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Epidemiology of Creutzfeldt-Jakob Disease in the United States, 1979–1990: Analysis of National Mortality Data

Key Words
Creutzfeldt-Jakob disease
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Abstract
The trends and current incidence of Creutzfeldt-Jakob disease (CJD) was examined by using a unique and potentially highly sensitive source for case ascertainment. We analyzed death certificate information for 1979–1990 from US multiple-cause-of-death mortality data, compiled by the National Center for Health Statistics, Centers for Disease Control and Prevention. We evaluated death certificate data for US residents for whom CJD was listed as one of the multiple causes of death on the death certificate (046.1) from the International Statistical Classification of Diseases, Injuries, and Causes of Death (9th revision). Age-adjusted and age-specific CJD death rates by gender, race, and region were calculated to measure the disease incidence because of the rapidly fatal course of the disease for most patients with CJD. We identified 2,614 deaths with CJD listed on the death certificates. The average annual age-adjusted mortality rate was 0.9 deaths per million persons (range 0.8–1.1). The mean age at death was 67 years. CJD-related deaths were uncommon among persons younger than 50 years of age (4.3% of all deaths). The highest average annual mortality rate was for those persons aged 70–74 years (5.9 deaths per million persons). A slight majority (53.0%) of the deaths was in females, but the age-adjusted mortality rate was 1.2 times higher for males. Most deaths (94.8%) were in whites; the mortality rate for blacks was only 40% of that for whites. The age-adjusted CJD mortality rate in the United States is similar to published estimates of the crude incidence of CJD worldwide. Annual review of national multiple-cause-of-death data may provide an efficient and cost-effective method to monitor the incidence of CJD in the United States. The relative paucity of cases among blacks requires further study to rule out detection biases, but may reflect, in part, differences in genetic and/or environmental factors.

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Introduction

Creutzfeldt-Jakob disease (CJD), a rapidly fatal dementing illness characterized by cerebral spongiform changes, is the prototype of human spongiform encephalopathies, which include Gerstmann-Sträussler-Scheinker disease and kuru [1]. In 1968, the transmissibility of this rare disease was first recognized in animals and subsequently verified with reports of iatrogenic transmission from a corneal transplant, electroencephalographic depth electrodes, neurosurgical procedures, and cadaveric dura mater and hormones [2–8]. Approximately 10% of CJD cases are hereditary, exhibiting autosomal dominant transmission and suggesting the possibility of genetic susceptibility to the disease. However, multiple population-based and case-control studies have not identified environmental risk factors for the majority of sporadic CJD cases [9], perhaps because of the long latency of as long as 20 years, or because the disease is due to abnormalities in the prion protein as suggested by molecular studies [10–12].

CJD is not a reportable disease in the United States, but the incidence of this illness has been estimated from earlier limited surveillance [13]. Although there is no evidence that the new bovine spongiform encephalopathy epizootic that appeared in the United Kingdom during the 1980s can spread to humans, this theoretical possibility has focused increased attention on the desirability of national CJD surveillance [14, 15]. This attention and the fact that CJD is rapidly and invariably fatal (nearly 90% of CJD patients die within 1 year of onset of symptoms) [16] led us to analyze national CJD mortality data as a possible surrogate for ongoing CJD surveillance in the United States.

