ELSEVIER

FEMS Immunology and Medical Microbiology 21 (1998) 97–100

FEMS IMMUNOLOGY AND MEDICAL MICROBIOLOGY

MiniReview

The new variant form of Creutzfeldt-Jakob disease

Richard Knight *, Gillian Stewart

National CJD Surveillance Unit, Western General Hospital, Crewe Rd., Edinburgh EH4 2XU, UK

Received 5 January 1998; revised 24 February 1998; accepted 26 February 1998

Abstract

A new phenotype of Creutzfeldt-Jakob disease termed new variant Creutzfeldt-Jakob disease (nvCJD) was first described in March 1996. This differs from other forms of CJD in terms of its epidemiology, clinical features and neuropathology. To date 24 cases of this new form of CJD have been described, 23 within the UK. This article describes nvCJD discussing clinical and epidemiological features and discusses possible links with the bovine spongiform encephalopathy epidemic in cattle in the UK.

Keywords: Creutzfeldt-Jakob disease; New variant Creutzfeldt-Jakob disease

1. Introduction

Creutzfeldt-Jakob disease (CJD) was first described in 1921 by Jakob and considered to be some form of neurodegenerative disease. The demonstration of laboratory transmissibility in 1968 led to the consideration that CJD was a naturally transmissible disease (i.e. some sort of natural infection). As a result, a great deal of clinical and epidemiological work was undertaken especially giving consideration to a possible link with the related animal disease of scrapie. In the UK, a surveillance project, based in Oxford, retrospectively identified cases between 1970 and 1979 and then looked at CJD, in England and Wales, over the 5-year period 1980–1984 [1–3]. In 1990, following concerns about the possible danger of transmission of bovine spongiform encephalitis (BSE) to humans, surveillance was restarted, this time looking at the whole of the UK and based in Edinburgh. Since 1993, surveillance has been undertaken in a number of other European countries [4]. Concern about the possible risks of BSE were increased by the identification of a new clinico-pathological variant of CJD (nvCJD) in 1996 [5]. This paper reviews the recognised classical types of CJD and describes the characteristic features of the new variant form. The relationship of nvCJD and BSE will also be discussed.

2. Types of CJD

CJD is a rare illness with an incidence of around 1 per million of the population per year. It is now considered to occur in four main forms: classical sporadic, genetic, iatrogenic and new variant.

Classical sporadic CJD has a very striking age-

* Corresponding author.

Presented at: Berrelius Symposium 39: Prion diseases – transmissible spongiform encephalopathy, Stockholm, Sweden, November 1997.

0928-8244/98/$19.00
PII: S0928-8244(98)00039-X

specific incidence. Young cases are extremely uncommon, the mean age of onset being 65. It is a rapidly progressive illness and its clinical progress is not typical of classically neurodegenerative disease with a median duration of approximately 4 months. A rapidly progressive dementia is the principal feature along with myoclonus and evidence of widespread neurological damage such as cerebellar ataxia and cortical blindness. The terminal state is generally one of akinetic mutism. The cerebral computerised tomographic (CT) scan is often remarkably normal. The EEG (electroencephalograph) often shows characteristic periodic complexes and the presence of these can be very helpful in clinical diagnosis.

Iatrogenic CJD results from the accidental transmission of disease from a case of CJD to another individual via medical or surgical treatments and investigations. Corneal transplantation, neurosurgical procedures and depth EEG electrodes have been implicated but, numerically, the most important instances relate to human growth hormone (hGH) treatment with cadaveric pituitary-derived hormone and the surgical use of human dura mater grafts [6].

Genetic CJD results from an autosomally inherited genetic defect. The prion protein (*PRNP*) gene is responsible for the production of a normal cellular protein designated PrP^{c}. In cases of CJD, the presence of an abnormal isoform (designated PrP^{RES}) correlates with both disease and infectivity. A mutation of this gene can predispose to the production of the disease-related isoform and thus leads to clinical illness. A number of underlying mutations have now been described [7]. Certain specific illnesses such as Gerstmann-Straussler syndrome (GSS) are perhaps now best considered special forms of genetic CJD. GSS was classified as a separate human spongiform encephalopathy with a different clinical phenotype. However, it is now known to be associated with a specific mutation in the protein gene. We are moving from an era of eponymously named diseases of uncertain cause to an era of more fundamental groupings based on characterised genetic underpinnings. It is a strange fact that material from cases of an autosomal dominantly inherited familial disease can result in infection of other individuals with a normal genetic constitution.

