



**WHO/EMC/ZDI/98.9**

**Global Surveillance, Diagnosis and Therapy of Human  
Transmissible Spongiform Encephalopathies: Report of a  
WHO Consultation**

**Geneva, Switzerland, 9-11 February 1998**

**World Health Organization**  
Emerging and other Communicable Diseases,  
Surveillance and Control

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## **1. BACKGROUND**

### **1.1 Introduction**

This report documents the conclusions and recommendations of the WHO Consultation on the Global Surveillance, Diagnosis and Therapy of Human Transmissible Spongiform Encephalopathies (TSE) which was held at WHO headquarters in Geneva, 9-11 February 1998. Dr Lindsay Martinez, the Deputy Director of WHO's EMC Division, opened the meeting and stated the need to review Creutzfeldt-Jakob disease (CJD) diagnostics with the aim of strengthening the Organization's ongoing activities to promote global surveillance of CJD and its variants. She noted that difficulties existed in detecting cases of CJD, particularly in areas where the key diagnostic procedures - autopsy and electroencephalography - were lacking, and requested that the meeting consider methods of increasing case ascertainment.

At the time of the Consultation a total of 24 cases of new variant CJD (nvCJD) had been reported to WHO, 23 in the United Kingdom and a single case in France. Dr Martinez noted that strong evidence indicated that nvCJD is linked with bovine spongiform encephalopathy (BSE) and that the possibility of many more nvCJD cases occurring in the future could not be dismissed. Furthermore, and adding to the seriousness of the situation, no treatment was known to prevent the occurrence of CJD or halt disease progression. Dr Martinez added, however, that there was no lack of ideas for potential therapeutic interventions and that concern for the possibility of a significant epidemic of nvCJD over the following 10-15 years emphasised the paramount importance of seriously evaluating these ideas. She concluded that by addressing this issue at the Consultation, WHO intended to stimulate the relevant bodies to further support research aimed at an early identification of an effective therapy.

Presented below are three sections documenting background information to the key topics discussed at the meeting. These sections have been prepared by the WHO Secretariat in close collaboration with the Consultation's chairman and rapporteurs.

### **1.2 Surveillance**

CJD is a rare and fatal human neurodegenerative condition characterised in most cases by a rapidly progressive dementia, myoclonus and a periodic electroencephalogram (EEG).<sup>1</sup> It is classified as a transmissible spongiform encephalopathy because of characteristic spongy degeneration of the brain and its ability to be transmitted to laboratory animals (see Reference 2 for further WHO information on CJD). TSE, alternatively known as prion diseases, also naturally affect a range of animal species including sheep, goats, cows, deer, mink and cats. The human TSE, of which CJD is by far the most common, occur sporadically in about 85% of cases, 10-15% are inherited and the remaining cases are iatrogenic. The other human prion diseases are Gerstmann-Sträussler-Scheinker disease (GSS) and fatal familial insomnia (FFI), both extremely rare hereditary disorders, and kuru, a disease seen in Fore-speaking people in Papua New Guinea and acquired via ritualistic cannibalism. CJD occurs worldwide, but as systematic surveillance has only been undertaken in a minority of countries, the incidence in much of the world is currently unknown.

BSE, a TSE affecting cattle, was first reported in the United Kingdom in 1986 and over 170 000 cases have been reported since then in that country alone. Relatively small numbers of cases have also been reported in native-born cattle in Belgium, France, the Republic of Ireland, Luxembourg, the Netherlands, Portugal and Switzerland. Cases have also been reported in Canada, Denmark, the Falkland Islands, Germany, Italy and Oman, but solely in animals imported from the United Kingdom.

In March 1996 the occurrence in the United Kingdom of ten cases of an apparently new clinicopathological variant of CJD (nvCJD) was announced. The temporal and geographical association with the BSE epidemic raised the possibility of a causal link. Evidence supporting this hypothesis has subsequently accumulated: firstly, neuropathological features similar to those of nvCJD are seen in macaque monkeys inoculated intracerebrally with brain material from confirmed cases of BSE; secondly, transgenic mice (mice carrying only a human prion protein gene) have been shown to be susceptible to BSE; and thirdly, the characteristics of the biological strain of the nvCJD agent (as defined by transmission characteristics in in-bred strains of mice) and the molecular 'strain' (as defined by the prion protein (PrP) glycosylation pattern) closely resemble those seen in experimentally and naturally BSE infected animals, but differ from those identified in sporadic CJD.

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, prevent the accurate prediction of the future number of nvCJD cases.<sup>3</sup> Populations in other countries may also have been exposed to the infective agent as a result of importation of live cattle and/or cattle products or by-products from BSE-affected countries. Thus, the possibility of a significant, and perhaps geographically diverse, nvCJD epidemic occurring over the next two decades cannot be dismissed at present.

