SHORT REPORT

Trends in mortality from sporadic Creutzfeldt-Jakob disease in France 1992-7

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Abstract

This study examined trends in mortality from sporadic Creutzfeldt-Jakob disease in France for 1992-7 by age, genotype at the codon 129 of the prion protein gene, and geographical area. Case ascertainment was based on notifications by neurologists, neuropathologists, and laboratories; 324 deaths from definite or probable Creutzfeldt-Jakob disease were registered during the study period. The yearly number of deaths increased significantly between 1992 and 1997. The rise was higher for older age groups. It was also higher in those who were homozygous for valine compared with other genotypes. Eighteen departments (geographical administrative areas) out of 95 showed a significant increase in the number of deaths from sporadic Creutzfeldt-Jakob disease. Intensive epidemiological surveillance is a likely explanation for the apparent increase in the number of sporadic cases of Creutzfeldt-Jakob disease over the 1992-7 period, particularly in older age groups and in departments with low mortality rate at the beginning of the study period. Intensive surveillance may also have led to a better identification of atypical valine homozygous cases.

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Prospective ascertainment of all cases of Creutzfeldt-Jakob disease was established in France in 1991 and continues. One objective of the survey was to be able to detect any changes in the epidemiological characteristics of Creutzfeldt-Jakob disease which might be related to the bovine spongiform encephalopathy epidemic. Since 1993, French data have been included in a European collaborative study on the incidence and risk factors of Creutzfeldt-Jakob disease.^{1,2} Comparison of European data has contributed to the identification of a new variant of Creutzfeldt-Jakob disease in young patients with unusual clinical and neuropathological signs.³ Available experimental⁴ and biochemical⁵ studies have shown that the agent of new variant

Creutzfeldt-Jakob disease cannot be distinguished from the causative agent of bovine spongiform encephalopathy. At the time of writing, 44 cases of new variant Creutzfeldt-Jakob disease had been registered in the United Kingdom⁶ and one case in France.⁷ Up to now, all genotyped cases of new variant Creutzfeldt-Jakob disease were methionine homozygotes at codon 129 of the prion protein gene.⁶

We analysed age specific trends in the number of deaths from sporadic Creutzfeldt-Jakob disease in France between 1992 and 1997. We also examined whether the frequency of the genotypes of the codon 129 of the prion protein gene and the geographical distribution of cases of Creutzfeldt-Jakob disease have changed over the study period.

Methods

Case ascertainment was based on direct notification of suspected cases of Creutzfeldt-Jakob disease by neurologists, neuropathologists, and the laboratories involved in the examination of the prion protein gene or detection of the 14.3.3 protein in the CSF.⁸

Between 1992 and 1997, suspected cases were examined, when possible, by the study neurologist (JPB). The diagnostic criteria for Creutzfeldt-Jakob disease did not change over the study period⁹ and about 60% of patients with suspected Creutzfeldt-Jakob disease were necropsied.

Cases were classified as iatrogenic when the patients had a known history of exposure to pituitary growth hormone or dura mater. Cases were classified as inherited Creutzfeldt-Jakob disease when the patients showed a mutation of the prion protein gene or a family history of Creutzfeldt-Jakob disease. The prion protein gene was examined in 83% of the suspected cases of Creutzfeldt-Jakob disease, with the informed consent of each family. All other cases were classified as probably sporadic. The French case of new variant Creutzfeldt-Jakob disease, which was identified in 1996⁷ was not included in this study.

The number of deaths from Creutzfeldt-Jakob disease between 1992 and 1997 was analysed using Poisson regression modelling, with the number of deaths as the dependent variable and the year of death serving as the explanatory variable. This analysis was made in

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Table 1 Rate of increase in mortality from sporadic Creutzfeldt-Jakob disease (definite and probable cases) by age group and genotype (1992–7)

	Number of deaths		Average yearly (%) increase in mortality (95% CI)	p Value
	1992–4	1995–7		
By age group:				
30–59	27	40	8.4 (–6.1 to 25.2)	0.27
60–69	48	88	17.8 (6.5 to 30.3)	0.001
70–79	37	58	21.4 (7.4 to 37.1)	0.002
≥80	6	20	42.5 (10.9 to 83.2)	0.005
By genotype:				
Met-Met	59	110	20.4 (9.9 to 31.8)	0.001
Val-Val	8	33	50.5 (22.4 to 85.1)	0.001
Met-Val	13	17	14.7 (–9.2 to 38.7)	0.28

the different subgroups defined on age, genotype, and place of residence (rural or urban).

