The impact of Creutzfeldt–Jakob disease on surgical practice

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ABSTRACT

Creutzfeldt–Jakob disease (CJD) is characterised by abnormal prion protein that can replicate and replace nervous tissue, with rapid lethal neurodegenerative consequences. The transmissible nature of CJD has been known for half a century and transmission has occurred through neurosurgical procedures. Variant Creutzfeldt–Jakob disease (vCJD) emerged in 1996, and the presence of abnormal prion in lymphatic tissue extended the number of surgical specialties dealing with infected material; transmission through blood transfusion raised the possibilities of a large carrier pool and spread of epidemic proportion.

The abnormal prion is difficult to remove and this could influence future decontamination programmes. Contaminated instruments must be withdrawn from surgical practice, and this can interfere with the efficient running of a surgical unit and optimal patient care.

There is an urgent need for reliable methods for the detection of abnormal prion, within and outside the body. These will help to clarify the epidemiology of CJD, and to reduce its transmission via blood and tissue. They will also allow determination of the efficacy of new decontamination products in surgical practice, and the value of any treatment of sufferers and carriers of CJD. In the meantime, continued vigilance and informed regulation of all aspects of CJD must remain.

KEYWORDS

CJD – BSE – Surgical practice

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Creutzfeldt–Jakob disease (CJD) is a fatal human neurodegenerative disorder. It is one of the transmissible spongiform encephalopathies (TSEs) that are found across the animal kingdom, and produce vacuolisation of cerebral cortex. The commonest form of CJD is sporadic (sCJD). It has been recognised since the 1920s and makes up approximately 85% of cases; it has a world-wide distribution, with an incidence of 1 case per million population per year. The disease occurs in the middle-aged and elderly (median age, 64–67 years), and the average survival, from the appearance of symptoms, is 4.5 months. Familial forms of CJD are all transmitted as an autosomal dominant; they make up 10–15% of cases.

The first suggestion of an infective basis to human TSEs came from epidemiological studies on kuru, a CJD identified in 1957 in Papua, New Guinea.¹ The Fore people practiced ritual cannibalism of their dead and over 2500 deaths from CJD have been recorded. The transmissible nature of CJD has also been vividly demonstrated by approximately 300 cases of iatrogenic CJD. These followed injection of pituitary extract and the implantation of dura mater, inadvertently taken from infected cadavers. The latter was mainly due to

manufactured Lyodura: local harvesting procedures were also practiced, but have not been fully documented. Dural implantation took place between 1969 and 1992; the subsequent appearance of CJD took from 9 to 25 years.

Three cases followed corneal transplantation and six from re-usable neurosurgical instruments; two of these were from implantable electrodes. The last reported CJD infection from this source was over 30 years ago.

BSE and variant CJD

Scrapie, a TSE infecting sheep, goats and moufflon, has been known for over 250 years and is endemic in many countries world-wide. However, in 1986 an outbreak of a new form of TSE in cattle occurred in the UK. It was termed bovine spongiform encephalopathy (BSE) and also became known as mad cow disease, on account of the severe agitated state of infected animals. Approximately 180,000 infected animals and over a million cattle were slaughtered, and their carcasses burned, before the epidemic was controlled. The source of the outbreak was not identified,

but it was variously attributed to imported infected food-stuff (probably originating from scrapie-infected animals).

Following the outbreak, strict regulations were introduced to control animal movement, and to regulate husbandry and veterinary practices. A ban was placed on the consumption of specified offal, and feeding rendered meats and bone meal to herbivores was abandoned. However, before the full extent of the problem was realised, the export of potentially infected animals continued into Europe, and the offal and meat of infected animals, entered both the animal and human food chains.

By 1990, infection by the same agent was reported in domestic and exotic cats, and in exotic ruminants in zoos. The ability of the agent to cause infection and disease in a wide range of species was unusual, and concerns were expressed that the species range might extend to humans. The Animal Advisory Committee on Dangerous Pathogens (ACDP) set up a TSE working group in the early 1990s to consider the implications and the regulation of feeding practices.

In March 1996, ten new cases of CJD were reported in the UK. Not only was this incidence well above that predicted for sporadic CJD, but the clinical picture was different; the patients were younger (median age, 29 years) and the time course for the symptomatic disease was longer (mean duration, 14 months). The early symptoms of progressive cognitive impairment, behavioural changes and ataxia differed from the rapid progressive dementia of sCJD. The condition became known as new variant CJD (nvCJD, later to become vCJD). Whereas in sCJD abnormal prion was confined to the CNS, with extension to the posterior eye and trigeminal ganglion, in vCJD the abnormal prion was also found in the reticulo-endothelial system (tonsils, gastrointestinal, lymph nodes and spleen), raising the possibility of an infectious agent within the blood stream.

