

## **Scientific Committee on Emerging and Zoonotic Diseases**

### **Epidemiology of Creutzfeldt-Jakob Disease in Hong Kong**

#### **Purpose**

This paper reviews the epidemiology of Creutzfeldt-Jakob disease (CJD) in Hong Kong.

#### **Introduction**

2. CJD is a rare and invariably fatal progressive degenerative brain disease with incubation period typically measured in years<sup>1</sup>. It belongs to a group of diseases called Transmissible Spongiform Encephalopathies (TSEs) that affect humans and animals. CJD was initially described in 1920 by two German neurologists<sup>2</sup> and is believed to be caused by a self-replicating host-encoded proteinaceous infectious particle (prion), which is an infectious agent composed only of protein.

#### **Prions**

3. Prions are believed to infect and propagate by refolding abnormally into a structure which is able to convert normal molecules of the protein into the abnormally structured form. Prions are generally quite resistant to denaturation by proteases, heat, radiation and treatments, although their infectivity can be reduced by such treatments.

#### **Different categories of CJD**

4. CJD falls into four categories: sporadic, genetic, iatrogenic and variant. The most common form of CJD is believed to occur sporadically (sporadic CJD, sCJD), representing about 85-90% of cases<sup>3</sup>,



which is caused by the spontaneous transformation of normal prion proteins into abnormal prions. About 5-10% of CJD cases are genetic<sup>3</sup>, caused by inherited mutations of the prion protein gene. Iatrogenically transmitted CJD (>5%) is inadvertently transmitted usually from a case with sCJD in the course of medical/surgical treatment, e.g. human pituitary hormone therapy, human *dura mater* grafts, corneal grafts or neurological instruments. A new variant known as variant CJD (vCJD) was identified in March 1996<sup>4</sup>, has been linked to a TSE of cattle called Bovine Spongiform Encephalopathy (BSE, commonly known as mad cow disease).

## **Incidence**

5. CJD, including probable and definite cases of sporadic, genetic and iatrogenically transmitted CJD, occurs at a rate of about 1-2 cases per million population per year worldwide<sup>3</sup>.

6. From 1996 through November 2007, 163 cases of vCJD, including definite and probable cases, have occurred in UK, 23 in France, 4 in Ireland, 3 in United States (US), 2 each in Netherlands, Portugal and Saudi Arabia and one each in Canada, Italy, Japan, Spain<sup>5</sup> and Hong Kong.

## **Routes of transmission**

7. The cause of sCJD remains unknown despite extensive study<sup>6</sup>; *de novo* spontaneous generation of self-replicating protein has been hypothesized. There has been no clear evidence of risk from diet, previous surgery, blood transfusion, occupational or animal exposure, although the possibility that sporadic CJD arises through other unrecognized environmental exposure cannot be dismissed. Genetic CJD is an inherited condition. Iatrogenically transmitted CJD (>5%) is inadvertently transmitted usually from a case with sCJD in the course of medical/surgical treatment, e.g. human pituitary hormone therapy, human *dura mater* grafts, corneal grafts or neurological instruments. Until recently, all vCJD cases were attributed to consumption of beef products contaminated with the infectious agent of BSE. There is evidence from a case-control study in UK showing that vCJD was probably caused by dietary exposure to high-titre bovine tissue in the food chain<sup>7</sup>.

8. Since December 2003, four individuals have been identified with vCJD infections probably acquired secondarily from blood transfusions in UK; three with typical vCJD symptoms and the other with pre-clinical vCJD involving spleen and lymph nodes but not the brain<sup>8</sup>. These four vCJD case-patients acquired infection from clinically healthy persons who became ill more than a year after donating blood. To date, epidemiological analysis does not indicate that most medicinal products, including plasma-derived products or occupational exposures have been sources of infection in vCJD cases identified<sup>6</sup>.

## Clinical features and diagnosis

9. The disease usually presented with subacute onset with confusion, progressive dementia and variable ataxia in patients aged 14 to over 80, almost all (more than 95%) 35 or older. Myoclonic jerks appear later, together with a variable spectrum of other neurological signs. Characteristically, routine laboratory studies and the CSF cell count are normal and there is no fever. Typical periodic high-voltage complexes are present in the electroencephalogram (EEG) in about 70% of cases and the CSG 14-3-3 protein is elevated in about 90%. The EEG is non-specific and the CSF 14-3-3 is not elevated in vCJD. The disease progresses rapidly and death usually occurs within months.

