Report of the WHO Workshop on the Surveillance of Creutzfeldt-Jakob disease (CJD) and other Transmissible Spongiform Encephalopathies (TSEs)

With the participation of the Office International des Epizooties (OIE)

Bangkok, Thailand
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1. INTRODUCTION

In March 1996 the occurrence in the United Kingdom of ten cases of an apparently new clinicopathological variant of Creutzfeldt-Jakob disease (nvCJD) was announced. The temporal and geographical association between these cases and the bovine spongiform encephalopathy (BSE) epidemic of cattle raised the possibility of a causal link, leading to great public concern. The size of the human population exposed and susceptible to the BSE agent in the United Kingdom is not known and in addition to uncertainties relating to the potential length and distribution of the incubation period, make a useful prediction of the future number of nvCJD cases difficult. Other populations may have also been exposed to the agent through importation from BSE-affected countries of live cattle or cattle by-products, food containing contaminated bovine offals, or from medicinal products containing bovine tissues. Thus the importance of analysing risks, conducting surveillance and monitoring for the occurrence of BSE is widely recognised as being essential to aid authorities to judge any risks there may be to the human population. Monitoring CJD incidence itself is also clearly important and it is noteworthy that this is not currently undertaken in many parts of the world.

The potential future global public health implications of nvCJD were addressed by a WHO expert consultation in May 1996 which recommended the establishment of worldwide surveillance of the new variant and other forms of CJD. Throughout 1997 and 1998 WHO will be running a series of regional workshops, particularly in developing countries, with the intention of helping individual countries establish national surveillance of CJD and its variants. The meeting in Bangkok was the second workshop, the first having been held in June 1997 in Dakar, Senegal, for western African countries. Further workshops have been planned to take place early next year in Cairo for eastern Mediterranean countries, China for countries in the Western Pacific region and in Buenos Aires for South American countries.

It is anticipated that WHO’s global CJD surveillance activities will lead to a greater understanding of CJD and its variants, including the potential causes of iatrogenic CJD and the distribution of the various hereditary forms, and will provide information important for enhancing the protection and planning of public health worldwide.

The second WHO workshop on Global CJD surveillance was held at the Prasat Neurological Institute in Bangkok between 6-8 October 1997. Representatives from each of the following countries participated in the meeting: Bangladesh, Indonesia, Myanmar, Sri Lanka and Thailand. Two countries, Indonesia and Sri Lanka, also sent veterinary representatives. A further six participants from Thailand in addition to approximately 20 students were also in attendance. The meeting was opened by Dr. Suchart Phudichareonrat, Head of Prasat Neurological Hospital and Institute’s Department of Neuropathology. Professor Thiravat Hemachudha then welcomed the participants and speakers and introduced the first lecture.
2. PRESENTATIONS

The first lecture, ‘An overview of the human TSEs’, was given by Dr. Martin Zeidler, former research fellow at the United Kingdom National Creutzfeldt-Jakob Disease Surveillance Unit in Edinburgh, Scotland, and now a medical officer with WHO in Geneva. He gave the history of CJD and kuru, presented the characteristic clinical features and discussed the diagnosis and aetiology of these conditions.

The second lecture, ‘The epidemiology of CJD, incidence, risk factors and survival in the European Union Collaborative Study’, was given by Dr. Dorothée Wientjens, former research fellow at the Department of Epidemiology and Biostatistics of the Erasmus University in Rotterdam, the Netherlands. She presented an overview of CJD epidemiology, emphasising the relatively consistent incidence of CJD in those populations studied (approximately 1 case per million persons annually), the familial occurrence of disease in almost 10% of cases and the lack of evidence to suggest important environmental risk factors for the development of sporadic CJD.

The third lecture, ‘The new variant of Creutzfeldt-Jakob disease’ was given in the afternoon of the first day. Dr. Zeidler presented up-to-date information on the new variant form of CJD, including important research that had been published the previous week in the journal Nature, which concluded that the agent causing BSE and nvCJD was the same, thus supporting a causal link between the diseases. An overview of the clinical, investigative and epidemiological features of nvCJD was also given in addition to a discussion on the evidence of an association between nvCJD and BSE.

National reports were then given by representatives from each of the five attending countries in the afternoon of the first day.

Thailand

Thailand has an estimated population of 60 million people. Although there had been no official statistics on CJD in Thailand, it was estimated from data accumulated from five different university hospitals that no more than 30 cases had been diagnosed in the previous 20 years. Approximately one in four cases would have undergone autopsy. There had been no reported case of iatrogenic CJD. Three new cases had been diagnosed in the previous year, one was a case of sporadic CJD and the other two were considered clinically to be fatal familial insomnia.

