

Classical and variant Creutzfeldt-Jakob diseases and their potential impact on the practice of clinical dentistry in Australia

SWY Chan,* S Collins,† CL Masters,† DM Walker*

Abstract

Following recent published evidence regarding the experimental transmission of prion diseases via blood transfusion, dental practitioners have expressed their concern about the potential impact of these transmissible spongiform encephalopathies on dental care provision. This review provides updated information on Creutzfeldt-Jakob disease and related disorders and highlights their potential significance for the practice of clinical dentistry. The current guidelines in Australia relating to infection control and clinical dental procedures are discussed together with recommended guidelines and considerations from the United Kingdom and the World Health Organization (WHO).

Key words: Prion disease; Creutzfeldt-Jakob disease; infection control; clinical dentistry.

(Received for publication February 2001. Revised March 2001. Accepted May 2001.)

INTRODUCTION

This review is aimed at providing information on transmissible spongiform encephalopathies (TSEs), in particular Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD). The significance of TSEs on clinical dentistry will be discussed. Proposed infection control guidelines for Australia will be provided together with a review of the recommended guidelines and considerations from the United Kingdom (UK) and from the World Health Organization.

Background

TSEs comprise a group of fatal neurodegenerative diseases which includes CJD in humans, scrapie in sheep and bovine spongiform encephalopathy (BSE) or 'mad cow disease'. Variant CJD is most likely zoonotically linked to BSE.¹ These diseases are

characterized histopathologically by microscopic vacuolation (spongiform change) in the cerebral grey matter, astrocytic proliferation and loss of neurones.²

Considerable scientific data supports the current belief that TSEs are caused by infectious particles (prions) composed predominantly, if not exclusively, by an abnormal conformation of a cell-surface glycoprotein which is protease-resistant and referred to as PrP^{Sc}.^{2,3} The normal cellular isoform, known otherwise as PrP^C, is encoded by a host gene (PRNP) on chromosome 20.^{3,4} PrP^{Sc} is insoluble and appears inextricably linked to disease pathogenesis in contrast to PrP^C which is soluble and protease-sensitive.^{4,6} PrP^{Sc} is found exclusively in neural tissues in classical CJD, while it is also found in lymphoreticular tissues in vCJD and may accumulate as amyloid-like deposits in the brain (Table 1).

Types of CJD

There are inherited, acquired or horizontally transmitted (including vCJD derived from BSE) and sporadic forms of human TSEs.⁷ The inherited forms of human TSEs are due to mutations in PRNP and include fatal familial insomnia (FFI) and Gerstmann-Sträussler-Scheinker syndrome (GSS). Individuals with FFI present with progressive insomnia, dysautonomia, motor dysfunction and cognitive deterioration; the age of onset is usually between 40 and 60 years. Neuropathologically, abnormalities are located predominantly within the anteroventral and mediodorsal thalamic nuclei. By contrast, individuals with GSS tend to present with progressive cerebellar dysfunction and dementia. Within FFI and GSS families with more variable phenotypes are well recognised, including those more akin to CJD.²

It has been shown that all forms of TSEs, including the inherited forms can be transmitted to experimental animals. A model that demonstrates the importance of the direct interaction between PrP molecules explains how this is possible. It is proposed that the disease-related isoform of PrP (PrP^{Sc}) interacts with the normal cellular isoform, PrP^C and causes a conformational change in the latter leading to progressive accumulation

*Oral Pathology Unit, Westmead Dental Clinical School, The University of Sydney.

†Department of Pathology, The University of Melbourne.

Table 1. Demonstrated or predicted infectivity of human body tissues and fluids for Creutzfeldt-Jakob disease*

Infectivity category	Tissues	Secretions and excretions
'High infectivity' sites (Demonstrated or predicted to be consistently infectious)	Brain Pituitary gland Spinal cord Eye (retina, optic nerve and possibly cornea)	
'Low infectivity' sites (Demonstrated or predicted to be infectious, but not consistently)	Dorsal root ganglia Kidney Liver Lung Lymph nodes/spleen Placenta Trigeminal ganglia Uterus	Cerebrospinal fluid
'No infectivity' (Have not been demonstrated to be infectious)	Adipose tissue Adrenal gland Blood Bone marrow Gingival tissue Heart muscle Intestine Peripheral nerve Prostate gland Skeletal muscle Testes Thyroid gland	Faeces Milk Nasal mucous Saliva Semen Serous exudate Sweat Tears Urine

