2 and 8, the rights to life and to respect for family life. It is not inconceivable that such analysis could allow patients to circumvent clinical trials by asserting
their rights to receive innovative therapy, and this development is of concern, particularly in the clinical field of human prion diseases. Finally, we may at some stage be confronted with a therapy that can eradicate prion infection without reversing the neural damage, which in extreme cases could condemn patients to years or decades of severe disability and dementia. This would lead to the ethical dilemma as to whether treatment should be withheld if the disease has progressed to a severe stage. Such situations could be prevented from arising if a diagnostic test were to be developed that would allow detection of prion disease in its preclinical stage. Whether such a test, if it ever became available, would in practice be applied to detect a disease with an incidence of 1 in a million per year, is a matter of debate; clearly, it would be practicable in the case of familial prion diseases.

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