The potential future global public health implications of nvCJD were addressed by a WHO consultation in May 1996 which recommended the establishment of worldwide CJD surveillance.<sup>4</sup> Although WHO's main concern is the identification of cases of nvCJD, it is felt that this is best achieved through surveillance of all forms of CJD as, first, the clinical phenotype of nvCJD may not always be distinct from that seen in other forms of CJD<sup>5</sup> and, second, the experience gained from identifying cases of the most common CJD subtypes should enhance the ability to detect nvCJD. Because surveillance has already been established in many developed countries, WHO will be concentrating its activities mainly in the developing world. Throughout 1997 and 1998 a series of regional workshops aimed at helping individual countries establish national CJD surveillance have been, or will be, conducted by WHO. The first meeting, for western African countries, was held in Senegal in June 1997 and the second, for countries of southeast Asia, was held in Thailand in October 1997. Three further workshops have been planned for later this year; the first for eastern Mediterranean countries, the second for countries in Latin America, and the third for China. At each regional workshop the national representatives are requested to set up a meeting in their own country to discuss the institution of national CJD surveillance. A national focal point or institution is elected for every country and it is their responsibility to collate data on CJD cases and report this on at least an annual basis to WHO. It is recommended that any suspect case of nvCJD is reported to WHO as soon as possible.

Experience from the WHO workshops held to date has indicated a number of areas in which difficulties may be experienced in surveillance of human TSE in developing countries. Indeed many of the countries that have participated in these meetings reported a zero incidence of CJD. Case detection is hampered by an extremely low autopsy rate, which reflects both cultural and religious values, unwarranted safety concerns for pathology staff and a lack of available facilities. Furthermore, neurophysiology services in some countries are scanty and the level of awareness of the diagnostic features of CJD low.

WHO is currently promoting a number of ways to improve case detection, including the adoption of novel and simple diagnostic procedures (see Section 3.1); the dissemination of information, including WHO's Global TSE Surveillance Training Document; and the training of personnel in pathological and other laboratory techniques required for CJD diagnosis.

### **1.3 Diagnostics**

#### ***Electroencephalography***

The EEG was first recognised as an important aid to the diagnosis of CJD in 1954 and was included as a component of the first published diagnostic criteria in 1979.<sup>6</sup> It has traditionally been considered the most reliable non-invasive diagnostic test for CJD. Approximately 60-80% of cases are reported to develop the characteristic appearance of 0.5-2Hz generalised bi/triphasic periodic complexes, the remaining cases usually showing only non-specific slow wave abnormalities. As the possibility of a characteristic tracing increases with time, it is recommended that following a non-diagnostic recording, further tracings should be repeated in suspected cases. The typical EEG appearance has not been reported in kuru, nvCJD or 'classical' GSS (i.e. progressive cerebellar ataxia) and has only rarely been described in growth hormone-related iatrogenic disease. A single normal EEG may be seen, particularly early in the clinical course, but a repeatedly normal EEG is not considered consistent with a diagnosis of sporadic CJD. Although the characteristic EEG is virtually diagnostic of CJD in the correct clinical context, similar appearances have rarely been described in other conditions, such as Alzheimer's disease or metabolic and toxic encephalopathies (see Table 2, Annex 3).

Although the classification of an EEG as 'characteristic' in CJD is usually straightforward, this is not always the case and differences may exist in interpretation between centres. The lack of an internationally agreed definition of a characteristic EEG could lead to inconsistencies in case ascertainment in different centres and thus indicates the need for standardised criteria to be adopted as part of WHO activities for CJD surveillance.

#### ***Brain biopsy***

When used to diagnose CJD, brain biopsy typically involves the removal of a small piece of non-dominant frontal cortex under general anaesthesia. Although usually diagnostic in CJD, approximately 5% of biopsies from subsequently confirmed definite cases are non-diagnostic, reflecting the variable distribution of brain pathology in CJD. Brain biopsy is attendant with risks that can lead to serious complications, including cerebral abscess formation or haemorrhage.

## ***Neuroimaging***

The main role of neuroimaging is to exclude other conditions. Computerised tomography is usually normal in CJD, but sometimes atrophy is found, especially in patients with a protracted illness. Magnetic resonance imaging (MRI) may also show cerebral atrophy, the degree of which tends to increase with the duration of illness. Although most MRI scan reports do not note any focal abnormalities, a recent retrospective study suggests that about 80% of scans actually have increased signal in the basal ganglia on T2- and proton-density-weighted images.<sup>7</sup> These high signal changes have probably been considered to be of little diagnostic significance in clinical radiological practice, as they are usually symmetrical and often not striking. It is noteworthy that two relatively new MRI processes: FLAIR and diffusion-weighted imaging, can make these basal ganglia abnormalities more prominent. A larger prospective study of MRI in CJD is currently in progress. The number of conditions that also show similar basal ganglia abnormalities is limited and includes Wilson's disease, cerebral hypoxia and mitochondrial cytopathies. High signal abnormalities largely confined to the pulvinar on T2- and/or proton-density-weighted MRI have been reported in some cases of nvCJD, a pattern not previously reported in other forms of CJD and therefore possibly specific for the new variant.

Positron emission tomography has been reported in only a few CJD cases and the clinical usefulness of this technique remains to be established. Using [<sup>18</sup>F] 2-fluoro-2-deoxy-D-glucose, regional hypometabolism of glucose has been shown to correlate in general with neuropathological lesions in familial and sporadic cases. The hypometabolism is thought to reflect loss of neuronal function.