*Draft NHMRC guidelines, 2001.

of PrP^{Sc}. The precise pathophysiological consequences remain to be elucidated.²

Kuru

Kuru is a horizontally transmitted human TSE first described in the Eastern Highlands of Papua New Guinea in the 1950s. Disease transmission resulted from endocannibalism and predominantly affected women and children who had the task of preparing the tissues of deceased relatives and also participated in the feasting of visceral organs as part of mourning rites to honour the dead. Progressive cerebellar ataxia is the salient clinical feature, with severe dementia less common. The practice of endocannibalism was outlawed around 1956 with the occurrence of kuru declining thereafter. The recent incidence of kuru is around five cases per annum.⁸

Sporadic/classical CJD

Sporadic or classical CJD accounts for the vast majority of human TSEs and has an annual incidence of approximately one case per million population. The disease was originally described by two German doctors, HG Creutzfeldt, a psychiatrist, and AM Jakob, a neurologist, in the 1920s. It occurs randomly and affects individuals in middle to late life with a peak age of onset between 60 and 65 years.⁹ It is characterized by rapidly progressive dementia accompanied by personality changes, psychiatric symptoms, cognitive and motor impairment, myoclonus and increasing difficulties with communication, swallowing and continence.¹⁰ Prodromal symptoms may include insomnia, depression, fatigue, headache, weight loss and ill-defined pain.^{2,11} Once symptoms appear, death follows after a median duration of four months. There

have been 486 reported cases of CJD in Australia of which 222 have been pathologically confirmed, 150 are probable and the rest are under investigation. Pre-mortem diagnosis of sporadic CJD is usually by clinical evaluation supplemented by electroencephalography (EEG) in which 60-70 per cent of patients show characteristic periodic triphasic complexes or sharp wave activity.^{2,12} Neuropathological features of CJD include spongiform degeneration, astrocytosis and neuronal loss, but amyloid plaques are usually absent. Table 1 outlines the distribution of CJD infectivity in tissues and body fluids. PrP^{Sc} is not found in the lymphoid tissues of individuals with classical CJD.¹³⁻¹⁵

Iatrogenic CJD

Iatrogenic CJD is rare, with evidence to support a genetic susceptibility to this form of disease.² There is a common polymorphism of human PRNP at codon 129 with either methionine or valine present. Most patients developing iatrogenic CJD are homozygous at this codon while heterozygosity is seen in approximately 50 per cent of the normal population. The routes of transmission of this disease include the use of human cadaveric-derived growth hormone and dura mater, corneal grafting and the use of contaminated stereotactic EEG electrodes or surgical instruments in intracranial neurosurgery. The majority of growth-hormone-related iatrogenic CJD occurs in individuals who are homozygous for valine at codon 129.¹⁶ There is no evidence to support human to human transmission following close (including sexual) contact or by aerosol spread.¹⁷

Variant CJD

Variant CJD was first reported in the United Kingdom in March 1996.^{18,19} It is restricted to

Europe, in particular to the UK, with young adults predominantly affected.^{1,20} There are currently 106 cases of vCJD in the UK (as of September 2001), but no cases have been recognised so far in Australia. It appears to be causally related to exposure to the agent causing BSE. The incubation period for this disease is presently unknown, but may extend beyond the normal human lifespan.²¹ The duration of disease is longer than that of sporadic or classical CJD, lasting a median of 14 months.^{10,22} Common early features include psychiatric disorders, such as depression, personality changes and sensory symptoms (which are often unpleasant). There is absence of the typical EEG features of sporadic CJD.^{1,22} Histopathologically, there is extensive PrP^{Sc} plaque deposition in the grey matter of the brain and PrP^{Sc} can be routinely detected in the lymphoreticular tissues, including the tonsils,¹⁵ but uncommonly in other non-neural tissues.^{23,24}

