Creutzfeldt-Jakob disease in Austria

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Abstract

Between 1969 and 30 September 1995, 79 Austrian patients had Creutzfeldt-Jakob disease (CJD) diagnosed neuropathologically by necropsy or biopsy. The annual incidence has significantly increased in recent years (average 0·18 per million in 1969–85, and 0·67 per million in 1986–94; estimate for 1995: 1·5 per million). Also, the percentage of patients with CJD over 70 years at death increased significantly until 1989 but is since in decline. There is no regional clustering, familial occurrence, or recognised iatrogenic risk. One patient had a 10 year history of intramuscular injection of purified bovine RNA preparation (Regeneresen®) from various organs including the brain. The ages at death are symmetrically distributed around the median of 64 years. The median duration of disease is four months. Most patients (76%) died within six months of onset. Retrospectively, 86% of patients fulfilled clinical criteria of probable or possible CJD. Neuropathology showed the classic triad of spongiform change, astrogliosis, and neuronal loss in most cases. Two cases did not show unequivocal tissue alterations, but anti-PrP immunocytochemistry detected PrP deposits also in these cases. It is concluded that the recent rise in incidence of CJD in Austria most likely reflects increased awareness and diagnosis of CJD rather than a real increase. As bovine spongiform encephalopathy (BSE) has not been reported in Austria, the data do not support a link between a rise in incidence of sporadic CJD and BSE.

(*J Neurol Neurosurg Psychiatry* 1996;**61**:139–142)

Keywords: Creutzfeldt-Jakob disease; epidemiology; neuropathology; prion protein; prion disease

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Received 13 December 1995 and in revised form 12 April 1996
Accepted 22 April 1996

Creutzfeldt-Jakob disease (CJD) is the most frequent and widespread human transmissible spongiform encephalopathy (hTSE) with a worldwide incidence of about one case/million/year.[1–7] In the United Kingdom and other European countries, the incidence of CJD is continuously surveyed to detect any changes in the pattern of disease that might be attributable to a link with bovine spongiform encephalopathy (BSE).[2 3]

Definite diagnosis of CJD relies on neuropathology that is characterised by the classic triad of spongiform change, neuronal loss, and astrogliosis, all of which are highly variable in extent in the individual case.[8] A protease resistant isoform of the constitutively expressed cellular prion protein (PrP^{c}), designated as PrP^{CJD}, specifically accumulates in brain tissue in all types of hTSE. Therefore, demonstration of PrP^{CJD} is useful as a hallmark of disease.[9] Recently, anti-PrP immunocytochemistry after specific procedures has emerged as a reliable tool for detection of PrP^{CJD} in formalin fixed, paraffin embedded brain tissue, thus allowing unequivocal diagnosis of hTSE in routinely processed and archived brain tissue.[10 11] We present epidemiological, clinical, and neuropathological features of neuropathologically diagnosed and immunocytochemically confirmed cases of CJD in Austria.

Materials and methods

Cases of CJD diagnosed in all five Austrian centres with neuropathology services were retrospectively collected. Neuropathological diagnosis was made according to recently proposed criteria[8] on sections of numerous brain tissue blocks stained with routine techniques. In each case, paraffin sections of at least one tissue block from the cerebral cortex and one block from the cerebellar cortex (not available in six of 79 cases) were stained immunocytochemically with a polyclonal anti-PrP rabbit serum against a synthetic peptide of human PrP.[12] The peroxidase-antiperoxidase technique was used as the secondary system. To enhance immunostaining, sections were pretreated by hydration for 30 minutes in an autoclave at 121°C and 1·2 bar pressure.

Clinical data were collected retrospectively from medical case records; CJD was clinically categorised as probable or possible according to criteria used in the EC Surveillance Group of CJD in Europe.[2 3 13]

Results

The total number of neuropathologically detected cases of CJD in Austria from 1969 (year in which the first definite case of CJD was diagnosed) until 30 September 1995, was 79, comprising 42 female and 37 male patients. Seventy seven cases were diagnosed at necropsy, one case by biopsy and necropsy, and another only by biopsy. The annual rate of detection has significantly increased (average annual death rate 0·18 per million in 1969 to 1985, and 0·67 per million in 1986 to 1994; estimation for 1995: 1·5 per million) (fig 1).