Single photon emission computed tomography (SPECT) scanning has also been reported in only a few cases of CJD, including nvCJD, and frequently showed abnormal perfusion when contemporaneous imaging by MRI or CT was considered unremarkable. However, the specificity of SPECT abnormalities, and hence its use as a diagnostic tool, also remains to be established.

## ***Cerebrospinal fluid***

The CSF of patients with CJD typically contains no inflammatory cells. A slightly elevated protein (0.5-1.0g/l) occurs in about one-third of cases. The presence of oligoclonal bands confined to the CSF has only very rarely been described. The pathological isoform of PrP cannot be detected in CSF (or blood or serum) by currently available methods.

Recent reports suggest that the detection using Western blotting of a 'marker of neuronal death' in the CSF, the 14-3-3 protein, is both a highly sensitive and specific test for the diagnosis of sporadic CJD.<sup>8,9</sup> Results show that this test can be positive even in the early stages of the clinical disease and, in an experimental animal TSE in a primate, in the presymptomatic phase as well. The 14-3-3 protein has been shown to be stable despite repeated freeze/thaw cycles or storage at +20°C for 12 days. It is important that samples are not contaminated by excess red cells. Unfortunately results of the 14-3-3 test to date in patients with nvCJD are less promising<sup>10</sup> with a high false-negative rate and one false-positive reported. Results from patients with familial TSE have been somewhat mixed, with a positive result in only 50% of a group of 10 genetic cases with various point mutations, but all of a

series of 16 CJD cases related to the codon 200 mutation. Most cases of iatrogenic disease test positive. A number of other conditions may also give a positive 14-3-3 CSF result, although these are usually easily distinguished from CJD (see Table 1).

**Table 1. Conditions other than CJD than can give a positive 14-3-3 result.**

- 
- Herpes simplex and other viral encephalitides
  - Recent stroke
  - Sub-arachnoid haemorrhage
  - Hypoxic brain damage
  - Metabolic encephalopathy after barbiturate intoxication
  - Glioblastoma
  - Carcinomatous meningitis from small-cell lung cancer
  - Paraneoplastic encephalopathy
  - Corticobasal degeneration
- 

As the 14-3-3 protein may be present in the CSF of patients with other conditions, the test is not useful as a general screening test for CJD, and should be reserved for use in cases where the diagnosis of CJD is considered a reasonable possibility.

The detection of neuron-specific enolase, another CSF marker of neuronal damage, is said to be a more rapid and simple diagnostic test, although it appears to be less accurate for CJD diagnosis than the detection of 14-3-3 protein. The use of CSF assays for tau protein (a constituent of neurofibrillary tangles in Alzheimer's disease) and S100b (a marker of astrocytic activation) are currently also undergoing evaluation as diagnostic markers for the diagnosis of CJD. Provisional results suggest that these tests lack specificity and are unlikely to be as clinically useful in the diagnosis of sporadic CJD as the detection of 14-3-3 protein.

The following centres have kindly agreed to perform the 14-3-3 CSF test on samples from suspect cases of CJD if required. Please contact the named person for more information before dispatching any specimens.

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Tel: (1) 301 496 4821

Fax: (1) 301 496 9946

E-mail: gibbs@codon.nih.gov

### ***Routine blood tests***

Routine haematological and biochemical investigations, including inflammatory markers, are usually normal in CJD and other TSE. In about one-third of CJD cases the liver function tests are mildly deranged, often in the form of transiently elevated transaminases. The reason for this is not known.

### ***Future diagnostic tests***

Recent studies have demonstrated that the abnormal form of human PrP may exist as one of at least four distinct molecular ‘strains’ determined, in part, by band shifts and variation in intensity of glycosylation patterns seen on Western analysis.<sup>11</sup> The strain appears to be associated with the clinical phenotype and may reflect disease aetiology, for example, the ‘type 4’ strain pattern is associated with nvCJD. Another report describes the presence of abnormal PrP in palatine tonsillar tissue obtained at autopsy from a patient with nvCJD.<sup>12</sup> Furthermore, it was possible to demonstrate the molecular ‘strain type’ from this tissue which was the same distinctive pattern (type 4) as in the brain. This raises the possibility that palatine tonsillar biopsy may be a useful test for nvCJD. Although it is not known how early in the disease course tonsillar biopsy would be diagnostic in nvCJD, it is interesting to note that a study of sheep genetically susceptible to scrapie showed that abnormal PrP could be detected in tonsillar tissue presymptomatically, early in the incubation period. The abnormal form of PrP has not been detected in the lymphoreticular system, including palatine tonsil, of the small number of cases of sporadic CJD and GSS studied so far.<sup>13</sup>

The normal protein is expressed in white blood cells and platelets and the possibility exists that some blood cells, perhaps B lymphocytes<sup>14</sup> might express the abnormal PrP isoform in affected individuals. This raises the possibility of a blood test for CJD, but would require an assay for PrP with a much higher degree of sensitivity than is currently available. However, progress is being made in this direction, with improved concentration methods coupled with the use of antibodies specific to just the abnormal PrP isoform<sup>15</sup> (unlike conventional PrP antibodies which require tissue pre-treatment with proteinase K to avoid confusion with the detection of normal PrP) bringing hope for the future availability of more accurate, more sensitive and simpler diagnostic techniques.