To examine whether some departments (French geographical administrative units) showed significant increases or decreases in Creutzfeldt-Jakob disease, the number of deaths from the disease during the period 1992–4 were compared with the number of deaths between 1995 and 1997. This analysis was made under the assumption that the observed number of cases during the period 1995–7 followed a Poisson distribution with mean equal to that observed during the period 1992–4. This analysis is valid if the demographic pattern (population size and age distribution) of the department did not change over the period 1992–7.

Results

A total of 324 patients with definite or probable sporadic Creutzfeldt-Jakob disease died between 1992 and 1997. The average annual death rate from Creutzfeldt-Jakob disease increased significantly from 0.68/million during 1992–4 to 1.19/million during 1995–7. The

rate of increase in the number of deaths from sporadic Creutzfeldt-Jakob disease was higher for older age groups (table 1). There was no evidence of increase in the youngest age group (39 years or less) and a non-significant trend in the age group 30–59 years.

Genetic data were available for 240 (74%) of the patients with definite or probable sporadic Creutzfeldt-Jakob disease. Analysis of the number of deaths by codon 129 genotype suggested a difference in trends during the period 1992–7. There was a significant increase of both valine and methionine homozygous cases and no increase of heterozygous cases. Moreover, data suggested that the yearly rate of increase was higher in valine homozygotes than in methionine homozygotes (table 1). Estimation of age-specific and genotype-specific yearly rates showed that the slight increase of mortality rate in younger people (30–59 years) was mainly due to patients who were homozygous for valine at codon 129.

There was no difference in trends for mortality rates from sporadic Creutzfeldt-Jakob disease between urban and rural areas. Between 1992 and 1997, the average yearly rates of increase in the number of deaths (95% confidence interval) were 17.5 (9.0–26.6) and 22.4 (7.0–40.0) in urban and rural areas respectively.

In 18 departments out of 95, the number of deaths from sporadic Creutzfeldt-Jakob disease was significantly higher in 1995–7 than in 1992–4; the number of deaths decreased significantly in only one department. The figure shows the geographical distribution of the departments where the number of deaths from definite and probable sporadic Creutzfeldt-Jakob disease increased significantly.

During the period 1992–7, 52 patients had been classified as possible cases of sporadic Creutzfeldt-Jakob disease. The results did not change when these patients were included in the analyses.

Discussion

Over the past few years, the reported number of deaths from sporadic Creutzfeldt-Jakob disease has increased in the European countries in which a prospective surveillance programme for the disease has been set up.¹ Given the poor survival of patients with the disease (mean survival 6 months), mortality rates can be considered as a proxy for incidence.

The data obtained in the present study have confirmed that intensive epidemiological monitoring permitted better ascertainment of the disease in people aged 70 and over. The increase in deaths from Creutzfeldt-Jakob disease in France between 1992 and 1997 is mainly a result of variation in older age groups; there was little variation in younger people. Cousens *et al* have also found that the greatest increase in incidence of Creutzfeldt-Jakob disease in England and Wales over the period 1970–96 was in people aged over 70.¹⁰

Our analysis showed differences in temporal trends according to the polymorphism of the prion protein gene at codon 129. The greatest

Location of the departments with significant increase in the number of deaths from sporadic Creutzfeldt-Jakob disease between 1992–4 and 1995–7 (numbers are department codes).

increase was found in valine homozygous people. Moreover, increase in valine homozygous cases explained most of the overall increase, which was found in the age group 30–59 years. Our findings can be compared with the results of a recent study which showed a relative excess of valine homozygotes in patients with sporadic Creutzfeldt-Jakob disease aged less than 50 years.¹¹