10. WHO has published the surveillance case definitions for the classification of human TSE in 2003<sup>9</sup>, (Annex 1) classifying CJD into definite, probable and possible cases according to a list of clinical features and investigation results.

11. Sporadic CJD and vCJD are also different in their clinical signs and symptoms, course of illness, neuropathological features, and investigation results (Table 1).

Characteristic	sCJD	vCJD
Mean age of onset	65 years	28 years
Early clinical features		
Psychiatric symptoms	Absent	Present
Sensory disturbances	Absent	Present
Rapid clinical progression	Present	Absent
Mean duration of illness	8 months	15 months
Periodic sharp-wave complexes on EEG	Often present	Absent
Bilateral symmetrical pulvinar high signal on magnetic resonance imaging (MRI)	Absent	Often present

Table 1. Characteristics distinguishing sCJD from vCJD (adapted from WHO<sup>9,10</sup>).

12. So far there is no treatment shown conclusively to slow or stop the disease process in humans with any form of CJD. Treatment remains supportive and aimed at palliation of any distressing symptoms<sup>9</sup>.

## Preventive and control measures

13. Isolation of patients is not necessary. However, organ or tissue transplant from any CJD patients or re-use for potentially contaminated

surgical instruments should be avoided. WHO guidelines to minimize the risk of transmission of CJD identify categories of individual at higher risk of human TSE (family history of CJD, prior treatment with human pituitary hormones, prior neurosurgery)<sup>11</sup>.

14. The identification of the cases caused by blood transfusion from clinically healthy persons has intensified the concern about possible unmapped ways in which the disease might spread. In response to this, World Health Organization (WHO) and other authorities have developed guidelines on how to minimize risks to humans from biological and pharmaceutical products in which ruminant materials are used during manufacture; and from human-derived materials<sup>6</sup>. Transfusion recipients should be deferred as blood donors in order to reduce substantially the risk of recycling vCJD, and theoretically other CJD, infections. This measure has been in place in France since 1998, in UK since 2005 and more recently in several other European countries such as Ireland, Netherlands and Switzerland. In some other countries, like Canada, Australia, Italy and US, persons who previously received transfusion in UK are deferred as donors.

15. Based on the understanding that consumption of beef products contaminated with the BSE agent remains the main way of exposure for vCJD, WHO recommended that 'countries should not permit tissues that are likely to contain the BSE agent to enter any food chain (human or animal)<sup>12</sup>. Control measures to achieve this include surveillance and control of BSE in animals; feed bans on meat-and-bone meal to ruminants, and specified risk materials bans<sup>13</sup>.

### **Local epidemiology**

16. Department of Health (DH) has established CJD surveillance since April 1996. All doctors are requested to report any suspected or confirmed case of CJD to DH. In addition, since 2004, a mechanism has been established between DH and Hospital Authority to ensure that every CJD case diagnosed is reported and investigated. Up to 5 December 2007, fifty-one CJD cases have been recorded (Figure 1), including 49 sporadic and 2 variant CJD cases. None of them were classified as genetic or iatrogenic. The mean annual incidence during this period was estimated to be 0.6 per million population, lower than that reported in some developed countries (US: 1 per million, Canada: 1.11 per million, UK: 1.11 per million).

