Articles

Surgical treatment and risk of sporadic Creutzfeldt-Jakob disease: a case-control study

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Summary

Background Apart from the small number of iatrogenic and familial cases, the cause of most cases of Creutzfeldt-Jakob disease (CJD) is not known. We aimed to identify risk factors for sporadic CJD.

Methods In a case-control study, we compared the medical history and selected demographic characteristics of 241 definite (neuropathologically confirmed) and probable (clinically likely) patients with CJD, ascertained from the Australian National Creutzfeldt-Jakob Disease Registry between Jan 1, 1970, and October 31, 1997, and of 784 controls, recruited from the community by random telephone interview in August, 1997. Standard logistic regression was used for the comparisons.

Findings Surgical procedures were significantly associated with the development of sporadic CJD. This risk progressively increased with the number of surgical treatments to a maximum for three procedures (odds ratio 2·13 [95% CI 1·34–3·41], p=0·002). There was also a significant association between risk of CJD and residence or employment on a farm (p<0·001) or market garden (p=0·002) for longer than 10 years. We found no significant risk associated with a history of blood transfusion, organ transplantation, major dental work, or occupation.

Interpretation Our findings accord with the hypothesis that a range of surgical treatments may serve as unrecognised contamination events and account for a proportion of cases of sporadic CJD. Possible biases in different methods and times for the acquisition of data on cases and controls suggest our findings need to be replicated in independent studies with community controls.

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Introduction

By contrast with iatrogenic and familial cases of Creutzfeldt-Jakob disease (CJD), the aetiology of the most common form, sporadic CJD, which constitutes 85–90% of all cases,[1,2] is unknown. One hypothesis is that sporadic disease is caused by a rare (one in a million) spontaneous somatic mutation within the cerebral neuronal pool of the prion protein (PrP).[3] An alternative is low-level contamination events.[4] The excess of homozygosity at codon 129 in iatrogenic disease[5] has also been found in sporadic CJD, and may increase the chance of normal PrP (PrP^{C}) converting to the abnormal, disease-associated isoform (PrP^{SC}) when the normal and abnormal conformers interact, as could occur after a contamination event.

Previous case-control studies have investigated possible causes or risk factors for sporadic CJD, without identifying any consistent or major influences.[7–14] In our case-control study of risk factors for sporadic CJD, we used the Australian National Creutzfeldt-Jakob Disease Registry to ascertain cases. Controls were recruited from the general community by random telephone survey, unlike most previous studies that used hospital-based controls.[9–14]

Methods

Cases

The Australian National Creutzfeldt-Jakob Disease Registry[15] collected cases retrospectively to Jan 1, 1970, and prospectively from Oct 1, 1993. 241 patients with sporadic CJD (122 men, mean age 63·1 years, 119 women, mean age 66·6 years; combined age range 25–84 years) represented all Australian cases of sporadic CJD that occurred up to Oct 31, 1997. The diagnostic subclassifications of this cohort were 151 definite (neuropathologically confirmed) and 90 probable (clinically likely) cases of CJD, according to previously published criteria.[1] For probable cases, clinical investigation excluded the possibility of an alternative explanation and triphasic periodic complexes on the electroencephalogram, the presence of 14-3-3 protein in the cerebrospinal fluid, or both were usually present. In all cases, a history of potential iatrogenic transmission in the form of dura mater and corneal grafts or exposure to human cadaveric pituitary hormones was sought and excluded.

The ascertainment methods were approved by an Ethics Committee of the University of Melbourne. The main sources of case reporting provided about 91% of the total cases and were: neurologists (32%) and neuropathologists (20%); death certificates (25%); searches of separation codes at university-affiliated hospitals with ICD-9 CM 046.1 (specific for CJD) and 290.1 (for presenile dementia), or the equivalent codes from earlier versions of the International Classification of Diseases when appropriate (12%); and similar systematic reviews of the Health Information Morbidity Data for each

	Cases (n=241)	Controls (n=784)	Odds ratio (95% CI)	p
Country of birth				
Australia	155	598	1·0	
UK	32	86	1·44 (0·92–2·23)	0·109
Other European	36	48	2·89 (1·81–4·62)	<0·001
Asia	3	19	0·61 (0·18–2·08)	0·430
Other	6	33	0·70 (0·29–1·70)	0·434
Not known	9	0	—	
Any surgery				
No	38	233	1·0	
Yes	153	550	1·71 (1·16–2·51)	0·007
Not known	50	1	—	
Any dialysis, chemotherapy, radiotherapy, or arterial embolisation				
No	171	758	1·0	
Yes	4	24	0·69 (0·23–2·01)	0·494
Not known	66	2	—	
Ever lived or worked on a farm or market garden or employed in an abattoir or as a butcher				
No	77	523	1·0	
Yes	94	261	2·61 (1·84–3·71)	<0·001
Not known	70	0	—	
Blood transfusion				
No	118	616	1·0	
Yes	27	158	0·89 (0·57–1·40)	0·621
Not known	96	10	—	
Relative with dementia				
No	156	632	1·0	
Yes	7	148	0·20 (0·09–0·43)	<0·001
Not known	78	4	—	
Close personal contact with non-relative with dementia				
No	133	695	1·0	
Yes	26	85	1·60 (0·99–2·59)	0·055
Not known	82	4	—	
Major dental work				
No	89	403	1·0	
Yes	62	375	0·75 (0·53–1·07)	0·115
Not known	90	6	—	
Transplant recipient				
No	165	780	1·0	
Yes	2	3	2·67 (0·44–16·3)	0·288
Not known	74	1	—	
Travel abroad >1 month*				
No	48	406	1·0	
Yes	29	377	0·70 (0·43–1·15)	0·157
Not known	36	1	—	
Lived in UK >1 month in 1980s*				
No	97	718	1·0	
Yes	4	65	0·46 (0·16–1·30)	0·132
Not known	12	1	—	

All factors adjusted for age, sex, and urban or rural residence. *Cases (n=113) since 1990 only.