## **1.4 Therapeutics**

To date, no treatment has been shown to alter the underlying disease process in patients with CJD. The search for such a therapy is considerably hampered by the enigmatic TSE agent, the precise nature of which remains unknown despite intensive investigation over the past three decades. Although initially considered a ‘slow-virus’, exhaustive efforts to find

such an agent have been unfruitful. Furthermore, a conspicuous lack of inflammatory response and the remarkable resistance of the infectious pathogen to virucidal treatments, such as ultra-violet and ionizing radiation, argue against a viral aetiology. Increasing evidence now indicates that a host-encoded protein, prion protein, plays a crucial role in disease aetiology and may constitute a major component of the transmissible agent. This hypothetical infectious pathogen, termed the 'prion', is thought to consist largely, if not wholly, of a conformational isoform of normal PrP, a cellular membrane protein encoded by a gene on the short arm of chromosome 20 in humans. Although the prion hypothesis elegantly explains many of the observed phenomena of the TSE agent and diseases, it remains unproven, and the presence of multiple agent strains, as observed in sheep scrapie, is arguably more compatible with a viral-like pathogen. A further theory, the 'virino hypothesis', combines elements of the prion and viral hypotheses and postulates that the infectious particle consists of an informational molecule containing nucleic acid that is closely associated with a host-encoded protein.

Despite the elusive nature of the transmissible agent, a number of therapeutic strategies for human and animal TSE have been tested.<sup>16</sup> Initial efforts concentrated on the use of anti-viral drugs, such as amantidine and interferon, and were unsuccessful. Amphotericin B (an antifungal drug), and iododoxorubicin (an anti-cancer agent) have been found to delay death in hamsters or mice experimentally infected with scrapie.<sup>17,18</sup> However, these drugs are potentially toxic and needed to be injected around the time of infection, or shortly afterward, to be most effective. Amphotericin B has been tried in human CJD without effect. Prophylactic administration of Congo red (a sulphonated amyloid-binding dye commonly used as a histological stain for amyloids) before or shortly after experimental scrapie infection, can significantly delay the onset of clinical disease in hamsters.<sup>19</sup> This compound has also been shown to inhibit the replication of scrapie infectivity in cell culture,<sup>20</sup> but has not been used as a therapy in humans.

In clinical practice, patients with CJD are frequently administered antibiotics, steroids, acyclovir or thiamine in the hope that they may have an occult treatable condition, such as a cerebral vasculitis, bacterial/viral infection or Wernicke's encephalopathy. None of these therapies have a noticeable effect in CJD.

Although treatments have been totally disappointing to date, a number of theoretical approaches may offer hope in the future. It has been shown that transgenic 'null' mice in which the *PrP* gene is absent (and which therefore do not produce PrP) appear clinically well and are resistant to TSE infection. This has led to the suggestion that ablative gene therapy, or the use of anti-sense oligonucleotides to 'turn off' the production of PrP, may be a useful treatment strategy. Although this is an interesting idea it is still unknown whether the neurophysiological damage associated with TSE infection results from the accumulation of abnormal PrP or the loss of the normal isoform. It has been suggested that if the latter is true *abrupt* cessation of PrP production may have a deleterious effect (theoretically not seen in null mice because of adaptation to hereditary PrP loss).

An increased understanding of the three-dimensional structure of PrP has also led to new treatment ideas. Evidence indicates that normal PrP contains four central  $\alpha$ -helices whereas the pathological PrP isoform has a greater  $\beta$ -sheeted structure. Therefore, molecules that bind and stabilise the central  $\alpha$ -helices may in turn prevent the conversion of normal PrP to the putative disease-causing moiety. Such 'beta-sheet blockers' have shown promise *in-vitro* and are currently undergoing investigation in laboratory animals.

A number of other therapeutic strategies have been suggested, including the use of drugs to block agent replication sites; polyanions, such as Dextran 500 and pentosan polysulfate, which are known to prolong the lifespan of mice infected with scrapie,<sup>21,22</sup> and compounds that inhibit agent replication by interfering with PrP glycosylation, a proposed major determinant of agent strain.

Due to the current lack of effective therapy, good nursing care to prevent the complications of immobility, such as pressure sores, is likely to be the most important treatment for a patient with CJD. Therapies aimed at palliation of any distressing symptoms, such as clonazepam or sodium valproate for myoclonus, are frequently successfully administered. Sedatives may be required for agitation, but such symptoms often abate naturally as the illness progresses.