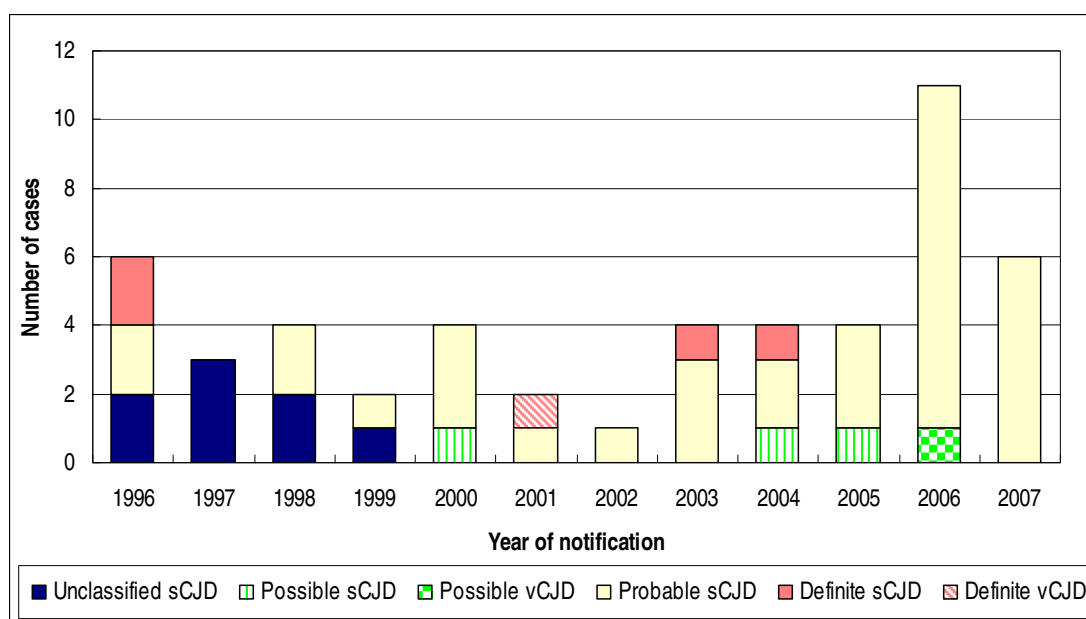


Figure 1. Number of sCJD and vCJD cases recorded by DH from April 1996 to November 2007 (as of 5 December 2007).

17. For the 49 sporadic cases, they were 21 men and 28 women, aged from 44 to 86 years (mean 65 years) at onset of symptoms. Four of them were classified as definite cases based on post-mortem neuropathological confirmation by brain tissue; 34 were classified as probable cases and three possible cases. Eight cases were unclassified due to limited clinical information. Majority of these sCJD cases presented with symptoms compatible with sCJD with typical EEG changes. Cerebrospinal fluid of 5 cases was tested positive for 14-3-3 protein. Forty-four of them had died of the disease at the time of writing this paper. Survival duration since onset of symptoms ranged from 1 to 23 months with a median of 8 months. No definite history of other risk factors for CJD could be identified from these cases<sup>14</sup>.

18. Two vCJD cases were reported in 2001 and 2006, and both were classified as imported cases from UK. The first case was reported in June 2001, affecting a 34-year-old woman who resided in UK during the 1980s and 1990s. She presented with progressive mental disorders since October 2000. Her EEG did not show the typical appearance of sCJD and MRI scan of the brain showed bilateral high signal from the pulvinar area. Tonsil biopsy was tested positive for prion protein by National CJD Surveillance Unit in Edinburgh. She passed away in 2002 and the diagnosis was confirmed by post-mortem neuropathological examination.

19. The second vCJD case was reported in May 2006, involving a 23-year-old man who has been residing in UK since birth. He came to Hong Kong in April 2006 and was admitted for investigation of abnormal behaviours. He was then noted to have deterioration of cognitive function and myoclonus. EEG did not show the typical appearance of sCJD and MRI was negative for

pulvinar sign. Tonsillar tissue was tested negative for prion protein by National CJD Surveillance Unit in Edinburgh. To date (19 months after his onset of symptoms), he is still alive, but unconscious and totally dependent. Based on the evidence obtained so far, the case is currently classified as possible vCJD.

20. Epidemiological investigations on these two cases identified no other risk factors for CJD. Both cases have no history of neurosurgery or organ transplant and have not donated blood in Hong Kong.

### **Local public health investigation and control measures**

21. All CJD cases reported to DH will be investigated with the main objective of confirming the diagnoses and the exclusion of possible iatrogenic sources of infection or vCJD. Detailed clinical, family, food and residency history will be obtained from the patients, attending physicians or the patients' closest relative.

22. Potential risk factors for iatrogenically transmitted CJD such as previous history of neurosurgery, administration of growth hormone or gonadotrophin and history of cornea transplant will be assessed.

23. History of transfusion and donation blood or blood products since 1980 will also be obtained. If a CJD patient is found to have been a blood donor, Blood Bank of Hong Kong Red Cross will be informed immediately to retrieve and destroy all in-date blood components that have been collected from that donor, including whole blood, blood components, source leukocytes, pooled platelets and unpooled source plasma. If the blood or blood products from a CJD patient are found to have been used for transfusion, Red Cross will notify the particular hospital(s) so that the attending physician(s) of the recipient(s) will be informed. Recipient tracing, appropriate notification and counselling will then be performed as appropriate with the collaboration of the care providers. This principle is also applicable to CJD donors of other tissues for transplantational use.

