CSSE 90/02

DIAGNOSTIC CRITERIA FOR CREUTZFELDT-JAKOB DISEASE

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The diagnostic criteria for CJD have evolved since the original descriptions and were defined formally by Masters et al[1] in 1979. With minor variations these criteria have been used in all recent epidemiological surveys, including the systematic study of CJD in England and Wales by Professor WB Matthews which covered the years 1970-1985. The issue of diagnostic criteria is currently being reassessed in the context of the DH funded study of CJD, which was initiated in May 1990 following the recognition of BSE and the possibility of an associated risk to public health.

The major aim of this study is to identify any change in the epidemiological characteristics of CJD and to assess whether any such change can be linked to the occurrence of BSE. The basic methodology involves comparing contemporary epidemiological information with that obtained in the previous study, and this has an important bearing on the issue of diagnostic criteria as it is essential that the information from the two studies is comparable.

There are three main questions in relation to diagnostic criteria for the current study:

1. What should be the clinical criteria for the referral of incident cases?

2. What criteria should be used for the final classification of cases?

3. When and in what way should either of these criteria be modified to take account of scientific developments, which indicate either an extension of the clinico-pathological spectrum of CJD or the possibility of more accurate diagnosis?

1. CLINICAL CRITERIA FOR THE REFERRAL OF INCIDENT CASES

In the original study of CJD in England and Wales all neurologists were circularised and asked to notify "suspected" cases of CJD. The circular did not include specific diagnostic criteria for the following reasons:

a) The clinical presentation of typical cases is relatively stereotyped and readily identifiable by neurologists.

b) A significant proportion of cases are atypical and would not fulfil strict clinical diagnostic criteria. The implementation of restrictive criteria for referral would result in these cases being missed; for example those cases in which there is not a characteristic EEG.

> "The many disguises that CJD can wear (atypical CJD), makes its consideration mandatory in the differential diagnosis of any mysterious neurological disorder, especially when higher cortical deficits are involved."(2)

c) Epidemiological and clinical information for the study were obtained by visiting referral centres. The application of rigid criteria for referral would have led in some patients to a delay in notification while clinicians waited for the illness to evolve to meet these criteria. The resultant delay would inevitably result in referral at a stage when patients were critically ill and some patients might die before being seen.

d) The use of deliberately non-specific referral criteria resulted in the referral of a spectrum of cases of subacute dementia and this allowed the identification of rare cases of clinically atypical CJD and an evaluation of the clinical components of the classification criteria.

The use of non-specific referral criteria inevitably resulted in the notification of cases which were later classified as not CJD (40% of referrals in England and Wales, 26% in France). This is unavoidable if a high degree of case ascertainment is to be achieved and may be important in minimising the risk of over-selection of cases and the application of self-fulfilling diagnostic criteria.

The current study of CJD in the UK has used the same criterion for the notification of patients as the original study. All neurologists have been asked to notify "suspected cases of CJD."

CRITERIA FOR THE CLASSIFICATION OF CASES OF CJD

Definitive criteria for the diagnostic classification of CJD were established by Masters at al in 1979[1]:

1. Transmissible virus dementia

   Cases experimentally transmitted to nonhuman primates and/or other animals, producing an experimental spongiform encephalopathy.

2. Definite or probable CJD

   A. Definite CJD

   Neuropathologically confirmed spongiform encephalopathy in a case of progressive dementia with at least one of the following features:
   1. Myoclonus
   2. Pyramidal signs
   3. Characteristic EEG
   4. Cerebellar signs
   5. Extrapyramidal signs

   B. Probable CJD

   Neuropathologically unconfirmed cases with the same clinical features as 2A.