## 2. LIST OF SCIENTIFIC PRESENTATIONS TO THE CONSULTATION

### 2.1 Surveillance

Dr Martin Zeidler	WHO's activities for global CJD surveillance
Prof Thiravat Hemachudha	CJD surveillance in Thailand
Prof Herbert Budka	CJD surveillance in Austria and pathological criteria
Dr Cornelia van Duijn	CJD surveillance in the European Union
Dr Gillian Stewart	CJD surveillance in the UK: an update on nvCJD
Dr Scott Ratzan	CJD - the communication of risk to the public
Dr Carlos Dora	Results of the WHO meeting on CJD surveillance standards. London, 22-23 January 1998

### 2.2 Diagnostics

Ms Alison Green	The 14-3-3 and other CSF assays: results from the UK
Dr Clarence Gibbs	The 14-3-3 and other CSF assays: results from the USA
Dr Inga Zerr	The 14-3-3 and other CSF assays: results from Germany
Dr Lev Goldfarb	Genetic testing in human TSE
Dr Richard Knight	The evaluation of a diagnostic EEG in CJD
Dr Bernhard Steinhoff	The evaluation of a diagnostic EEG in CJD
Dr Michael Finkenstaedt	Magnetic resonance imaging in sporadic CJD
Dr Robin Sellar	Magnetic resonance imaging in nvCJD
Dr James Ironside	The use of non-neural tissue biopsy in CJD diagnosis
Dr Toshiro Kawashima	Analysis of lymphoreticular tissues in CJD and GSS
Dr Bruno Oesch	The potential diagnostic use of the 15B3 antibody
Dr Henry Baron	Rapid and sensitive prion detection methods

## 2.3 Therapeutics

Prof John Collinge	The use of tonsillar biopsy in the diagnosis of CJD and potential therapeutic approaches to human prion disease
Dr Paul Brown	Early experimental attempts to treat TSE
Prof Adriano Aguzzi	Determinants of prion neuroinvasion
Dr Byron Caughey	Formation of protease-resistant prion protein
Prof Heino Diringer	Chemoprophylaxis of scrapie in mice
Dr Dominique Dormont	Polyene antibiotics in transmissible subacute spongiform encephalopathies
Dr Claudio Soto	Inhibition and reversion of prion protein specific conformational changes by synthetic peptides designed as $\beta$ -sheet breakers
Prof Fabrizio Tagliavini	The anthracycline iododoxorubicin in experimental scrapie
Mr Ray Bradley	BSE/Scrapie/CJD: What possibility is there for a vaccine?

## 3. CONCLUSIONS AND RECOMMENDATIONS

### 3.1 CJD clinical diagnosis: criteria for probable sporadic CJD

The clinical diagnosis of CJD is currently based upon the combination of progressive dementia, myoclonus and multifocal neurological dysfunction, associated with a characteristic periodic EEG.<sup>4</sup> However, nvCJD, most growth hormone-related iatrogenic cases, and up to 40% of sporadic cases are not noted to have the characteristic EEG appearance. This hampers clinical diagnosis, and hence surveillance, and illustrates the need for additional diagnostic tests. Advances in CJD diagnostics have occurred in the past two years, in particular the assay for 14-3-3 protein in CSF, which appears to have a high sensitivity and specificity for sporadic CJD diagnosis. We propose the following criteria for probable sporadic CJD.

Progressive dementia; and

At least two out of the following four clinical features:

- Myoclonus
  - Visual or cerebellar disturbance
  - Pyramidal/extrapyramidal dysfunction
  - Akinetic mutism;
- and
- A typical EEG during an illness of any duration and/or  
A positive 14-3-3 CSF assay and a clinical duration to death <2 years;
  - Routine investigations should not suggest an alternative diagnosis.

Results from a recent study suggest that the detection of high signal from the basal ganglia on T2- and proton-density-weighted MRI supports the diagnosis of sporadic CJD.<sup>7</sup> These abnormalities can be particularly prominent if a FLAIR sequence or diffusion-weighted images are obtained. The Consultation recommends that further research be conducted into the use of MRI in human TSE.

### 3.2 EEG Interpretation

No widely agreed and validated definition of a diagnostic EEG tracing is available, leading to potential inconsistencies in case ascertainment between centres. To enhance CJD surveillance a workable definition of a diagnostic EEG is required. We propose that the following criteria devised by Steinhoff and Knight be adopted now and results be further evaluated (see Annex 3 for important related information).

- Strictly periodic activity
  - variability of intercomplex intervals is <500 ms
  - Periodic activity is continuous for at least one 10 second period
- Bi- or tri- phasic morphology of periodic complexes
- Duration of majority of complexes ranges from 100 to 600 ms
- Periodic complexes may be generalised or lateralised, but not regional or asynchronous

### 3.3 New variant CJD: suspect case definition

New variant CJD cannot be diagnosed with certainty on clinical criteria alone at present. However, on the basis of the 23 neuropathologically confirmed cases, the diagnosis of nvCJD should be considered as a possibility in a patient with a progressive neuropsychiatric disorder with at least 5 out of the following 6 clinical features in Box A:

#### BOX A

- |   |
|---|
| <ul style="list-style-type: none"> <li>• Early psychiatric symptoms</li> <li>• Early persistent paraesthesia/dysaesthesia</li> <li>• Ataxia</li> <li>• Chorea/dystonia or myoclonus</li> <li>• Dementia</li> <li>• Akinetic mutism</li> </ul> |
|---|

The suspicion of nvCJD is strengthened by the following criteria in Box B,

## BOX B

- The absence of a history of potential iatrogenic exposure
- Clinical duration >6 months
- Age at onset <50 years
- The absence of a *PrP* gene mutation
- The EEG does not show the typical periodic appearance
- Routine investigations that do not suggest an alternative diagnosis
- An MRI showing abnormal bilateral high signal from the pulvinar on axial T2- and/or proton-density-weighted images.