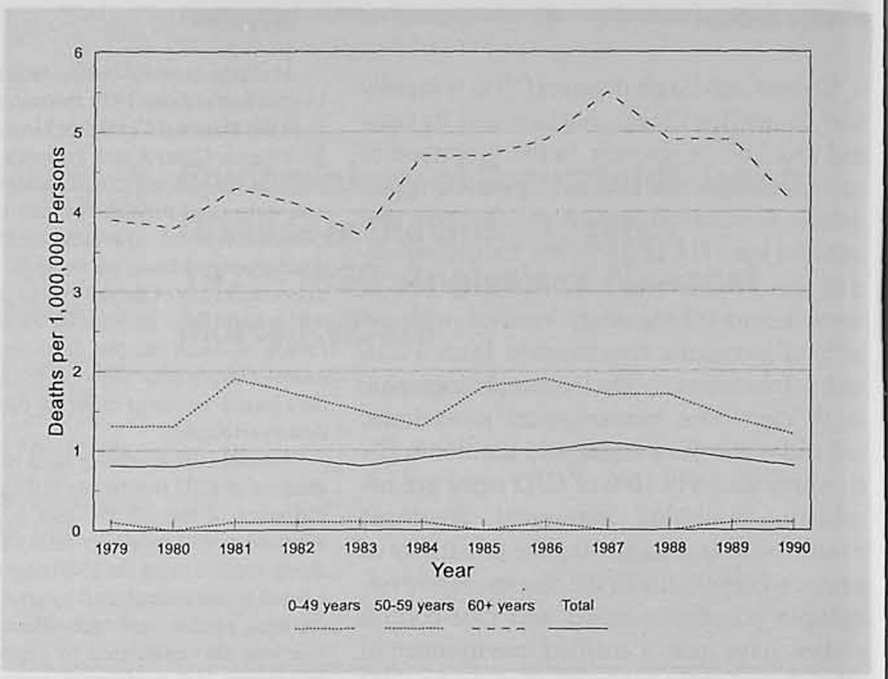
Methods

Multiple-cause-of-death mortality data for the United States from 1979 through 1990 were obtained from the National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Md. [17]. Cause-of-death classifications from death certificate data used the 9th revision of the International Classification of Diseases (ICD-9) [18–20]. CJD deaths were defined as those for which code 046.1 appeared in any of the entity-axis codes (i.e., deaths for which CJD was mentioned as any of the multiple causes of death on the death certificate). Multiple-cause-of-death data allow for the analysis of mortality data based on one of different causes reported on the death certificate.

Annual CJD mortality rates were calculated as the number of CJD deaths per million persons, based on estimates of the US resident population [21]. Age-adjusted annual mortality rates were calculated by the direct method using the 1980 census population for the United States overall, and by gender, race, and region; the age-, gender- and race-adjusted annual mortality rate was also calculated by region [22]. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using Poisson regression analysis [23]. Mortality rates were classified by age groups in two ways: (i) 5-year intervals from 0 to 84 years, and 85 years and older, and (ii) 0–49, 50–59, 60–69, 70–79, and 80 years and older. To examine racial differences and trends, we used the categories of white, black, and other races as provided in the national mortality data. Geographic comparisons were analyzed by standard US census regions: northeast, north central, west, and south. The percentage of the metropolitan population in the United States was based on the standard metropolitan areas [18].

Results

From 1979 to 1990, 2,614 deaths were reported in the United States with CJD coded as a cause of death. The average annual age-adjusted mortality rate during this 12-year period was 0.9 deaths per million persons (0.8 per million in both 1979 and 1990, and approximately 1.0 per million from 1985 to 1988; fig. 1). The mean age at death was 67 years (median age 68 years).



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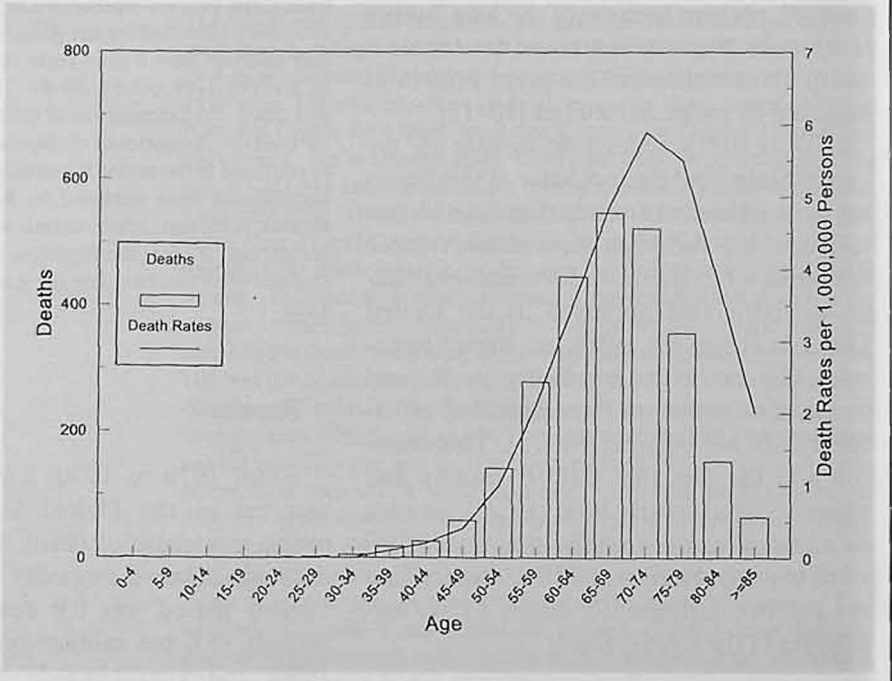

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Fig. 1. CJD age-adjusted and age-specific mortality rates in the US, 1979–1990.
Fig. 2. CJD deaths and mortality rates by age group in the US, 1979–1990.