3. Possible CJD

   History, without medical records allowing confirmation, of progressive dementia with:

   A. Myoclonus and a course of less than three years; or

   B. A member of the family having transmissible, definite

or probable CJD; or

C. At least two of the clinical features listed for 2A together with the appearance of prominent and early signs of lower motor neurone involvement (the amyotrophic form of CJD)

These criteria have been adapted in the light of subsequent developments in the field and the criteria for the classification of cases in both the original and current studies are as follows:

1. Transmissible virus dementia

Cases experimentally transmitted to nonhuman primates and/or other animals, producing an experimental spongiform encephalopathy.

NOTE: In the UK there are limited facilities for transmission to marmosets. There are no facilities for transmission of CJD to rodents. Important issues, including the transmission characteristics of CJD, strain-typing, and attempted transmission in cases of specific interest, cannot currently be examined.

2. Definite or probable CJD

A. Definite CJD

Neuropathologically confirmed spongiform encephalopathy in a case of progressive dementia with at least one of the following features:

1. Myoclonus
2. Cortical blindness
3. Pyramidal, cerebellar or extrapyramidal signs
4. Akinetic mutism
5. Characteristic EEG

Rapidly progressive dementia / HSD.

NOTE: Analysis of the clinical features in systematic surveys of CJD suggests that cortical blindness and akinetic mutism are important and relatively specific diagnostic criteria.

B. Probable CJD

Neuropathologically unconfirmed cases with at least two of the clinical features mentioned above and the characteristic EEG.

NOTE: The presence of the characteristic EEG has proven to be an accurate, but not absolute, indicator of the presence of typical pathological changes. Cases which are otherwise typical but do not exhibit the characteristic EEG are classified as "possible" because a significant proportion of these cases are likely to be not-CJD.

3. Possible CJD

Progressive dementia plus three of the above clinical features but either an uncharacteristic EEG or no EEG recording.

NOTE: Possible cases have been excluded from analysis in previous surveys and are excluded from analysis in the current study.

These diagnostic criteria were used in Professor Matthews study and were discussed at the MRC on 21.10.85: "The diagnostic criteria which were used were satisfactory and easy to apply but there were difficulties in too rigid an application. For example, in otherwise typical cases of comparatively long duration, spongiform degeneration, the major factor used in identifying CJD might not be detected. The diagnostic criteria could be applied to advanced cases or in retrospect but were of little use in the early diagnosis of CJD."

Problems in classification

Max Imm.

1. Familial cases.

In the previous study in England and Wales all members of pedigrees with CJD were classified according to the above criteria rather than those of Masters at al. This may have led to an underestimate of familial cases (for example the clinical details in old case notes were often sketchy), but it was felt appropriate to apply diagnostic criteria rigidly because of the possibility of attributing the label of CJD to any dementing illness.

Other studies have used the criteria of Masters et al[1] which define a case of familial CJD as: an individual with a

history of progressive dementia in a family with a known definite or probable case. The prevalence of Alzheimer's disease(DAT) suggests that the concurrence of CJD and DAT may occur by chance and that the use of these criteria for familial CJD may result in an overestimate of familial cases.

2. Amyotrophic CJD

Attempted transmission studies using inocula from this variant of CJD have, almost without exception, been unsuccesful. The consensus is that amyotrophic CJD should no longer be regarded as a transmissible dementia and is therefore excluded from the current study.

3. Iatrogenic cases

The clinical features in human growth hormone recipients who develop CJD are atypical. The clinical diagnostic criteria in this group of patients, and two recent recipients of human gonadotrophin who developed CJD, are not applicable. In these patients the diagnosis of probable CJD rests on the development of a progressive cerebellar syndrome in the context of prior treatment with a pituitary derived hormone. An alternative explanation for the clinical presentation must be excluded eg recurrence of the original condition. Criteria for classification as a "definite" case stand.

MODIFICATION OF THE DIAGNOSTIC CRITERIA

Recent developments in molecular biology and immunocytochemistry have the potential to redefine the clinico-pathological spectrum of CJD and may have implications for epidemiological surveillance. Other developments are to be expected and a strategy for incorporating changes in the diagnostic criteria is essential.