Possible blood transmission of CJD or vCJD

Much of the recent debate about the potential transmission of prion diseases via blood transfusions is related to the paucity of epidemiological data on vCJD and whether blood and derived products from these individuals can transmit disease. Concerns have been heightened by the recent publication of an animal study in which the infective agent causing BSE was transmitted from a single sheep by whole blood transfusion during the incubation period of experimental BSE infection.²⁵ In view of their preliminary data, Houston et al.²⁵ have suggested that blood donated by symptom-free vCJD-infected humans may represent a transmission risk. Prior to this, the UK National Blood Transfusion Service had already implemented universal leucodepletion of donated blood as a possible protective measure (as the prion may selectively infect leucocytes). In Australia, a recent announcement by the Commonwealth Chief Medical Officer, has prompted deferral of blood donations from people who have lived in the UK for more than six months between 1980 and 1996.

A recent review by Wilson et al.²⁶ reported on five case-control studies (involving a total of 793 patients with CJD and 1686 controls) where the strength of association between a history of blood transfusion and development of sporadic CJD was examined. The authors concluded that case-control studies do not support an association between blood transfusions and sporadic CJD, but emphasised that these findings should not be generalised to vCJD. The fact that TSEs can exist in a subclinical form has heightened concern about the risk of transmission via blood and blood products, and from the re-use of inadequately sterilised surgical instruments utilised on symptom-free carriers of vCJD.²¹

Diagnosis of CJD

With respect to sporadic CJD, routine haematological and biochemical investigations are usually unhelpful in

the diagnosis as the results are typically normal. Likewise, immunological markers and acute-phase protein levels are not specifically affected in the disease, but occasionally, there may be elevations of serum transaminases and alkaline phosphatase. Imaging techniques including computed tomography (CT) and magnetic resonance imaging (MRI) help to exclude other neurological diseases. In addition, they may demonstrate non-specific cerebral and/or cerebellar atrophy and MRI may demonstrate suggestive findings such as increased long repetition, e.g., T₂ signal intensities in the basal ganglia. However, there is an absence of definitive diagnostic features. As stated before, EEG is a useful, non-invasive means of diagnosing CJD, but a recent study in a large series of patients has confirmed the superiority of 14-3-3 protein detection in the CSF.²⁷ Neuropathological evaluation is required for definitive diagnosis with demonstration of typical changes and PrP^{Sc} deposition.

In vCJD, the characteristic periodic discharges seen in sporadic CJD are absent despite abnormal EEG findings. There is also a different neuropathological profile; namely, the presence of PrP^{Sc} plaques which are extensively distributed throughout the cerebrum and cerebellum.¹ In addition, PrP^{Sc} is present in lymphoid cells, specifically follicular dendritic cells, of affected individuals and a tonsillar biopsy is a means of establishing the diagnosis of vCJD.^{15,28} With neuro-imaging, MRI scans of symptomatic individuals have shown bilateral increased pulvinar signal in 75 per cent of cases, which in turn correlates with gliosis histologically.^{22,29}

Significance of TSEs in dentistry

In animal studies utilising hamsters, intraperitoneal inoculation of scrapie-infected brain homogenate was followed by detection of high levels of infectivity in the gingivae and pulpal tissues.³⁰ It was suggested that the scrapie agent had spread to the oral cavity via the terminal endings of the trigeminal nerve, knowing that prions can be located within the trigeminal ganglion. Inoculation of the same infectious agent into healthy hamster tooth pulp resulted in the development of scrapie.³⁰ Despite this, the protease-resistant prion protein has not been detected in dental pulp homogenates derived from eight patients diagnosed with sporadic CJD using the Western blot technique.³¹ Nevertheless, Blanquet-Grossard et al.³¹ emphasised that the risk of occupational exposure from, and iatrogenic contamination by, endodontic surgery cannot be 'entirely dismissed'.