Although the vast majority of CJD cases are not genetically determined, it has become quite clear that the genetic make-up of an individual has an effect on the expression of the disease. There is a common polymorphism at codon 129 of the gene such that an individual may code for valine (V) or methionine (M). Being an MM homozygote appears to confer additional risk of developing CJD and the phenotype of CJD is influenced by the polymorphism type [8].

NvCJD has certain distinct epidemiological, clinical and neuropathological features which mark it off from the previously described types. It is believed that nvCJD has resulted from contamination of human food with BSE-infected material. To date (December 1997), there have been 22 pathologically confirmed cases and one probable (not pathologically confirmed) case in the UK with a single pathologically confirmed case in France.

3. NvCJD: epidemiology

NvCJD has affected a much younger age group than classical sporadic CJD, with 21 out of 23 cases having an onset at or below the of 35. The other two cases were 39 and 48 years old respectively. The mean age of onset was 27 years. NvCJD has a relatively long duration; in the first 21 cases, the mean duration of illness was 14 months with a range of 9–35 months. Details of the initial cases have been published [5,9].

The other most notable feature is its geographical distribution with all but one case occurring in the UK. No cases have been found to be genetic but all those with genetic analysis have been codon 129 MM homozygotes.

4. NvCJD: clinical

The presenting symptoms typically include psychiatric features and sensory disturbances [9,10]. Of the first 17 cases, 15 saw a psychiatrist during their investigation and seven of them as the first specialist referral. Withdrawal, apathy and depression were particularly common and fleeting delusions, usually ill-sustained (lasting from hours to days), were a feature in 12 of the first 14 cases.

The sensory symptoms included paraesthesia, dysaesthesia and pain affecting the limbs, trunk or face.

Ten of the initial 17 cases had such symptoms in the early course of the disease and in five they were the presenting features. Typically, there were no sensory signs on examination.

Indeed, clear evidence of neurological involvement was generally not obvious for some time (median approximately 6 months from onset). However, evidence of 'organic' neurological disease was eventually clear with typically cerebellar features along with other neurological signs. Abnormalities of eye movements were relatively common (up gaze impairment). Involuntary movements were a characteristic feature. In some cases chorea and/or dystonia developed prior to myoclonus. Cognitive decline became obvious and the clinical picture tended towards that of the classical form with dementia, involuntary movements (including myoclonus), and akinetic mutism.

There are published and reliable clinical diagnostic criteria for the three older forms of CJD (classical sporadic, genetic and iatrogenic). However, the diagnosis of nvCJD is not as clear cut.

The EEG has not shown the typical periodic pattern seen in classical sporadic CJD and the precise role of the CSF 14-3-3 test in nvCJD remains to be defined [11]. Out of six definite cases, only two had positive 14-3-3 tests. Some interest has been expressed in the possibility that MRI might show helpful abnormalities in the thalamic region, but this needs further study. At present, the definitive diagnosis of nvCJD rests absolutely on neuropathological examination of cerebral material obtained by biopsy in life or at autopsy. There is a single case report concerning diagnosis on the basis of tonsillar biopsy but this needs much further evaluation [12].

5. Is nvCJD BSE in humans?

There are three broad lines of evidence to link nvCJD to BSE. First, the epidemiology of nvCJD disease requires explanation. Sporadic CJD occurs on a world-wide basis and yet nvCJD cases are almost entirely confined to the UK. It is, of course, the case that the highest prevalence of BSE was found in the UK. Surveillance has been undertaken in a number of countries including the UK and one can be certain that nvCJD is indeed a new disease. The nvCJD form is a relatively long duration disease and we know that 'peripheral' routes of infection (such as occurred with hGH cases) tend to produce long duration illness. In addition, if one extrapolates from the incubation periods derived from other forms of 'peripheral' transmission, then nvCJD cases have started to appear at a reasonably typical time from what was probably the period of greatest potential contamination of food. Investigation of the reported nvCJD cases has failed to suggest any iatrogenic source of infection and no *PRNP* mutations have been found.

Secondly, transmission of BSE to macaque monkeys has produced a disease with neuropathological findings similar to those of nvCJD in humans [13].