Regulation

The ACDP and the Spongiform Encephalopathy Advisory Committee (SEAC) requested an outside review of the latter possibility and, from 1997, all blood components known to have originated from patients with CJD, or who later developed CJD, were withdrawn. A ban was placed on the use of UK plasma products in 1998; from 1999 all blood donations underwent leukodepletion.

A ban was placed on organ donation from anyone with a history of dementia or progressive neurological disease, and a similar ban on the donation of bodies for anatomical dissection. Europe placed a ban on British beef and beef products; in the UK, a ban was placed on serving beef on the bone in restaurants.

The CJD Incidents Panel was set up in 2000 to examine all cases of CJD, to monitor their management, and to

determine the risk potential of transmission of CJD through clinical interventions and the public health risk of CJD.

The full advice on the management of incidents is provided in the Panel's Framework document.² From October 2006, it is the requirement of each hospital trust to have a CJD policy.

In 2003, the Engineering and Scientific Advisory Committee into the decontamination of surgical instruments including prion removal, was established, to identify and prioritise areas of necessary research in all aspects of vCJD decontamination.⁵

In 2004, a NICE CJD Advisory Sub-Committee was set up to study patient safety and reduction in risk of transmission of CJD via interventional procedures. The Committee reported in November 2006:⁴ it emphasised, the need to eliminate the migration of instruments between sets coming into contact with high-risk tissues (neurosurgery and posterior eye surgery); the report highlighted the problems of quality control of single-use, disposable instruments, and the urgent need for appropriate valid decontamination methods in this field. The Committee will reconsider its guidance in November 2008 or earlier if new relevant evidence becomes available.

Blood

As well as the precautionary measures of leukodepletion and banning the use UK blood products, the Blood Transfusion Service modelled the likely effects on the blood supply of stopping blood donation from any prior transfusion recipient and considered the possible effects of introducing a donor test for CJD (should one become available). The former was likely to produce a 12% loss of donors, and the latter possibly 40%, since many potential donors would not wish to know their CJD status.

In December 2003, a case of possible vCJD transmission by blood transfusion was reported.⁵ To date, four cases have been identified; two of these cases have been traced to the same donor. Three of the subjects had clinical vCJD. The fourth patient died of unrelated causes, but was known to have received a transfusion from a patient who later developed vCJD. In this subject, abnormal prion was found in a neck node and in the spleen, but not in the central nervous system.

After the first announcement, donations were stopped from all individuals who had previously received blood or blood products. All recipients of blood or blood products from known CJD sufferers were traced and those at high risk were notified.

Further modelling took into account the size of plasma pools. Using a 0.5% probability of transmission from a pre-clinically infected donor, and a population prevalence of 1:4000, recipients reached the 1% threshold level after 80 transfusions. This occurs in approximately 3600 individuals

each year in the UK; using these criteria, an estimated 15,000–50,000 of the population are at high risk of vCJD from prior transfusion.

Work is taking place on pre-operative screening questions to identify the prior transfusion risk of patients undergoing surgery in high-risk specialties. These are neurosurgery and ophthalmic surgery, but other specialties, such as ENT, general and endoscopy are in the medium-risk category.

Prion protein

In 1982, Prusiner proposed that the transmissible agent in TSEs is a modified naturally occurring host prion protein.⁶ Normally expressed prion protein (PrP^c) is predominantly found in the central nervous system; its function is unknown. It has a short half-life with a rapid metabolic turnover and is rapidly degraded by proteolytic enzymes. It is situated on codon 129 on the prion gene, on the short arm of chromosome 20; polymorphism at codon 129, may influence susceptibility to the disease. Three genetic sub-groups are found: methionine homozygous (M/M, 40%); valine homozygous (V/V, 10%) and methionine/valine heterozygous (M/V, 50%).

All current vCJD patients and 65% of sCJD patients are M/M homozygous. A histological study on 12,674 operative tonsil specimens located abnormal prion in three cases – equivalent to 237 per million population. Two of the three cases were in M/V heterozygous subjects, emphasising the need for further epidemiological studies. The asymptomatic recipient of infected blood, found to have lymphatic vCJD, was of the M/V heterozygote genetic sub-group; this opened the possibility of infection by an asymptomatic carrier of abnormal prion.