There is no clinical evidence at present to indicate that dental surgeons and/or other dental healthcare providers are at risk of contracting a TSE in routine dental clinical practice. Moreover, there are no reported cases of iatrogenic transmission of TSE by dental health care providers.³²

Data analyses of 241 patients with sporadic CJD from the Australian National CJD Registry

Table 2. Risk assignment of tissues and of patients for infectivity by a transmissible encephalopathic agent.*

(1) HIGH RISK TISSUE (e.g., brain, pituitary gland, dura mater, eyes)	(2) HIGH RISK PATIENT (i.e., known/suspected CJD or vCJD or familial CJD with or without a known PRNP mutation)
(3) LOW RISK TISSUE (e.g., teeth, gingiva, etc.)	(4) LOW RISK PATIENT (e.g., recipient of a dura mater graft or transdural neurosurgery between 1972 and 1989)

*As provided by the CJD Reference Group of Australia, 2000, and Woods, 1997.³⁷

(1)+(2) require infection control procedures for CJD

(3)+(4) require standard universal precautions

(1)+(4) require infection control procedures for CJD

(2)+(3) require infection control procedures for CJD

Abbreviations: CJD – Creutzfeldt-Jakob Disease

vCJD – variant Creutzfeldt-Jakob Disease

PRNP – gene for the normal cellular isoform of the prion protein (PrP^C) located on chromosome 20.

(Department of Pathology, The University of Melbourne) and 784 community-based controls showed no significant risk of sporadic CJD associated with ‘major dental work’ (not specified) ($p=0.115$).¹² Collins et al.¹² found that surgical procedures were the factor most significantly associated with risk of CJD, with the risk progressively increasing with the number of surgical procedures, but not necessarily with regard to anatomical site or complexity of the surgery. Interestingly though, earlier reports using smaller patient series showed that certain surgical procedures, in particular those involving the head, face and neck, revealed a positive association with risk of CJD.³³ There is no equivalent analysis for vCJD due to the low number of recorded cases worldwide.³⁴

The oral manifestations of human TSEs include dysphagia and dysarthria, and orofacial dysaesthesia or paraesthesia has been reported in patients with vCJD.^{35,36}

Identification of the at-risk population

Porter et al.³⁵ have emphasised the need to categorize those individuals with known or suspected CJD or a

related disorder, i.e., iatrogenic or vCJD (considered ‘higher risk’ in Australia) separately from those patients that are considered ‘at-risk’ (considered ‘lower risk’ in Australia). Those individuals considered to be ‘at-risk’ (considered ‘lower risk’ for developing CJD in Australia) include:

- (a) recipients of human-derived pituitary hormone;
- (b) recipients of dura mater grafts.

In Australia, pre-symptomatic individuals with a history of familial CJD in whom PRNP genotyping has not been performed and pre-symptomatic persons genotyped positive for a causal PRNP mutation are considered higher risk. However, it is acknowledged that there is no international consensus on the best way to manage infection control risks in such persons, but within Australia the leaning is towards considering them higher risk. The parents and other family members of individuals with variant, sporadic or iatrogenic CJD are not considered ‘at-risk’.³⁵

Patient risk status as defined by Woods³⁷ differed slightly in that individuals with undiagnosed,

Table 3. Summary of recommended infection control procedures in the management of higher risk patients, i.e., known/suspected familial, sporadic, iatrogenic or variant Creutzfeldt-Jakob disease requiring dental treatment and of ‘at-risk’ (considered ‘lower risk’ in Australia) patients in whom neurovascular tissue is handled.*

ITEMS TO BE TREATED	SUMMARY OF RECOMMENDATIONS
Dental instruments, including endodontic instruments and burs	To be destroyed after use by incineration. NB. Disposable dental handpieces are available; alternatively, the patient can be provided with their own dental handpiece. (In cases of suspected CJD, dental instruments should be quarantined after use in a leak-proof, sealed container until the status of the patient is determined).
The water supply of the dental unit	The handpiece should not be connected to the waterline of the dental unit; a separate source of water should be used where necessary.
The suction system and the spittoon of the dental unit	Should not be used; these can be replaced by a separate suction unit with a disposable reservoir and a disposable bowl, both of which can be discarded for incineration after use.
Single-use needles, cartridges and syringes	Should be used and discarded for incineration.
Linen, gowns, gloves and masks	Should be placed into sealed and marked bags for incineration. Where possible, schedule procedures involving neurovascular tissue at end of day to permit more extensive cleaning and decontamination.
	Other dental equipment will need to be adequately shielded using impermeable guards or coverings (it may be necessary to seek the manufacturer’s advice). If coverings are breached, the equipment will have to be destroyed by incineration.