Finally, there is accumulating evidence concerning the 'strain' type of the agent in nvCJD disease.

Analysis of the glycoforms of PrP^{RES} has shown the same pattern in BSE and nvCJD, a pattern that is different from that found in sporadic CJD [14]. Recently published papers describing transmission studies of nvCJD to mice have provided evidence that the same agent strain is involved in both BSE and nvCJD [15,16].

6. Conclusions

CJD surveillance was begun in the UK in 1990 in response to concern that BSE might pose a risk to the human population. A previously unrecognised form of CJD was identified and named 'nvCJD'.

There is accumulating epidemiological, clinical, neuropathological and experimental evidence that nvCJD has resulted from BSE contamination of human food.

So far, relatively few cases have been verified and it is uncertain how many further cases will occur. A recent publication has estimated that there may be as few as 75 or as many as 80 000 cases in the UK [17]. Careful surveillance in the UK will continue. CJD surveillance is under way in many other countries and it remains to be seen whether nvCJD will be a problem for countries other than the UK.

References

[1] Will, R.G., Matthews, W.B., Smith, P.G. and Hudson, C.

(1986) A retrospective study of Creutzfeldt-Jakob disease in England and Wales 1970–1979. II: Epidemiology. J. Neurol. Neurosurg. Psychiatry 49, 749–755.
[2] Cousens, S.N., Harries-Jones, R., Knight, R. et al. (1990) Geographical distribution of cases of Creutzfeldt-Jakob disease in England and Wales 1970–84. J. Neurol. Neurosurg. Psychiatry 53, 459–465.
[3] Harries-Jones, R., Knight, R., Will, R.G., Cousens, S., Smith, P.G. and Matthews, W.B. (1988) Creutzfeldt-Jakob disease in England and Wales, 1980–1984; a case-control study of potential risk factors. J. Neurol. Neurosurg. Psychiatry 51, 1113–1119.
[4] Wientjens, D.P.W.M., Will, R.G. and Hofman, A. (1994) Creutzfeldt-Jacob disease: a collaborative study in Europe. J. Neurol. Neurosurg. Psychiatry 57, 1285–1299.
[5] Will, R.G., Ironside, J.W., Zeidler, M. et al. (1996) A new variant of Creutzfeldt-Jakob disease in the UK. Lancet 347, 921–925.
[6] Brown, P., Preece, M.A. and Will, R.G. (1992) 'Friendly fire' in medicine: hormones, homografts, and Creutzfeldt-Jakob disease [see comments] [Review]. Lancet 340, 24–27.
[7] Collinge, J. and Palmer, M.S. (1997) Human prion diseases. In: Prion Diseases (Collinge, J. and Palmer, M.S., Eds.) Oxford University Press, Oxford.
[8] Windl, O. et al. (1996) Genetic basis of Creutzfeldt-Jakob disease in the United Kingdom: a systematic analysis of predisposing mutations and allelic variation in the *PRNP* gene. Hum. Genet. 98, 259–264.
[9] Zeidler, M. et al. (1997) New variant Creutzfeldt-Jakob disease: neurological features and diagnostic tests. Lancet 350, 903–907.
[10] Zeidler, M. et al. (1997) New variant Creutzfeldt-Jakob disease: psychiatric features. Lancet 350, 908–910.
[11] Will, R.G., Zeidler, M., Brown, P., Harrington, M.G., Lee, K.H. and Kenney, K.L. (1997) Cerebrospinal fluid test for new-variant Creutzfeldt-Jakob disease. Lancet 348, 955.
[12] Hill, A.F. et al. (1997) Diagnosis of new variant Creutzfeldt-Jakob disease by tonsil biopsy. Lancet 349, 99–100.
[13] Lasmezas, C.I. et al. (1996) BSE transmission to macaques. Nature 381, 743–744.
[14] Collinge, J. et al. (1996) Molecular analysis of prion strain variation and the aetiology of nvCJD. Nature 383, 685–690.
[15] Bruce, M.E. et al. (1997) Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. Nature 389, 498–501.
[16] Hill, A.F. et al. (1997) The same prion strain causes vCJD and BSE. Nature 389, 448–450.
[17] Cousens, S.N. et al. (1997) Predicting the CJD epidemic in humans. Nature 385, 197–198.