1. Molecular biology

Mutations of the PrP gene have been found in GSS, familial CJD and in a small number of sporadic cases of CJD. The number of identified mutations is increasing, but the description of a mutation in a healthy individual aged 75 and the lack of information on the relationship between the presence of a mutation and transmissibility suggests that, at present, PrP gene anomalies should not be regarded as diagnostic of a transmissible dementia.

However the identification of mutations of the PrP gene in atypical familial dementia may have important epidemiological implications and one course of action would be to establish a register of individuals in the UK who are found to have a mutation. This would enable the prevalence of these mutations to be assessed, thereby indicating whether these mutations are found only in highly selected pedigrees or whether there are more general implications for the surveillance of CJD.

2. Immunocytochemistry

The application of immunocytochemical techniques for the identification of PrP has the potential to allow the prompt diagnosis of CJD and related disorders. Recent publications have advocated caution in interpreting PrP staining, but it is likely that the clinico-pathological spectrum of CJD will be extended. Some cases of rare forms of dementia such as primary atypical dementia, Type 2 Pick's disease and Neumann-Cohn syndrome are candidates for staining with PrP antisera, but even if positive the rarity of these disorders would not seriously compromise the study of the epidemiology of CJD. On the other hand the possibility that some cases of dementia with minimal neuropatholgical abnormality might be due to "prion" disease[3] would have serious implications for surveillance. The prevalence of this type of dementia is a matter of controversy and previous investigation does not suggest transmissibility, but the issue of atypical dementia requires further investigation.

The issue of the relationship between mutations of the PrP gene and atypical familial dementia is being addressed in at least one systematic survey, while staining for PrP is to be carried out on a cohort of unselected demented patients in another study. At present there is insufficient evidence to justify an alteration in the criteria for referral or classification, but this will have to be reviewed in the light of research developments.

Any alteration of diagnostic criteria will have to be carefully judged in relation to practicality and the comparability of historical control data. As Sir Donald Acheson stated to the Agriculture select committee: "...bearing in mind that the major interest is to determine whether the incidence of CJD in the next 20 years will be the same as in the last 20 years, it is undesirable to alter the system of ascertainment during the period of the study[4]." This argument also applies to extending the categories of specialists who are asked to notify suspect cases, but it would be unrealistic to ignore scientific developments, particularly as the project may continue for many years.

NEUROPATHOLOGICAL VERIFICATION OF THE DIAGNOSIS

A basic assumption in assessing the theoretical possibility of BSE being transmitted to the human population is that the resulting disease would resemble CJD[5]. Although this assumption is reasonable, the atypical clinical features in human growth hormone recipients indicates that the clinical presentation of CJD may vary, perhaps in relation to the route of exposure to the agent. CJD in human growth hormone recipients was identified by the discovery of typical neuropathological changes in clinically atypical patients and it is essential to continue to obtain details of all neuropathologically verified cases of CJD so that any change in clinical presentation can be identified and, if necessary, the entry criteria adapted.

Neuropathological verification of the diagnosis is also crucial in clinically "possible" and "probable" cases and will be essential in individuals who are at high risk of exposure to the BSE agent, eg through occupational exposure. A high post-mortem rate was achieved in the original study and it is important that a similar rate is achieved in the current project.

CONCLUSIONS

1. Criteria for the referral of patients should remain non-specific. Neurologists and neurophysiologists should continue to be asked to notify "suspected cases of CJD".
2. Criteria for the classification of cases, adapted from Masters et al[1], have been validated and should continue to be used in their present form.
3. Criteria for referral and classification may have to be adapted in the light of scientific developments. There is no immediate necessity to alter these criteria, but it is essential to establish close liaison with those working in relevant areas of research.
4. A register of individuals with mutations of the PrP gene should be established.
5. Neuropathological verification is an essential component of surveillance and every effort should be made to achieve a high post-mortem rate.
6. Any alteration of referral or diagnostic criteria will have to be carefully judged in relation to practicality and the use of historical control data.

REFERENCES

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