*Modified from the WHO Guidelines, 1999³⁸ and CJD Reference Group, Australia, 2000.

Table 4. Disinfectants and physical processes that are ineffective against transmissible spongiform encephalopathy agents.¹⁰

Chemical disinfectants	Gaseous disinfectants	Physical processes
Alcohols	Ethylene oxide	Dry heat
Ammonia	Formaldehyde	Ionising radiation
B-propiolactone		UV radiation
Chlorine dioxide		Microwave treatment
Formalin		Gamma radiation
Glutaraldehyde		Moist heat at 121°C for 15 minutes
Hydrochloric acid		
Hydrogen peroxide		
Iodophors		
Peracetic acid		
Phenolics		
Sodium dichloroisocyanurate		
10,000ppm sodium hypochlorite		

progressive neurological illness with or without dementia and family members of kindreds with a strong history of undiagnosed neurological illness/dementia are considered 'lower risk'. Further distinction is made by Woods³⁷ between recipients of dura mater grafts and individuals who have undergone transdural neurosurgery between 1972 and 1989, in whom use of dura mater is unclear, are considered 'lower risk', and those who received their treatment thereafter being classified risk-free. Table 2 provides a summary guide to the various categories of 'tissue risk' and 'patient risk' and the recommended infection control procedures as provided by the CJD Reference Group of Australia.

There are unresolved issues regarding the risk status of those individuals who are restricted from donating blood in Australia because of their residence in the UK between 1980 and 1996, and those who have received blood transfusions or blood products (such as Factor VIII) from donors who have lived in the UK during that time, particularly from donors who have subsequently developed CJD as has recently occurred in the UK.

Guidelines for infection control: precautions in the management of patients with, or suspected of having, CJD

Australian guidelines

The National Health and Medical Research Council (NHMRC) of Australia guidelines¹⁷ for the prevention of transmission of human spongiform encephalopathies recommend that additional precautions be taken with known or suspected cases of CJD. These precautions include high temperature autoclaving at 134°C in porous load sterilizers for a minimum of a single 18 minute cycle or six separate 3 minute cycles (Table 3). The CJD Reference Group of Australia has put forward the following recommendations to the NHMRC; routine dentistry for individuals in the lower risk category only require standard universal precautions with the exceptions of dental procedures involving 'higher risk' tissue such as in certain oral and maxillofacial surgical procedures and endodontics (Table 3).

The NHMRC guidelines are currently being revised to ensure optimal practice in the light of recent research

and non-Australian TSE infection control recommendations.^{12,26,31} Furthermore, the NHMRC has recently established a Special Expert Committee with an advisory role on issues relating to TSEs.

World Health Organization (WHO) guidelines

The WHO guidelines for TSEs³⁸ recommend that general infection control practices as outlined by national dental associations are sufficient in the management of patients with TSE in dental procedures not involving neurovascular tissue. With the lack of consensus on the risk of transmission of TSEs through major dental procedures, extra precautions have been provided for 'consideration without recommendation'. These optional precautions for major dental work have been incorporated into Table 3.

United Kingdom guidelines

The guidelines put forward by the Department of Health, United Kingdom¹⁰ are the most detailed and stringent to date. This is not surprising as the confirmed cases of vCJD are largely confined to and increasing progressively in the United Kingdom. It has been recommended that dental equipment and instruments used on those individuals who fall into the 'at-risk' (considered 'lower risk' in Australia) category be either decontaminated using sodium hypochlorite (20,000 ppm chlorine) or 2M sodium hydroxide for one hour, or be autoclaved in a porous load sterilizer at 134°C for a minimum of a single 18 minute cycle or six separate 3 minute cycles, or be discarded for incineration. Furthermore, disposable instruments are being used for operations on tissues that might harbour the infective agent, e.g., for tonsillectomies in the UK.