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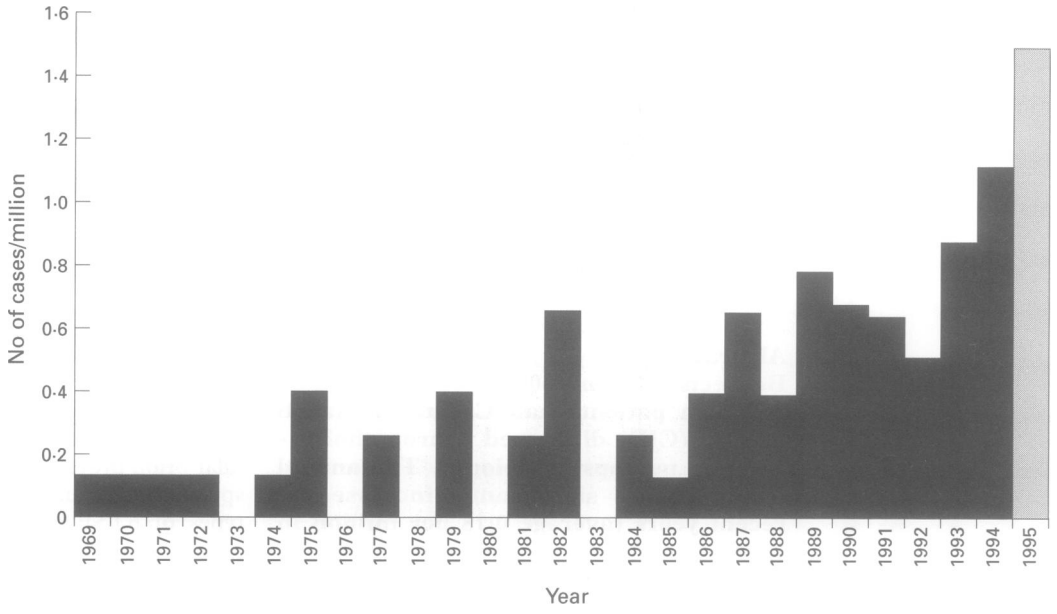

Figure 1 Incidence of neuropathologically diagnosed CJD in Austria 1969–95. Lighter column shows incidence for the period 1 January–30 September 1995 extrapolated for the full year.

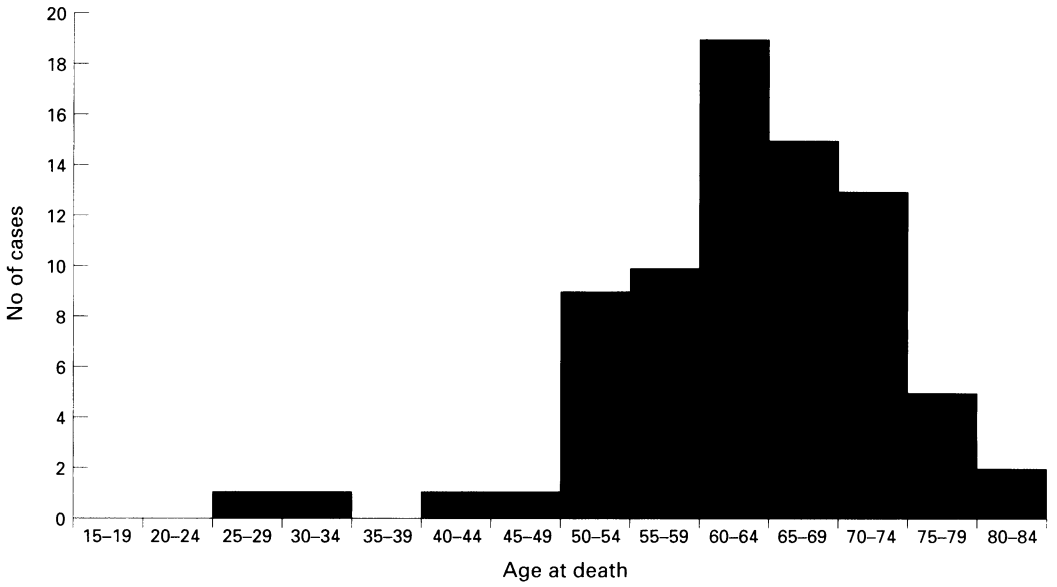

Figure 2 Age distribution at death of 77 neuropathologically confirmed Austrian patients with CJD.