Myanmar

It was reported that four neurologists, two neuropathologists and 240 epidemiologists were available for a population of 46 million people. Six centres were known with EEG facilities, two in Upper and four in Lower Myanmar. There had never been a reported case of CJD.

Sri Lanka

Eight neurologists served a population of 18 million people. Three centres were known to have EEG facilities but there were no neurophysiologists. There was a very low social acceptance of autopsy. Cadaveric-derived growth
hormone had been used, but very rarely. Cadaveric-derived dura mater homografts had not been used. CJD was not a notifiable disease and no confirmed case had been documented.

**Bangladesh**

Fifteen neurologists were currently working in Bangladesh, a country with a population of 120 million. EEG facilities were available in urban areas but autopsies were reported to be uncommon for religious reasons. It was noted that there was a department of neuropathology in Dhaka. Cadaveric-derived dural homografts and pituitary growth hormone had been used very little. No case of CJD had ever been documented.

**Indonesia**

The population of Indonesia was reported to be 200 million people and the country has approximately 80 EEG departments. No case of CJD had been reported.

The first two lectures on the second day, ‘The pathology of human TSEs’ and ‘Safety Issues’, were given by Prof. Herbert Budka, Professor of Neuropathology at the University of Vienna, Austria, and Head of the European Union Concerted Action ‘The human prion diseases from neuropathology to pathology and molecular genetics’. The first lecture gave an overview of the neuropathology of human TSEs, including advances in immunocytochemistry and other molecular biological techniques. The unusual pathological features of the familial TSEs, including fatal familial insomnia, were demonstrated and a further clarification of the unproven prion hypothesis of disease aetiology given. Prof. Budka noted that the previous evening it had been announced that Professor Stanley Prusiner’s pioneering work on the prion hypothesis was to be rewarded by the 1997 Nobel Prize for Medicine. The second lecture concentrated on safety aspects relating to the TSEs. The inability to inactivate the infectious agent by conventional sterilisation techniques was noted and guidelines for appropriate decontamination procedures given. The morning session ended with a 30 minute video presentation on the clinical features of kuru.

The final lecture, ‘The Animal TSEs’, was given by Mr. Ray Bradley, a BSE consultant representing the OIE, from the Central Veterinary Laboratory, Weybridge, England. An overview of the animal TSEs was presented, particularly describing the occurrence and the epidemiology of BSE and the control methods used in the United Kingdom and the European Union. Also presented were recommendations from the OIE International Animal Health Code relating to BSE risk analysis, the need to develop a risk management strategy and institute continuous surveillance and monitoring for BSE.

The final morning was given over to an in-depth discussion of the practicalities of initiating surveillance of CJD and BSE in the nations represented.

3. DISCUSSION

**Logistics of national Surveillance**

The participants stated that they considered surveillance of nvCJD of more importance than other forms of CJD. They also emphasised that although CJD surveillance was important, it had to be appreciated that there were many other areas of human medicine with more pressing needs for the resources of their countries. Dr. Zeidler stressed that although WHO concurred with the view that the ascertainment of nvCJD would be the main objective of surveillance, it would be detrimental to separate this from surveillance of other forms of human TSEs for two main
reasons. First, nvCJD and some cases of sporadic CJD may be clinically indistinguishable and, second, the necessary diagnostic skills required to detect a case of nvCJD are likely to be greatly strengthened through the experience gained in surveillance of the more common forms of CJD. With regard to funding, WHO should be able to largely cover the cost of establishing national surveillance by supporting the organisation of national training workshops, training key personnel, providing educational material and assisting with laboratory diagnosis of disease.

Clarification of the definition of a ‘case’ for surveillance purposes was requested and Dr. Zeidler explained that standard diagnostic criteria were printed at the back of the training booklet. He emphasised that in the correct clinical context the occurrence of the characteristic periodic EEG predicts a pathological diagnosis of CJD with almost 100% accuracy. A clinically probable case with a typical EEG, but who dies without pathology being performed, is therefore included as a case of CJD for surveillance purposes. As the possibility of a characteristic tracing increases with time, it was recommended that following a non-diagnostic recording further tracings should be repeated at regular intervals (days or weeks) depending on the tempo of the patient’s illness. The lack of provision of EEG facilities in some countries was noted, and it was suggested that if an EEG could not be performed CSF should be taken if possible, and stored frozen for the 14-3-3 assay. This could then be tested at a later date at one of WHO’s collaborating centres.