The infectious agents subserving TSEs are known to be resistant to the action of commonly used disinfectants including detergents, alcohols and proteases (Table 4). The use of ethylene oxide, irradiation, autoclaving at 121°C, freezing and drying are also ineffective, and formalin fixation of infected tissues is not only ineffective but may stabilise infectivity against autoclave sterilisation.³²

The use of commercially available lyophilised and irradiated cadaveric dura mater allografts in the reconstruction of maxillofacial defects, including for

temporomandibular joint surgery and orbital floor reconstruction,³⁹ and even as periodontal free graft material⁴⁰ may have presented the most likely risk of exposure to prion-induced disease in the past for dental surgeons and their patients and thus, these procedures should be avoided. Exposure to blood, particularly through needle-stick injuries, is another potential occupational risk to dental practitioners.³²

Recommendations for the procurement of allogeneic tissues for reconstructive surgery have been provided by Marx and Carlson³⁹ and they are as follows:

- (i) select a registered and accredited tissue bank which can guarantee sterility of the tissues provided;
- (ii) be aware of the tissue bank's protocol for donor selection, exclusion and testing prior to harvesting of the allogeneic tissues;
- (iii) informed consent with regard to the remote possibility of transmitting infectious diseases from these tissues is required from patients receiving the allogeneic tissues;
- (iv) the details of the tissue bank, lot and item numbers of the allogeneic tissues and recipient information should be recorded.

Although there is no evidence that CJD and vCJD are occupational risks for dentists or that they can be transmitted to patients during dental care, universal precautions against cross-infection still remain essential, particularly in the present context of a potential population of healthy carriers of vCJD. Current recommendations regarding infection control in the dental surgery put forward by Porter et al.³⁵ in the UK, by the World Health Organization³⁸ and by Woods³⁷ are comprehensive and provide the framework for similar guidelines in Australia.

Given all considerations, patients who fall into the 'higher risk' categories outlined in Table 2 are probably best treated in a hospital-based dental clinic. Other general considerations as provided by the WHO³⁸ and the Department of Health, UK¹⁰ include:

- contaminated items should be cleaned as soon as possible after use to reduce the difficulty in removing dried blood or body fluids;
- all potentially contaminated items should be cleaned at least twice before treatment with moist heat or liquid chemicals. Items should NOT be soaked in disinfectants prior to cleaning;
- avoid mixing instruments used on no detectable infectivity tissues with those used on high and low infectivity tissues in the same autoclave cycle;
- minimize manual handling of used instruments by introducing automated decontamination processes where possible, e.g., a designated covered ultrasonic bath and an automated thermal washer;
- the ultrasonic bath and automated washer should be run through an empty cycle following the processing of contaminated instruments;
- any cleaning aids, such as brushes, should be discarded for incineration after use;

- be familiar with and observe safety guidelines when working with hazardous chemicals such as sodium hydroxide and hypochlorite;
- the correct labelling and transportation of soiled instruments for incineration or sterilisation as appropriate;
- ensure the correct disposal of biohazard, potentially contaminated waste;
- adequate communication between clinical and laboratory technical staff where biopsy samples of known, suspect or 'at-risk' (considered 'lower risk' in Australia) individuals are concerned. However, it is crucial that patient confidentiality is maintained;
- spillages of prion-infected material should be treated in a manner similar to that for other infected clinical waste by incineration.

Dental care by 'at-risk' dental practitioners

At present, there are no proposals to restrict or discourage dentists or other members of the dental team who are in an 'at-risk' category for CJD from providing dental treatment. It has been advised that those members of the dental team should confine themselves to the provision of non-exposure-prone clinical procedures in their practice of dentistry in view of any possible motor or cognitive dysfunction that may arise.

Accidental injury and contamination of the clinician during the management of individuals with known and suspected CJD or at-risk of CJD

Infection control measures for clinicians should include the covering of open skin wounds using a waterproof dressing. Contamination of unbroken skin with blood or other bodily fluids arising during the treatment of such patients requires the skin to be washed with detergents and copious warm running water in the absence of vigorous scrubbing.

The accidental contamination or creation of an open wound or needlestick injury from instruments used on known, suspected or at-risk of CJD patients requires the wound to be washed instantly with copious warm running water and dressed prior to lodging a report of the injury to the relevant authorities. Injured clinicians should seek advice and assistance from an infectious disease specialist.