There was no definite regional clustering. No case had an unequivocal family history or recognised risk for iatrogenic transmission; thus all presented as sporadic CJD. One case had a history of 10 years of intramuscular injection of purified bovine RNA preparation (Regeneresen®) from various organs including the brain.

The ages at death distribute roughly symmetrically around the median of 64 years (fig 2). The percentage of patients older than 70 years gradually increased since 1969 with a peak in the period 1985–9, and has subsequently decreased (fig 3); these differences between periods, however, are non-significant (χ^2 analysis). The overall percentage of patients with CJD older than 70 years was 23%. The distribution of the duration of illness was uneven (fig 4). Most patients (76%) died within six months of onset of disease. Retrospectively, 56% of the patients fulfilled clinical criteria of probable CJD and 30% of possible CJD. Fourteen per cent did not meet criteria for probable or possible CJD. Reasons for falsely negative categorisation were disease manifestations with typical EEG and progressive dementia but without or with insufficient additional clinical criteria; duration of disease longer than two years without typical EEG; and sudden death due to cardiac failure in the early or intermediate phase of disease.

Neuropathology in most cases showed the classic triad of spongiform change, astroglio-

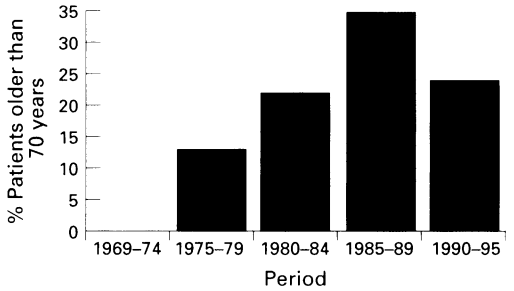

Figure 3 Percentage of patients with CJD older than 70 years in five-year periods from 1969 to 30 September 1995.

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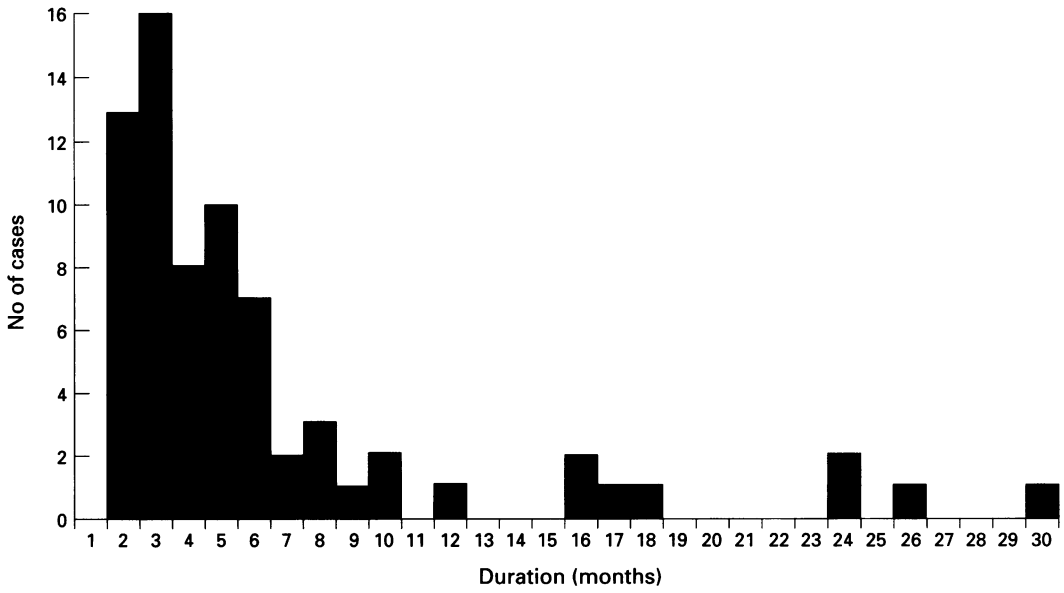

Figure 4 Duration of disease in 71 Austrian patients with neuropathologically confirmed CJD.

sis, and neuronal loss. Three out of 79 cerebral cortices, and eight of 73 cerebellar cortices had no unequivocal tissue alterations. In two brains, routine neuropathology was non-diagnostic. In these and all other brains, anti-PrP immunocytochemistry after hydrated autoclaving disclosed variably prominent PrP deposits in a synaptic pattern, a perivacuolar/patchy pattern, or of a plaque type. Deposits of PrP were sometimes few and only focally detectable, especially in cases with minor tissue lesioning.