The logistics of surveillance were discussed at length, in particular which group of medical professionals should be targeted and the method of collecting information. Prof. Hemachudha noted that he had recently had a very poor response to a mail-out to neurologists in Thailand asking them to provide information on cases of multiple sclerosis. Methods of encouraging referrals of cases were discussed and Dr. Zeidler said that he hoped that the general level of concern regarding CJD, in addition to educating the relevant professional groups and requesting zero reporting, should hopefully help to attain a high degree of case notification. The possibility of using death certificates for additional ascertainment of cases was raised by Dr. Zeidler. The national representatives explained that this was unlikely to provide any significant and useful information because often only the immediate cause of death, such as bronchopneumonia, was recorded, records may be inaccessible or they may be coded inadequately.

A discussion followed on whether making CJD notifiable would aid case ascertainment. It was pointed out, however, that this had paradoxically led to decreased detection of cases in Slovakia. Furthermore, experience with other notifiable diseases questioned whether this would benefit surveillance.

Mr. Bradley suggested that it would be useful to define clear objectives for CJD surveillance and the meeting identified the following major aims:

1. To provide information important for enhancing the protection and planning of public health worldwide
2. To provide information that would be helpful in establishing more accurate diagnosis of all forms of CJD
3. To prevent iatrogenic spread of disease (e.g. through the use of contaminated neurosurgical instruments or via human-derived tissue/material)
4. To increase global scientific knowledge of the human and animal TSEs
5. To help to identify underlying occult risk factors
6. To established a baseline that would allow any relevant change to be detected (e.g. in clinical features, pathology and incidence)
Diagnosis

It was noted that in view of difficulties in obtaining an autopsy, clinical diagnostic tests were likely to be of the utmost importance in identifying cases of CJD. As the diagnosis of a probable case of sporadic CJD currently relied on the presence of a typical EEG, one participant requested the definition of such an appearance. Dr. Zeidler stated that unfortunately no widely accepted and validated criteria existed for a ‘typical’ EEG, but that examples were given in the back of the training document. It was suggested that the criteria recommended by Steinhoff could be used in a case whose EEG was considered borderline (1996, Steinhoff BJ, Racker S, Herrendorf G, Poser S, Grosche, Zerr I, Kretzschmar H, and Weber T, Accuracy and reliability of periodic sharp wave complexes in Creutzfeldt-Jakob disease. Archives of Neurology, 53:162-166)

Questions were also raised about potential new diagnostic tests, in particular CSF assays and tonsillar biopsy. It was explained that the 14-3-3 CSF test has recently become available at some specialist centres in Europe and North America, and that initial results suggest a very high sensitivity and specificity in sporadic CJD. However, it was noted that false positives had been documented, in particular in patients with recent strokes, but also in other conditions such as Alzheimer’s disease. The experience of the test in nvCJD was limited, but provisional results suggest that it may be less useful than in sporadic CJD. Other CSF markers were currently being investigated, including S100, tau and neuron-specific enolase. It was advised that CSF, particularly for some of the latter tests, should be stored deep frozen immediately after being taken. The results of a palatine tonsillar biopsy have been published for a single case of nvCJD. The biopsy was performed post-mortem and demonstrated the presence of abnormal prion protein with the type 4 glycosylation pattern characteristic of nvCJD. Although there have been press reports of a young British patient with a positive tonsil biopsy taken during life, this is currently unconfirmed. A Japanese study failed to identify abnormal prion protein in the lymphoreticular of 11 patients with conventional CJD or GSS.

The participants reiterated that their main concern was diagnosing nvCJD, and the difficulties with this were discussed, particularly the current lack of ante-mortem diagnostic test and clinical diagnostic criteria. It was noted that bilateral MRI abnormalities of the thalamus may be a useful sign and that this was currently undergoing further investigation. The importance of neuropathological examination in any suspect case of nvCJD was emphasised A question was raised about the possibility of performing brain biopsy during life. Dr. Zeidler cautioned against this procedure, noting that brain biopsy was unlikely to significantly benefit the patient unless a potentially treatable condition was also considered a possibility and therefore, although diagnostic in most cases, brain biopsy could not be recommended to confirm the clinical suspicion of CJD. Furthermore he noted that brain biopsy was potentially hazardous, not only to the patient (who may develop a surgical complication such as infection or haemorrhage) but also to hospital staff. He added that it would be mandatory to store and destroy the neurosurgical instruments if the diagnosis of CJD was confirmed, as adequate inactivation could not be guaranteed.