Table 1: **Risk of CJD by medical and demographic variables**

	Cases (n=241)	Controls (n=784)	Odds ratio (95% CI)	p
Total number of surgical procedures				
0	38	233	1·0	
1	55	241	1·36 (0·86–2·14)	0·185
2	43	154	1·67 (1·03–2·71)	0·037
⩾3	55	155	2·13 (1·34–3·41)	0·002
Not known	50	1	—	
Type of surgery				
No surgery	38	233	1·0	
Skin lesions	27	141	1·17 (0·69–2·01)	0·557
Appendix	25	115	1·33 (0·77–2·31)	0·307
Tonsils	9	93	0·59 (0·28–1·28)	0·181
Heart	11	19	3·55 (1·57–8·04)	0·002
Hip/knee	5	41	0·75 (0·28–2·01)	0·565
Hysterectomy	28	58	2·96 (1·68–5·21)	<0·001
Thyroid	4	9	2·73 (0·80–9·29)	0·109
Haemorrhoids	8	11	4·46 (1·69–11·8)	0·003
Gall bladder	18	51	2·16 (1·14–4·09)	0·018
Hernia	18	46	2·40 (1·26–4·57)	0·008
Cataract/eye	24	24	6·13 (3·16–11·9)	<0·001
Ear	3	5	3·68 (0·84–16·0)	0·083
Varicose veins	10	15	4·09 (1·71–9·76)	0·002
Carpal tunnel	6	4	9·20 (2·48–34·1)	0·001
Prostate	4	16	1·53 (0·49–4·83)	0·466
Other	89	203	2·69 (1·76–4·11)	<0·001

Factors adjusted for age, sex, urban or rural residence, except reasons for surgery or treatment.

Table 2: **Risk of CJD by surgical procedures**

State and Territory (2%). The medical histories of all cases, detected through the death certificate and hospital separation coding, were reviewed and validated on-site by a field researcher. Registry staff compiled a medical and demographic profile of each case of sporadic CJD with a standard comprehensive questionnaire (72% of cases) that was completed by the spouse or a first-degree relative (92%) and occasionally in consultation with the patient's general practitioner. Questionnaires were routinely posted to the appropriate relative or spouse for completion at his or her leisure, without time constraints; a few case questionnaires were completed by telephone interview.

The retrospective retrieval of information was more difficult the longer the time since death; the datasets least likely to be complete were for cases from the 1970s.

Controls

Controls were recruited and interviewed through a random dialling telephone survey. All interviews were in English and took place over 3 days at the end of August, 1997. We developed an abridged questionnaire for controls to find out: surgical procedures; specific selected non-surgical hospital treatments (controls were asked about dialysis, chemotherapy, radiotherapy, and arterial embolisation); temporally separate episodes of blood transfusion; recipience of organ transplantation; major dental work (beyond fillings and dental hygiene); travel outside Australia for longer than 1 month (including specifically to the UK); residence or employment on a farm (of any type including a market garden); work in an abattoir or as a butcher; relative with dementia; and close personal contact with a person with dementia who was not a relative. This abridged questionnaire was specifically based on that used for cases, with the retained questions selected because of their a priori relevance to transmission of CJD. However, telephone interviews necessitate more direct questions, and the responses captured, if possible, through a restricted series of options rather than through an open-ended approach.

We intended to interview 750 controls (about three for each case of CJD), matched to the cases by age (in 5-year age groups), sex, and urban or rural residence (as defined by the Australian Bureau of Statistics[16]) and in proportion to the resident population of each State and Territory. Listed telephone numbers were called randomly and on answer we asked for the oldest man in the household to give his verbal consent to the interview. If the relevant male age stratum was already completed, or if no man was available in the household, the oldest woman was asked to give her consent. In each case, we sought the oldest person in the household because of the age distribution of CJD cases.[5] A person in an incomplete age and sex stratum who gave his or her consent was directly questioned. We did not seek independent corroboration of the volunteered information, nor verify data provided by respondents from independent sources such as general practitioners.

Statistical analysis

Cases and controls were compared by standard logistic regression techniques. All analyses were adjusted for age, sex, and urban or rural residence. Because of the incompleteness of datasets in the cases from the 1970s, we did statistical analyses for the 128 sporadic CJD cases that occurred after 1987, and all 241 cases from 1970. In view of the similar results, we mostly present findings for the entire group. However, analyses of travel abroad and residence in the UK in the 1980s were based on cases of CJD diagnosed after 1989.