Two female patients died at the unusually young ages of 27 (patient A) and 30 years (patient B). Except for the young age, there were no clinical or neuropathological peculiarities: duration of disease in patient A was eight months and in patient B 10 months. Clinically, patient A was possible CJD, and patient B was probable CJD. Neuropathologically, both cases had characteristic tissue pathology and synaptic type PrP deposits with additional infrequent and indistinct plaques in the cerebellum of patient B. Both patients died before the appearance of BSE (patient A in 1969, patient B in 1982).

Discussion

In recent years, the annual incidence of neuropathologically confirmed CJD in Austria has risen significantly. Considering cases diagnosed until 30 September, the estimated incidence for 1995 is 1·5 per million. Incidence figures reported from other European countries and other continents are all lower,[1–7] in many instances to a considerable degree. The increasing incidence of CJD in Austria is most likely attributable to recently increased awareness among neurologists and other medical doctors; thus fewer patients are likely to remain undiagnosed. Moreover, Austria is a small country with a high necropsy rate and well developed neurology and neuropathology services. Thus probably most or all cases of CJD undergo neuropathological examination here. The increase in the percentage of CJD cases detected in elderly people until 1989 most likely results from increased awareness of CJD as an entity distinct from other dementing conditions. As BSE has not been reported in Austria, our data do not support a link between a rise in incidence of sporadic CJD and BSE.

Although in our opinion our data are best interpreted as recently optimised CJD surveillance in Austria, a real change in the incidence of CJD cannot be excluded at this moment. Thus further careful follow up in the future is mandatory.

Recently, a similar increase in the incidence of CJD was reported from the United Kingdom. In 1994 the incidence there was higher than in any previous year[14]; it is, however, only 62% of the incidence of CJD in Austria in 1995. Analysis of age specific incidence rates indicates that most of the rise in the United Kingdom is due to improved ascertainment of CJD in the elderly population.[14] In Austria, a similar increase of CJD diagnosed in elderly people was seen until 1989 but has levelled off since.

By contrast with other studies reporting around 10% of cases of CJD as familial, all cases of CJD retrospectively collected in Austria had no definite family history. A family history of CJD may not be apparent in cases with non-paternity or because of premature death of a gene carrying parent. Definite exclusion of familial cases of CJD would require molecular genetic analysis. This is not yet available in this series. A few of our cases might turn out not to be sporadic CJD after determination of the *PRNP* genotype.

Epidemiological surveillance of CJD in Europe, currently reported from five countries (United Kingdom, France, Germany, Italy, The Netherlands), is based on direct notification, mainly from neurologists applying clinical criteria of the EC surveillance group.[2,3] Retrospective evaluation of clinical features in our series of neuropathologically definite cases of CJD showed that 14% of the cases did not fulfil clinical criteria of probable or possible CJD. Despite increased awareness of CJD among neurologists, some cases with atypical

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presentation or cases dying from other causes in the early stage of disease may clinically remain undiagnosed or misdiagnosed. This further emphasises the need for neuropathological evaluation in patients with all types of neurological disorders.

Note added in proof

Since submission of this manuscript the annual incidence for the whole year 1995 became available. It is 1·25 per million (only neuropathologically confirmed CJD). If, as in other European series, another case of probable CJD (necropsy not available for religious reasons) is added, the 1995 incidence figure rises to 1·38 per million.

This study was performed within the EC Biomed-1 Concerted Action "The Human Prion Diseases" (Project Leader H Budka). Mrs H Flicker provided invaluable technical assistance. We gratefully acknowledge the collaboration of many neurologists and pathologists in Austria.

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