**A patient with a progressive neuropsychiatric disorder and 5 out of the 6 clinical features in Box A and all of the criteria in Box B should be considered as a suspect case of nvCJD for surveillance purposes.**

**(Note: The pathological characteristics of nvCJD are given in Annex 5)**

### 3.4 Pathological diagnosis

The Group discourages the use of cerebral biopsy in living patients except to make an alternative diagnosis of a treatable disease. The Consultation concurs with the previous WHO recommendation that instruments used for neurosurgery on patients with CJD should be destroyed.<sup>23</sup> If re-use is unavoidable, instruments must be immersed in 1N NaOH or fresh undiluted hypochlorite for at least one hour, cleaned, and then autoclaved at 134°C for one hour.

A definite diagnosis of CJD, including nvCJD, is established only by neuropathological examination. The group recommends that autopsy be strongly encouraged in any suspect case of CJD. Where autopsy is not possible or permitted, *post-mortem* biopsy of the brain should be sought.

Experience to date of the use of palatine tonsillar biopsy in CJD diagnosis is limited. Because the abnormal isoform of PrP has been detected in tonsillar tissue from patients with nvCJD but not patients with sporadic CJD, analysis of tonsillar tissue may provide potentially diagnostic information in nvCJD, but requires further *post-mortem* evaluation.

### 3.5 Genetic analysis

Screening cases of CJD for the mutations associated with the hereditary forms of disease raises ethical and logistical concerns. Written consent for genetic testing is considered mandatory in many countries but may be culturally unacceptable in others. The Consultation recommends that genetic counselling of patients and/or their families should be performed prior to any *PrP* gene analysis and that ideally written consent, but if not documented oral consent, should be obtained. The genetic counsellor should be provided with information on the genetics of human TSE to be used when seeking consent (for example see Annex 4). Because of the low *PrP* gene mutation detection rate in 'sporadic' CJD it is recommended that

at present only those patients with a family history of a TSE be considered for *PrP* gene analysis as part of WHO's surveillance activities. Analysis could be performed via one of the proposed WHO collaborating centres (see Annex 7).

All cases suspected of having nvCJD should undergo *PrP* gene analysis (if consent is obtained) to exclude a mutation and, for research purposes, to identify codon 129 status.

### **3.6 Geographical attribution of cases and proposed network of WHO collaborating centres**

When a diagnosis of CJD is made the initial geographical attribution should be the country of residence at the onset of clinical disease. Final attribution should be decided on a case by case basis.

As part of WHO activities to promote the global surveillance of human TSE the Consultation recommends that collaborating centres be established to aid in diagnosis and training (see Annex 7).

### **3.7 Communication of information**

The communication of any important new information to the public benefits from planning. This is particularly the case when the information is complex and has the potential to cause great concern. The Consultation recommends that each national authority plans a strategy for disseminating information that may result from CJD surveillance. Maxims for effective communication on health and risk issues are reproduced in Annex 8. A copy of this report and the Global TSE Surveillance Training Document should be sent to all the WHO Regional Offices.

### **3.8 Therapy**

The Group concluded that at present there is no available therapy that is known to alter the underlying disease process for any human TSE. Animal and *in vitro* studies have demonstrated that a number of therapeutic compounds have the potential for interfering with the underlying disease process. Although some compounds are known to delay the onset of disease (in some cases beyond the animal's natural lifespan), no compound is known that can 'cure' a clinically affected animal.

### **3.9 Future evolution of nvCJD**

The Consultation noted that the possibility of a significant epidemic of nvCJD occurring within the next 10-15 years cannot be dismissed and therefore emphasised that the early identification of an effective therapy is of paramount importance. Such a treatment would also offer hope to those individuals who are at risk of developing familial or iatrogenic disease.

### **3.10 Further research**

The Consultation stressed the pressing need for further research into the molecular properties of the TSE agent that could lead to potential disease modifying compounds. In parallel, efforts should be made to identify pre-symptomatic diagnostic tests, to enable any future therapy to be used as early as possible in the disease course.

## ANNEX 2

**Revised WHO Definition of CJD Subtypes**

(Incorporating the new definition of probable sporadic CJD as per Section 3.1)

***Sporadic CJD.***Definite:

Diagnosed by standard neuropathological techniques; and/or  
 Immunocytochemically and/or Western blot confirmed protease resistant PrP and/or  
 Presence of scrapie-associated fibrils.

Probable:

Progressive dementia; and  
 At least two out of the following four clinical features:

- Myoclonus
  - Visual or cerebellar disturbance
  - Pyramidal/extrapyramidal dysfunction
  - Akinetic mutism;
- and
- A typical EEG during an illness of any duration and/or  
 A positive 14-3-3 CSF assay and a clinical duration to death <2 years;
  - Routine investigations should not suggest an alternative diagnosis.