Approximately 95% of the deaths were in persons 50 years of age and older. The age-specific mortality rates were highest for persons in their 70s (fig. 2).

Although 53.0% of the deaths were in females, the age-adjusted mortality rate for males was 1.2 times that for females (1.0 per million males compared with 0.8 per million females; table 1). The CJD mortality rate for males was higher than that for females in all age groups 60 years and older, but lower than that for females in the younger age groups (table 2). Most deaths (94.8%) were in whites. The age-adjusted mortality rate for blacks was only 40% that for whites (table 1). The other races accounted for only 1.5% of the CJD deaths, with an age-adjusted rate higher than that for blacks. The CJD mortality rate for blacks was lower than that for whites in all age groups. Geographically, the age-, gender- and race-adjusted rate for the south region was slightly lower than that for each of the other regions (south compared with northeast, RR = 0.7, 95% CI = 0.6–0.8; north central, RR = 0.8, 95% CI = 0.7–0.9; west, RR = 0.9, 95% CI = 0.8–1.0), and the previously noted race and gender differences remained consistent for each region. The proportion of deaths in metropolitan counties of residence (75.4%) was consistent with the proportion of the US metropolitan population in 1980 and 1990 (76.2 and 77.5%, respectively).

Approximately 80% of the CJD deaths were in persons 60 years of age and older. The average annual mortality rate during the study period for this age group was 4.5 per million persons (range from 3.7 per million in 1983 to 5.5 per million persons in 1987). Among persons 50–59 years old, the average annual mortality rate was 1.6 per million persons (range 1.3–1.9 per million). Among persons younger than 50 years of age, the annual mortality rate was consistently at or below 0.1 per million persons, with at most 11 deaths per year (fig. 1).

Table 1. Creutzfeldt-Jakob disease mortality rates (per million persons) by gender, race, age group, and region, in the United States, 1979–1990

Characteristics		Rate	Deaths
Gender[1]	Male	1.0	1,229
	Female	0.8	1,385
Race[1]	White	1.0	2,479
	Black	0.4	95
	Other	0.8	40
Age group, years	0–4	<0.1	1
	5–9	0.0	0
	10–14	0.0	0
	15–19	0.0	0
	20–24	<0.1	1
	25–29	<0.1	2
	30–34	<0.1	5
	35–39	0.1	18
	40–44	0.2	26
	45–49	0.4	59
	50–54	1.0	141
	55–59	2.1	278
	60–64	3.5	445
	65–69	4.9	546
	70–74	5.9	521
	75–79	5.5	355
	80–84	3.8	152
	85+	2.0	64
Region[2]	Northeast	1.0	667
	North central	1.0	733
	South	0.8	745
	West	0.9	469
Total[1]		0.9	2,614

[1] Age-adjusted mortality rates.
[2] Age-, gender- and race-adjusted rates.

The most common causes of death listed with CJD on the death certificate were cardiac arrest (17.6%), respiratory arrest (12.9%), and pneumonia (11.4%). During the 12-year period, 741 persons who died of CJD-

Table 2. CJD age-specific mortality rates (per million persons), age group by gender and race, in the US, 1979–1990

Age group years	Gender				Race			
	male		female		white		black	
	rate	deaths	rate	deaths	rate	deaths	rate	deaths
0–49	0.1	56	0.1	56	0.1	98	<0.1	9
50–59	1.5	194	1.6	225	1.7	390	0.7	18
60–69	4.6	502	3.8	489	4.4	948	1.4	29
70–79	6.2	387	5.4	489	6.1	842	2.3	29
80+	3.9	90	2.6	126	3.1	201	1.9	10

related causes were autopsied, which is 31.5% of those with known autopsy status. The proportion of autopsies ranged from 23.5% in 1989 to 37.8% in 1983; the proportion in 1990 was 36.1%.