CONCLUSION

There has been much publicised discussion recently concerning this biologically unique group of diseases both in the scientific arena and in the lay press. In order to allay the concerns of patients attending for dental care, it is essential that dental health care providers have a sound and current understanding of TSEs and implement adequate preventive measures accordingly. Although the risk of transmission of such diseases remains low, updated recommendations by the NHMRC are due to be published detailing highly specific infection control measures that apply to the

management of individuals with known, suspected or at-risk of classical or variant CJD.

ACKNOWLEDGMENTS

The authors would like to thank Dr G Condon (dental representative on the CJD Reference Group of Australia) for his comments on an earlier draft of this manuscript. This review has been compiled in consultation with the Infection Control Committee of the Australian Dental Association Inc.

REFERENCES

1. Will RG, Ironside JW, Zeidler M, et al. A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet* 1996;347:921-925.
2. Collinge J. Prion diseases. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford Textbook of Medicine*. 3rd edn. Oxford: Oxford Uni Press, 1996:3977-3981.
3. Prusiner SB. Prion encephalopathies of animals and humans. *Dev Biol Stand* 1993;80:31-44.
4. Goldman W. PrP gene and its association with spongiform encephalopathies. *Br Med Bull* 1993;49:839-859.
5. Merz PA, Somerville RA, Wisniewski HM, Manuelidis L, Manuelidis EE. Scrapie-associated fibrils in Creutzfeldt-Jakob disease. *Nature* 1983;306:474-476.
6. Taylor DM. Inactivation of the unconventional agents of scrapie, bovine spongiform encephalopathy and Creutzfeldt-Jakob disease. *J Hosp Infect* 1991;18 (Suppl A):141-146.
7. Cousens SN, Linsell L, Smith PG, et al. Geographical distribution of variant CJD in the UK (excluding Northern Ireland). *Lancet* 1999;353:18-21.
8. Alpers MP. Kuru. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford Textbook of Medicine*. 3rd edn. Oxford: Oxford Uni Press, 1996:3981-3983.
9. Cousens SN, Zeidler M, Esmonde TF, et al. Sporadic Creutzfeldt-Jakob disease in the United Kingdom: analysis of epidemiological surveillance data for 1970-96. *Br Med J* 1997;315:389-396.
10. Advisory Committee on Dangerous Pathogens and Spongiform Encephalopathy Advisory Committee. Transmissible spongiform encephalopathy agents: safe working and the prevention of infection. The Stationary Office, 1998. URL: 'http://www.official-documents.co.uk/document/doh/spongifm/report.htm'. Accessed September 2000.
11. Collinge J, Palmer MS. Prion diseases. Oxford: Oxford Uni Press, 1997:30-32.
12. Collins S, Law MG, Fletcher A, Boyd A, Kaldor J, Masters CL. Surgical treatment and risk of sporadic Creutzfeldt-Jakob disease: a case-control study. *Lancet* 1999;353:693-697.
13. Collinge J, Owen F, Poulter M, et al. Prion dementia without characteristic pathology. *Lancet* 1990;336:7-9.
14. Lantos PL. From slow virus to prion protein: a review of transmissible spongiform encephalopathies. *Histopathol* 1992;20:1-11.
15. Hill AF, Butterworth RJ, Joiner S, et al. Investigation of variant Creutzfeldt-Jakob disease and other human prion diseases with tonsil biopsy samples. *Lancet* 1999;353:183-189.
16. Collinge J, Palmer M, Dryden A. Genetic predisposition to iatrogenic Creutzfeldt-Jakob disease. *Lancet* 1991;337:1441-1442.
17. National Health and Medical Research Council (Australia). Creutzfeldt-Jakob disease and other human transmissible spongiform encephalopathies. Masters CL (Chair, working party). Canberra: AGPS 1996.