Possible:

Progressive dementia; and  
 At least two out of the following four clinical features:

- Myoclonus
  - Visual or cerebellar disturbance
  - Pyramidal/extrapyramidal dysfunction
  - Akinetic mutism;
- and
- No EEG or atypical EEG; and
  - Duration <2 years.

***Iatrogenic CJD***

Progressive cerebellar syndrome in a recipient of human cadaveric-derived pituitary hormone;  
or  
 Sporadic CJD with a recognised exposure risk, e.g. antecedent neurosurgery with dura mater graft.

***Familial CJD.***

Definite or probable CJD plus definite or probable CJD in a first degree relative; and/or  
 Neuropsychiatric disorder plus disease-specific *PrP* gene mutation.

## Electroencephalogram Interpretation

### *Preliminary notes*

- The finding of a characteristic periodic EEG pattern is very helpful in the diagnosis of sporadic CJD.
- Some cases of sporadic CJD never show this pattern. A 'negative' result cannot exclude the diagnosis.
- A periodic EEG like that seen in CJD may rarely be found in a number of other conditions and these must be considered in the clinical context. A list of these conditions is given below in Table 2.
- The EEG changes in CJD undergo evolution. A periodic pattern may not be seen in the early phases of disease. The EEG may progress from showing non-specific abnormalities to the characteristic appearance within days. Therefore, frequent serial EEG recordings should be undertaken whenever possible.
- If a typical periodic EEG is obtained, then it is not absolutely necessary to repeat it, although this should be considered if there is any clinical doubt about other possible causes of the EEG pattern (such as metabolic factors).
- A repeatedly normal EEG is not consistent with a diagnosis of sporadic CJD.

### *Technical notes*

- Bipolar montages including the vertex should be used
- Referential montages including vertex and CZ reference electrodes should be used
- The ECG should be coregistered
- External alerting stimuli should be used
- The whole record should be viewed whenever possible and a five minute continuous sequence as a minimum

**Table 2. Conditions which may cause a CJD-like EEG**

• Alzheimer's disease	• Hyperammonaemia
• Lewy body disease	• Hyperparathyroidism
• Binswanger's disease	• Hypo and hypernatraemia
• AIDS dementia	• Hypoglycaemia
• Multiple cerebral abscesses	• Hepatic encephalopathy
• MELAS syndrome	• Baclofen, mianserin, metrizamide and lithium toxicity
• Post-anoxic encephalopathy	

### *Footnote*

The EEG criteria (Section 3.2) are based on considerable experience with the EEG in CJD but have not been formally evaluated prospectively in large numbers of suspect CJD cases. Such evaluation is being undertaken and the results of this may necessitate some revision.

## Genetic Information

### *Information to be given to relatives of CJD patients when consent is being obtained for blood to be taken for genetic studies*

The cause of CJD in the great majority of patients is unknown.

A small proportion of cases are hereditary in nature due to a faulty gene.

In nearly all the hereditary cases, the family are already aware of other affected family members. In these families about half the family members can be affected by CJD and the disease may occur from generation to generation. Some family members may have the faulty gene but never develop CJD.

When patients with CJD have a family history of dementia, this is often coincidental (e.g. Alzheimer's disease) and blood relatives do not then have an increased risk of developing CJD.

The chances of finding a faulty gene in a case of CJD without any other affected family members is very small, probably less than 1 in 50.

We wish to take blood from cases of CJD in order to look for abnormalities in the gene and we also store blood for future research.

In this way we hope to advance knowledge in CJD which may, in the future, lead to a better understanding of the disease.

If you do not want to know the result of this test, we will not inform you, your family doctor or the hospital doctor of the result.

If you do want to know the result of the test, this can be done through the local genetic counselling clinic.

## Summary

Only a small proportion of cases are hereditary.

The result of the genetic test will only be made available on request.

The blood sample will help research.

### **Pathological Characteristics of nvCJD**

The neuropathology of nvCJD shares the key characteristics of all human TSE - spongiform change, neuronal loss, reactive astrocytosis and the accumulation of the disease-associated isoform of PrP in the brain. However, the nature and distribution of the neuropathology in nvCJD is relatively constant from case to case, and differs in key respects from other forms of human spongiform encephalopathy. These key features can be summarised as follows:

1. Multiple fibrillary PrP plaques in the cerebral and cerebellar cortex, often surrounded by a halo of spongiform change (the 'florid' plaque).
2. Multiple small PrP plaques which are only detectable by immunocytochemistry, occurring in clusters within the cerebral and cerebellar cortex, not related to spongiform change.
3. Amorphous PrP deposits around neurones and blood vessels in the cerebral and cerebellar cortex, best visualised on immunocytochemistry.

The other commoner features of sporadic CJD - perivacuolar accumulation of PrP, widespread confluent spongiform change and status spongiosus have not been identified in the 23 cases of nvCJD in whom brain biopsy or autopsy has been performed. Immunocytochemistry for PrP is an invaluable aid to diagnosis, although the large fibrillary plaques are easily visualised on haematoxylin and eosin sections; both the large fibrillary plaques and the small cluster plaques can also be visualised on period acid/Schiff preparations. Gallyas silver impregnation will stain the large and small plaques, and also demonstrates some of the amorphous PrP deposits although these are best visualised on immunocytochemistry. New variant CJD can be diagnosed on brain biopsy, but limitations exist with respect to sampling error; Western blotting studies may help establish a diagnosis under such circumstances.