Discussion

This analysis of US multiple-cause-of-death data for 1979–1990 demonstrated an average annual age-adjusted mortality rate of 0.9 deaths per million persons, a rate consistent with published estimates of the crude incidence worldwide of 1 case per million persons [8, 13]. The estimated worldwide incidence based on a retrospective review of deaths and prospective surveillance, however, is higher than the observed incidence for Italy (0.09 per million for 1972–1986) [24], Chile (0.31 per million for 1955–1977) [25], France (0.56 per million for 1978–1982) [9], and England and Wales (0.49 per million for 1980–1984) [26], but similar to rates for Finland (0.91 per million for 1979–1984) [27] and many metropolitan areas (e.g., Paris, Genoa, Santiago) [9, 25, 28]. Some of this variability in observed rates probably reflects differences in the sensitivity of case ascertainment. In our study, we used routinely compiled multiple-cause-of-death data from death certificates, which constitute a unique and presumably more sensitive source for case ascertainment than do referrals to major medical centers. The absence in this study of lower observed rates of CJD for residents of nonmetropolitan areas compared with metropolitan areas may reflect this presumably higher sensitivity of case ascertainment [13].

On the basis of CJD cases referred to the Laboratory of Central Nervous System Studies, National Institutes of Health, and published reports of cases that occurred from 1973 to 1977, the minimum average annual mortality rate for the United States was estimated at 0.26 deaths per million persons, with an age-specific mortality rate of 0.4 deaths per million for adults aged 18 years or older [13]. A retrospective survey of CJD cases in the urbanized area of Boston from 1957 to 1976 yielded an annual mortality rate of 0.43 per million persons [13]. On the basis of autopsies performed from 1959 to 1975 in Staten Island and Brooklyn, N.Y., the CJD mortality rate was 0.24 per million; on the basis of 5 deaths reported during the 1976–1977 academic year, the CJD mortality rate was 1.8 per million per year [29]. In our study,

we found that over the 12-year period the total annual CJD mortality rates varied between only 0.8 and 1.1 deaths per million, and that for persons younger than 50 years of age the peak annual number of deaths was only 11 in 1979, 1981, 1982, 1986, and 1990. Overall, the age-specific CJD mortality rates increased rapidly with age, particularly between 50 and 75 years of age. As previously described in a study in France [9], our study found an unexplained sharp decline in the CJD mortality rate in persons older than 79 years of age.

In previous reports, female cases have outnumbered male cases (e.g. France, England and Wales, Finland, and Hungary) [9, 26, 27, 30]. Although some investigators have hypothesized varying exposures to explain the apparent higher proportion of CJD cases among females, in the United States males have a slightly higher age-adjusted rate. Thus, the higher absolute number of deaths from CJD primarily reflects the greater proportion of females in the older age groups that are at highest risk for CJD in the United States. Analysis by race indicated a difference in the age-adjusted rate between whites and blacks that, to our knowledge, has not been previously reported. Although this lower rate for blacks may be due to an undescribed, decreased genetic susceptibility or differences in environmental factors, further studies to rule out detection biases are required. Studies on the incidence of CJD in black populations in other countries would also be helpful. The similarity and magnitude of the relatively low CJD-specific mortality rates for blacks in all four regions of the country suggest that detection biases alone may not account for the lower rates.

The validity of multiple-cause-of-death data is potentially a problem because of possible coding and reporting discrepancies [17, 31, 32], including misdiagnoses. For example, the single case of CJD in an individual less than 5 years old was a case of spongioform degeneration in infancy, a disease which shares the ICD-9 code with CJD. However, mortality data have been shown to be ideal for providing a national perspective, identifying patterns of associations between diseases, and monitoring secular trends [33], and have recently been used epidemiologically to describe mortality caused by neurologic disease, such as progressive multifocal leukoencephalopathy, Parkinson's dementia, and neurodegenerative disease [34–36]. Clearly, the sensitivity and specificity of the system is dependent on physician awareness of the disease and its diagnosis. To this end, the number of published reports describing CJD has increased steadily since its transmissibility was first demonstrated in 1968, and by 1979 CJD was well described in medical textbooks and other sources [37]. Higher autopsy rates for neurologic deaths in the United States could further improve the specificity of the multiple-cause-of-death data. However, counting only autopsied cases would markedly reduce sensitivity. Because many true CJD cases are probably still misdiagnosed as Alzheimer's and other dementias, the current estimate is probably a minimum estimate of the true CJD incidence in the United States. Nevertheless, despite its limitations, this purported surveillance is clearly more sensitive than methods used for previous estimates in the United States and has the important advantages of being currently available and ongoing.

Annual review of CJD multiple-cause-of-death data could provide an efficient and cost-effective method to monitor CJD incidence, especially among those persons younger than 50 years of age for whom the low baseline incidence would enable detection of a relatively small cluster of cases. The US annual average age-adjusted mortality rate of

0.9 cases per million persons for 1979–1990 is consistent with rates reported from other countries. The previously unreported racial differences in the CJD mortality rates should be studied further.

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