24. Handling of instruments depends on a combination of the classification of the patient, infectivity of tissue(s) involved in the procedure, and the type of CJD. Diagnostic and surgical instruments that have been used on a possible CJD or vCJD will be traced and put under decontamination procedures according to patient category and tissue infectivity<sup>6</sup>. They may be quarantined until the diagnosis is confirmed or refuted. If the case is confirmed as CJD or vCJD, or if after testing the diagnosis is inconclusive, the instruments should be destroyed by incineration.

25. To better understand the local epidemiology and prevent the possible spread of CJD, we shall include CJD in the revised list of statutory notifiable disease in Hong Kong during the revision of the Quarantine and

Prevention of Disease Ordinance (Cap 141).

Centre for Health Protection  
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## Annex 1

### Surveillance case definitions for the classification of human transmissible spongiform encephalopathies (WHO 2003)<sup>9</sup>

#### 1. Sporadic CJD

##### Possible

- Progressive dementia and
- EEG atypical or not known and
- Duration <2 years and
- At least 2 of the following clinical features:
  - myoclonus
  - visual or cerebellar disturbance
  - pyramidal / extrapyramidal dysfunction
  - akinetic mutism.

**Probable** (in the absence of an alternative diagnosis from routine investigation)

- Progressive dementia and
- At least 2 of the following 4 clinical features:
  - myoclonus
  - visual or cerebellar disturbance
  - pyramidal/extrapyramidal dysfunction
  - akinetic mutism and
- A typical EEG, whatever the clinical duration of the disease, and/or
- A positive 14-3-3 assay for CSF and a clinical duration to death <2years

##### Definite CJD

- Neuropathological confirmation; and/or
- Confirmation of protease-resistant prion protein (immunocytochemistry or western blot) and/or
- Presence of scrapie-associated fibrils.

#### 2. Iatrogenically transmitted CJD

##### Probable

- a. Progressive cerebellar syndrome in human pituitary hormone recipients.
- b. Probable CJD with recognized iatrogenic risk

##### Definite

Definite CJD with a recognized iatrogenic risk.

### 3. Genetic human TSEs

#### **Probable**

- a. Probable TSE plus definite or probable TSE in a first-degree relative.
- b. Progressive neuropsychiatric disorder plus disease-specific mutation.

#### **Definite**

Definite TSE with a recognized pathogenic Pr mutation plus definite or probable TSE in a first-degree relative.

*Note:* For purposes of surveillance, this includes Gerstmann-Sträussler-Scheinker disease and fatal familial insomnia.

### 4. Variant CJD

- I
  - A Progressive neuropsychiatric disorder
  - B Duration of illness > 6 months
  - C Routine investigations do not suggest an alternative diagnosis
  - D No history of potential iatrogenic exposure
  - E No evidence of a familial form of TSE

#### **Definite case**

I A **and** neuropathological confirmation of vCJD<sup>1</sup>

#### **Probable case**

I **and** 4/5 of II **and** III A **and** III B **OR** I **and** IV A

#### **Possible case**

I **and** 4/5 of II **and** III A

- II
  - A Early psychiatric symptoms<sup>2</sup>
  - B Persistent painful sensory symptoms<sup>3</sup>
  - C Ataxia
  - D Myoclonus or chorea or dystonia
  - E Dementia
- III
  - A EEG does not show the typical appearance of sporadic CJD<sup>4</sup> (or no EEG performed)
  - B MRI brain scan shows bilateral symmetrical pulvinar high signal<sup>5</sup>
- IV
  - A Positive tonsil biopsy<sup>6</sup>

- 
1. Spongiform change and extensive PrP deposition with florid plaques, throughout the cerebrum and cerebellum.
  2. Depression, anxiety, apathy, withdrawal, delusions.
  3. This includes both frank pain and/or dysaesthesia.
  4. Generalized triphasic periodic complexes at approximately one per second.
  5. Relative to the signal intensity of other deep grey matter nuclei and cortical grey matter.
  6. Tonsil biopsy is not recommended routinely, nor in cases with EEG appearances typical of sporadic CJD, but may be useful in suspect cases in which the clinical features are compatible with vCJD and where MRI does not show bilateral pulvinar high signal.