The abnormal prion (PrP^{sc}) has identical amino-acid sequences to natural prion, but a different conformation and membrane folding. This abnormal conformation is associated with neurotoxicity and infectivity. Abnormal prion is exceptionally stable and not broken down by proteases; it is resistant to biodegradation, and insoluble in aqueous and alkaline fluids. As abnormal prion is a modified cellular, rather than a foreign, protein, it produces no immune response and, as it has no nucleic acid component, there are no standard markers and no standard diagnostic tests. Diagnosis is by an invasive tissue biopsy (usually brain); a blood-based diagnostic assay is thus urgently needed.

Abnormal prion withstands autoclaving at 120°C, and between 134–137°C for more than 3 min (denaturation requires autoclaving at 134°C for over an hour); it is resistant to all currently used gaseous disinfectants and unaffected by most chemical detergents. It is not easily removed from metal instruments and may replicate if left in contact with other proteins on these surfaces.

Surgery and vCJD

In surgical practice, tissues have been categorised as high-, medium- and low-risk, and a 1% threshold used to categorise patients as at risk of vCJD for public health purposes. All instruments used on high-risk tissue are to be destroyed, or forwarded to institutes researching in this area; when the diagnosis is in doubt, instruments are to be quarantined until the status has been clarified.

The risks of infectivity are highest for the first 2–6 patients on subsequent re-use, and once an instrument has been through 10 cycles for medium-risk, and 20 cycles for high-risk tissues, the risk of infection is reduced to negligible levels. However, passing instruments through artificial cycles does not equate to their use in clinical practice.

As a precautionary measure, all re-usable tonsillectomy instruments were withdrawn in early 2001, but the unreliable nature of disposable instruments led to their re-instatement within the year. However, the slow return to the original levels of competence in this procedure highlighted the difficulties of replacing tried and tested instruments and techniques.

The surgical community has particular anxieties in its approach to vCJD, fuelled by the knee-jerk response to tonsillectomy and its sequelae, and the current uncertainties of risk analyses based on empirical models. There is hesitancy and reluctance to change practices that could affect the care of all other patients, together with the destruction or

Table 1 Risk factors in CJD

- vCJD is a uniformly fatal disease
- There is no cure
- There is no way of eliminating or reducing abnormal prion from infected individuals
- vCJD is transferable by transfusion
- The whole population may have been exposed
- The number of carriers is unknown
- The risks of transmission are unknown
- The size of an infective inoculation is unknown, or whether repeated exposures will reach a threshold level
- There is no prophylaxis
- An epidemic cannot yet be excluded
- The incubation period is 10–30 years, and the full epidemiological pattern may not be available for 40 years

Table 2 Favourable factors in the management of CJD

- No person-to-person transmission has been reported by contact, cuts, coughs, trans-uterine or breast feeding
- There are no current trends to suggest a likely epidemic
- There has been no case of surgical transmission of vCJD
- There have been no occupational hazards to animal handlers, abattoir workers or health professionals
- Controls are in place on animal feeding products, and the entry of animal products into animal and human food chains
- Guidance for the management of individual cases is in place
- A number of informed skilled bodies are involved in monitoring and researching into the epidemiology and other characteristics of the disease
- Methods for detection of abnormal prion are under investigation^a
- The study of detergents and other methods capable of removing abnormal prion from instruments are well advanced^b
- Prion filters, to reduce transferable risks of vCJD during blood donation, are under study
- Therapeutic drugs are under investigation.

^aA blood test will probably identify more false than true positives, and this could impact erroneously on many persons for the rest of their lives.

^bThe relation of the abnormal animal prion, used in these studies, to abnormal human prion is not known.

quarantine of tried and tested valuable instruments; also to the introduction of guidelines, when there is no recorded

case of transmission of vCJD through surgical practice.

However, against this must be balanced the current status of the disease, as outlined in Table 1, although some positives do exist (Table 2).

The eventual elimination of vCJD may have to await natural evolutionary forces, but the mechanisms are in place to support its demise. In the meantime, it is essential to provide optimal care to sufferers, whilst protecting public health. Awareness and understanding of the problems associated with the disease are essential throughout the surgical community.

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Other useful websites

Health Protection Agency

<www.hpa.org.uk/infections/topics_az/cjd/menu.htm>.

Department of Health

<www.doh.gov.uk/cjd/index.htm>.

Spongiform Encephalopathy Advisory Committee

<www.seac.gov.uk>.

National CJD Surveillance Unit

<www.cjd.ed.ac.uk/index.htm>.

National Prion Clinic

<www.uclh.org/services/national_prion_clinic/index.shtml>
<http://cjd.ed.ac.uk>>.