It was noted that approximately 10-15% of cases of CJD were familial, associated with a mutation of the prion protein gene. Screening cases for these defects was possible but raised ethical questions, many of which were common to other hereditary disorders, such as Huntington’s disease. It was suggested that if genetic testing was to be performed it would probably be best to test those cases with a family history before deciding whether it would
be possible to screen all cases (sometimes cases are found to have a mutation without a clear family history of CJD). It was recommended that informed consent be sought and genetic counselling performed, before genetic testing. WHO collaborating centres should be able to perform the DNA analysis if sent a small sample of blood. Consent forms as used in other countries for genetic testing in CJD would be available from Dr. Zeidler at WHO in Geneva.

Concern was expressed by several delegates regarding the logistics of performing an autopsy on a suspect case of CJD and the incineration of potentially contaminated materials. Prof. Budka reassured the participants that an autopsy could be performed safely and that he would consider the risks to medical personnel from occupational exposure to be very small in comparison to other disorders such as HIV or hepatitis B. It was noted that no case of a health professional or laboratory research worker contracting a TSE through occupational exposure had ever been documented. It was apparent that religious and cultural objections may lead to difficulties in obtaining an autopsy in many populations and Prof. Hemachudha suggested that a *post-mortem* retro-orbital biopsy may be more acceptable. This technique had been used in rabies diagnosis and would involve the insertion of a needle and trocar through the supra-orbital fissure into the brain. No external sign of trauma should therefore be apparent, but the body would need to be handled with care after such a procedure because of possible contamination of the skin, particularly of the head and face. Biopsy material could be either fixed for conventional histology and/or frozen for western blotting. A request was made for histological slides of CJD using both conventional and immunocytochemical stains and Prof. Budka kindly offered to help in this regard. Mr. Bradley pointed out that electron microscopy could be used to detect scrapie-associated fibrils (SAFs) in countries where immunological techniques using anti-PrP sera were not available, and that the presence of SAFs was considered diagnostic.

N.B. WHO is hoping to hold a consultation in early 1998 to discuss the state-of-the-art regarding diagnostic tests in CJD and the possibility of establishing provisional clinical diagnostic criteria for nvCJD and the methods by which these could be validated.

**Animal TSE Surveillance**

Delegates reported that there was considerable concern in their countries regarding BSE and the possible transmission of the BSE agent to humans. The possible modes through which a population may have been exposed to the BSE agent were discussed, including the importation of infected animals, contaminated meat and bone meal, human food and medicinal products. It was considered that if the BSE agent was the cause of nvCJD, and assuming an origin from cattle CNS tissues, a logical preventative step would be to ensure effective surveillance for BSE as recommended by the OIE. If any cases of BSE were found it would give advance warning of a potential human health risk because disease in cattle would probably ante-date any associated occurrence of nvCJD as the incubation period of BSE in cattle is likely to be significantly shorter than nvCJD in man. Mr. Bradley placed an emphasis on the importance of conducting a BSE risk assessment and developing a risk management strategy to deal with any risks identified and to initiate a programme of continuous surveillance and monitoring for the disease in line with the recommendations of the OIE *Code*. 
Particular assistance was requested by some of the delegates to aid countries to set up diagnostic procedures for BSE according to the protocols set out in the OIE Manual of Standards or otherwise to provide facilities in the Region or elsewhere.
RECOMMENDATIONS

The meeting recommended that:

- Participants should disseminate information relevant to national CJD surveillance to the appropriate professional groups in their countries, particularly neurologists, neurophysiologists and epidemiologists, using established networks, such as neurological societies, and printed material.

- In each country, the health care professionals most likely to be in a position to diagnose cases of CJD should be contacted on at least an annual basis reminding them to report cases of definite or probable CJD.

- Each of the countries represented would identify a national focal point, most probably one of their delegates attending the workshop, who would be responsible for organising a national CJD surveillance meeting in their own county.

- The national focal point would collect data on the number of probable and definite cases of CJD in their country and forward this (even if zero) on an annual basis to WHO.

- WHO will financially support the national workshops and help provide training material.

- WHO, through its CJD collaborating centres, will provide short periods of training in diagnostic techniques, including neuropathology, molecular genetics and the emerging CSF assays, for key personnel.

- The usefulness of the retro-orbital *post-mortem* cerebral biopsy will be ascertained by assessing its use in a number of suspect CJD autopsies performed in WHO collaborating centres and the Prasat Neurological Hospital and Institute in Thailand. The results of this study will be published.

- WHO, through its collaborating centres, will make slides available to interested pathologists of various forms of CJD, using both conventional and immunocytochemical stains.

- Workshops should be set up to enable the OIE Code recommendations on BSE to be implemented. Training at the bench should be included.
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