One explanation for these findings is a better identification of atypical valine homozygous cases. During the period covered by the study, the 14.3.3 protein test was not used for the diagnosis of probable sporadic Creutzfeldt-Jakob disease. This diagnosis required the presence of a typical EEG, which is less frequent in valine homozygous patients than in other genotypes. Diagnostic uncertainty could have led to a genotype related differential necropsy rate, especially in younger patients. However, our data did not suggest any significant variations of the yearly necropsy rate according to age and genotype over the study period. Other explanations, which remain speculative and unfounded, are the emergence of a new type of Creutzfeldt-Jakob disease or the increased incidence of a pre-existent type of Creutzfeldt-Jakob disease involving interaction between genetic characteristics and agent strain.

The most likely explanation of the increase in the incidence of reported cases of sporadic Creutzfeldt-Jakob disease (definite and probable) in 18 French departments is the incomplete ascertainment of the disease before 1995. Indeed, eight of these departments did not detect any cases during the period 1992–4, and in three other departments, the annual incidence of Creutzfeldt-Jakob disease was at least 50% lower than the national rate during the same period. There was only one department in which the incidence of Creutzfeldt-Jakob disease was high both in the first (1992–4) and the second (1995–7) periods.

Several of the departments where case ascertainment was improved over the study period were affected by bovine spongiform encephalopathy since 1990. This concern may have contributed to a more complete detection of cases of Creutzfeldt-Jakob disease. Assuming that the duration of the incubation period of Creutzfeldt-Jakob disease is of the order of 10 years, a link between bovine spongiform encephalopathy and increase in mortality from sporadic Creutzfeldt-Jakob disease during the period 1995–7 is very unlikely. Incidentally, it is emphasised that no new variant Creutzfeldt-Jakob case was diagnosed in these departments.

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- 1 Will RG, Alperovitch A, Poser S, *et al.* Descriptive epidemiology of Creutzfeldt-Jakob disease in six European countries, 1993–5. EU Collaborative Study Group for CJD. *Ann Neurol* 1998;43:763–7.
- 2 van Duijn CM, Delasnerie LN, Masullo C, *et al.* Case-control study of risk factors of Creutzfeldt-Jakob disease in Europe during 1993–5. European Union (EU) Collaborative Study Group of Creutzfeldt-Jakob disease (CJD). *Lancet* 1998;351:1081–5.
- 3 Will RG, Ironside JW, Zeidler M, *et al.* A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet* 1996;347:921–5.
- 4 Bruce ME, Will RG, Ironside JW, *et al.* Transmissions to mice indicate that new variant CJD is caused by the BSE agent. *Nature* 1997;389:498–501.
- 5 Collinge J, Sidle KC, Meads J, *et al.* Molecular analysis of prion strain variation and the aetiology of new variant CJD. *Nature* 1996;383:685–90.
- 6 Will RG, Cousens S, Ferrington CP, *et al.* Deaths from variant Creutzfeldt-Jakob disease. *Lancet* 1999;353:979.
- 7 Chazot G, Broussolle E, Lapras C, *et al.* New variant of Creutzfeldt-Jakob disease in a 26 year old French man. *Lancet* 1996;347:1181.
- 8 Brandel JP, Beaudry P, Delasnerie-Lauprêtre N, *et al.* Maladie de Creutzfeldt-Jakob: valeur diagnostique de la détection de la protéine 14.3.3 et du dosage de la NSE dans le liquide céphalo-rachidien. *Rev Neurol* 1999;155:148–51.
- 9 Brandel JP, Delasnerie-Lauprêtre N, Alperovitch A. Diagnosis of Creutzfeldt-Jakob disease: effect of clinical criteria on incidence estimates. *Neurology* 2000 (in press).
- 10 Cousens SN, Zeidler M, Esmonde TF, *et al.* Sporadic Creutzfeldt-Jakob disease in the United Kingdom: analysis of epidemiological surveillance data for 1970–96. *BMJ* 1997;315:389–95.
- 11 Alperovitch A, Zerr I, Pocchiari M, *et al.* Codon 129 prion protein genotype and sporadic Creutzfeldt-Jakob disease. *Lancet* 1999;353:1673–4.