18. World Health Organization consultation on public health issues related to bovine spongiform encephalopathy and the emergence of a new variant of Creutzfeldt-Jakob disease. *MMWR* 1996a;45:295-296.
19. World Health Organization, Public health issues and clinical and neurological characteristics of the new variant of Creutzfeldt-Jakob disease and other human and animal transmissible spongiform encephalopathies: memorandum from two WHO meetings. *Bulletin WHO* 1996b;74:453-463.
20. Deslys JP, Lasmezas CI, Striechenberger N, et al. New variant Creutzfeldt-Jakob disease in France. *Lancet* 1997;349:30-31.
21. Bonn D. Healthy carriers could increase vCJD risk, scientists say. *Lancet* 2000;356:833.
22. Will RG, Zeidler M, Stewart GE, Macleod MA, Ironside JW. Diagnosis of new variant Creutzfeldt-Jakob disease. *Ann Neurol* 2000;47:575-582.
23. Ironside JW, Head MW, Bell JE, McCardle L, Will RG. Laboratory diagnosis of variant Creutzfeldt-Jakob disease. *Histopathol* 2000;37:1-9.
24. Wadsworth JD, Joiner S, Hill AF, et al. Tissue distribution of protease resistant prion protein variant Creutzfeldt-Jakob disease using a highly sensitive immunoblotting assay. *Lancet* 2001;358:171-180.
25. Houston F, Foster JD, Chong, A, Hunter N, Bostock CJ. Transmission of BSE by blood transfusion in sheep. *Lancet* 2000;356:999-1000.
26. Wilson K, Code C, Ricketts MN. Risk of acquiring Creutzfeldt-Jakob disease from blood transfusions: systematic review of case-control studies. *Br Med J* 2000;321:17-19.
27. Zerr I, Pocchiari M, Collins S, et al. Analysis of EEG and CSF 14-3-3 proteins as aids to the diagnosis of Creutzfeldt-Jakob disease. *Neurology* 2000;55:811-815.
28. Collinge J. Variant Creutzfeldt-Jakob disease. *Lancet* 1999;354:317-323.
29. Zeidler M, Sellar RJ, Collie DA, et al. The pulvinar sign on magnetic resonance imaging in variant Creutzfeldt-Jakob disease. *Lancet* 2000;355:1412-1418.
30. Ingrosso L, Pisani F, Pocchiari M. Transmission of the 263K scrapie strain by the dental route. *J Gen Virol* 1999;80:3043-3047.
31. Blanquet-Grossard F, Sazdovitch V, Jean A, et al. Prion protein is not detectable in dental pulp from patients with Creutzfeldt-Jakob disease. *J Dent Res* 2000;79:700.
32. Gonzales TS, Rushing EJ. Bad news and good news: what the dentist needs to know about transmissible spongiform encephalopathies. *Quintessence Int* 1998;29:319-321.
33. Davanipour Z, Alter M, Sobel E, Asher D, Gajdusek D. Creutzfeldt-Jakob disease: possible medical risk factors. *Neurology* 1985;35:1483-1486.
34. Andrews NJ, Farrington CP, Cousens SN, et al. Incidence of variant Creutzfeldt-Jakob disease in the UK. *Lancet* 2000;356:481-482.
35. Porter S, Scully C, Ridgway GL, Bell J. The human transmissible spongiform encephalopathies (TSEs): implications for dental practitioners. *Br Dent J* 2000;188:432-436.
36. Zeidler M, Stewart GE, Barraclough CR, et al. New variant Creutzfeldt-Jakob disease: neurological features and diagnostic tests. *Lancet* 1997;350:903-907.
37. Woods R. Additional precautions to prevent transmission of Creutzfeldt-Jakob disease and other prion diseases. *FDI World* 1997;6:11-16.
38. World Health Organization Infection Control Guidelines for TSEs, 1999. URL: 'www.who.int/emc-documents/tse/docs'. Accessed December 2000.
39. Marx RE, Carlson ER. Tissue banking safety: caveats and precautions for the oral and maxillofacial surgeon. *J Oral Maxillofac Surg* 1993;51:1372-1379.
40. Bartolucci EG. A clinical evaluation of freeze-dried homologous dura mater as a periodontal free graft material. *Study in humans. J Periodontol* 1981;52:354-361.

Address for correspondence/reprints:

Dr Sheena Chan
Oral Pathology Unit
Level 2, Westmead Centre for Oral Health
Darcy Road, Westmead NSW 2145