The full spectrum of the characteristic neuropathology of nvCJD also includes:

1. Spongiform change most marked in the basal ganglia, with dense perineuronal and periaxonal PrP deposition.
2. Severe thalamic gliosis and neuronal loss, particularly involving the dorsomedial and posterior nuclei (including the pulvinar).
3. Massive accumulation of PrP, often in the focal distribution, in the cerebellar cortex including the molecular layer and granular layer with occasional plaques in the white matter.
4. Punctate neuronal staining for PrP in the pontine nuclei.

## ANNEX 6

**Neuropathological Criteria for CJD and other Human TSE**

***Creutzfeldt-Jakob disease*** *Sporadic, iatrogenic* (recognised risk) or *familial* (same disease in 1st degree relative or disease-associated *PrP* gene mutation):

- Spongiform encephalopathy in cerebral and/or cerebellar cortex and/or subcortical grey matter; and/or
- Encephalopathy with prion protein (PrP) immunoreactivity (plaque and/or diffuse synaptic and/or patchy/perivacuolar types).

***New variant CJD***

- Spongiform encephalopathy with abundant PrP deposition, in particular multiple fibrillary PrP plaques surrounded by a halo of spongiform vacuoles ('florid' plaques, 'daisy-like' plaques) and other PrP plaques, and amorphous pericellular and perivascular PrP deposits especially prominent in the cerebellar molecular layer.

***Gerstmann-Sträussler-Scheinker disease (GSS)*** (in family with dominantly inherited progressive ataxia and/or dementia and one of a variety of *PrP* gene mutations):

- Encephalo(myelo)pathy with multicentric PrP plaques.

***Familial fatal insomnia (FFI)*** (in member of a family with a *PrP* gene mutation at codon 178 in frame with methionine at codon 129):

- Thalamic degeneration, variable spongiform change in cerebrum.

***Kuru***

- Spongiform encephalopathy in the Fore population of Papua New Guinea.

The above criteria are modified from those published by Budka et al.<sup>24</sup>

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## ANNEX 8

**Maxims for Effective Communication on Health and Risk Issues**

- I. Develop a theme/goal with common interest(s) (e.g., ‘we are interested in the health and safety of our community’).  
Identify clear and explicit objectives (short-term and long-term).  
Establish a common agenda while recognising political/economic interests and hidden agendas.  
Base information on needs assessment and ethical community values.
- II. Identify all parties that have an interest in the issue (non-governmental organizations, trade associations, media, government, public, etc.).  
Build coalitions/partnerships with those integral for successful delivery of information.  
Work with other credible sources.  
Recruit competent spokespeople with your participants.  
Establish roles for the media, advocacy groups, organizations, the public, etc.
- III. Identify the intended audiences, their concerns, and the potential mechanisms to reach them.  
Listen and understand your audience, including cultural variables.  
Measure public opinion - survey, polls, baseline, etc.  
Conduct formative research - focus groups, observational studies, survey/baseline.  
Identify communication patterns of the audience (e.g. how do they get information)
- IV. Develop a strategic approach to communicate with public(s).  
Open communication channels immediately in crisis.  
Choose a competent spokesperson, recognise emotions, speak clearly and understandably.  
Choose a message, pre-test and adapt it, and establish tracking mechanism(s).  
The actual audience may care more about fairness, competence, and empathy than data and statistics.  
Build trust with honest and open disclosure - never lie.  
Use objective criteria, standards, and benchmarks for your planning and implementation.
- V. Communicate a consistent and credible message.  
Create inter- and intra-organizational mechanisms for delivery of messages.  
Consult with appropriate parties before making major decisions or announcements.  
Use risk comparisons to help put risks in perspective; avoid comparisons that trivialise.  
Focus on credibility with a high-level, consistent messenger.
- VI. Establish mechanisms for direct public/audience communication.  
Utilise existing media with openness and accessibility.  
Establish trust and interactivity - news media, radio call-in, free calls, bulletin boards, etc.  
Tell people what your limitations are; you cannot do everything.  
Discuss actions underway or to be taken.  
If in doubt, share more rather than less information.

VII. Maximise your communication effectiveness.

Acknowledge and respond to emotions.

Avoid instant, abstract, or harsh language about deaths, injuries, and illnesses.

Speak with compassion, using simple, non-technical language.

Use visual, vivid, and vocal images that connect at a personal level.

Use examples and anecdotes that are culturally sensitive and make data come alive.

Create a relationship with the public(s) by offering realistic, compliance-prone actions.

VIII. Evaluate your interventions/efforts on intended audiences.

Tracking - Did your audience make the desired decision?

Assess and evaluate with outcome and impact measures.

Did you build relationships with key participants?

Are you more prepared for the next intervention...the next steps?

## ANNEX 9

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