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Creutzfeldt–Jakob Disease in Recipients of Corneal Transplants

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Abstract

Purpose: Creutzfeldt–Jakob disease (CJD) transmission has been documented to occur from the use of corneal grafts. We report 4 cases of CJD with a history of corneal transplantation and assess the frequency of coincidental CJD among corneal transplant recipients.

Methods: Medical records and eye bank documents were reviewed. Genetic and neuropathologic tests on available specimens were performed at the National Prion Disease Pathology Surveillance Center. Statistical analyses were used to determine the expected number of coincidental CJD cases among the US population with a history of corneal transplantation.

Results: Four CJD decedents with histories of corneal transplantation were identified: 3 from the United States and 1 from Japan. The time from transplant to onset of CJD symptoms ranged from 2 years, 11 months to 18 years. Available eye bank records did not suggest evidence of neurologic illness in the donors. Using corneal transplantation and CJD death data from 1990 through 2006, statistical analyses suggest that a case of coincidental sporadic CJD will occur among the population of corneal transplant recipients approximately every 1.5 years.

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Conclusions: It is likely that these 4 recipients of transplanted corneas had sporadic CJD. Because of the many corneal transplantations performed each year in the United States, occasional cases of sporadic CJD in this population are expected.

Keywords

Creutzfeldt–Jakob disease; transmissible spongiform encephalopathy; prion disease; iatrogenic; corneal transplant

Creutzfeldt–Jakob disease (CJD) is a transmissible spongiform encephalopathy (TSE) with an incidence of ~1 case per million population per year in the United States.[1] It is always fatal, with most cases occurring sporadically and only a small proportion of cases having an iatrogenic origin.[1] CJD transmission has been documented to occur from the use of contaminated cadaveric pituitary-derived gonadotropin and human growth hormone, dura mater grafts, neurosurgical instruments, electroencephalogram (EEG) depth electrodes, and corneal grafts.[1,2] The use of pituitary-derived human growth hormone and dura mater grafts account for most iatrogenic CJD cases[1,2]; only 6 cases of corneal graft–associated CJD have been reported.[2–4] This report describes 4 additional instances of CJD in corneal transplant recipients and offers an evaluation of the expected occurrence of coincidental CJD among those persons with transplanted corneas.

CJD cases with a history of corneal transplantation were reported to the Centers for Disease Control and Prevention (CDC), and medical records for these cases were reviewed to assess each patient's illness and the presence of any additional CJD risk factors. If possible, records from the eye bank that processed the corneas were examined to gather information on the cornea donors and on the recipients of the donors' other corneas. Genetic and neuropathologic tests on available specimens were performed at the National Prion Disease Pathology Surveillance Center (NPDPSC).[5]

The expected number of coincidental CJD cases among corneal transplant recipients from 1990 through 2006 was calculated by using the following data: (1) the annual number of corneal transplantations in the United States, (2) the approximate age distribution among the recipients, and (3) the average annual mortality rates for 1990–2003 for CJD and for deaths of all causes excluding CJD by age group (<55, 55–64, 65–74, and ≥75 years old). From data from the Eye Bank Association of America (EBAA) from 1997 and 1998, it was estimated that 35% of corneal transplant recipients were <55 years old, 10% were 55–64 years old, 10% were 65–74 years old, and 45% were ≥75 years old.[6] There was no adjustment for multiple transplantations. The person-years of follow-up among corneal transplant recipients since 1990 were calculated. Person-years were adjusted by removing the expected number of deaths by CJD and all other causes annually and by movement of person-years to older age groups to account for aging within the corneal transplant recipient population; the remaining person-years for each year were carried over to the subsequent years of follow-up. The expected number of CJD cases per year by age group was calculated by multiplying the age group's annual person-years of risk by its average annual CJD rate. By assuming a Poisson distribution, a 95% confidence interval for the total number of expected CJD cases for the study period was calculated.

CASE REPORTS

Case 1

A 67-year-old man who traveled regularly to Europe experienced gait imbalance, dizziness, and decreased handwriting abilities in early July 2000. These symptoms progressed, and the next month he began to suffer from cognitive impairment and some forgetfulness. By early September, the patient was increasingly confused and walking with a cane. At this time, he was diagnosed with carbon monoxide poisoning caused by high levels of carbon monoxide in his apartment. Treatment and rehabilitation yielded brief improvement in his condition, but midway through October, the patient began to progressively decline. By the end of the month, he had severe rigidity and ataxia, was nearly mute with incomprehensible speech, could no longer walk, and was extremely impaired cognitively. Magnetic resonance imaging (MRI) showed signal abnormality in the basal ganglia, thalami, and hippocampi bilaterally, and an abnormal EEG was consistent with encephalopathy. He died in December 2000 at the age of 68 years after an illness of ~5-month duration. A prion disease diagnosis by Western blot and immunohistochemical analyses of biopsy samples and autopsy brain tissues was confirmed at the NPDPSC. Prion protein gene (PrP) sequencing was used to further characterize the disease as being consistent with sporadic CJD type VV2. No PrP mutations were identified, excluding a genetic form of the disease.

The patient had a chronic history of macular edema and glaucoma and was the recipient of two corneas, 1 in January 1989 and 1 in August 1990, 11 years, 5 months and 9 years, 10 months before CJD onset, respectively. The donor of the first cornea was a 44-year-old man who had quadriplegia since 1961 and died in late December 1988 of myocardial infarction and respiratory failure. No evidence of a prion disease was noted on eye bank records. The donor’s other cornea was given to an 18-year-old man who was lost to follow-up. The second cornea donor was a 16-year-old boy who died in August 1990 of multiple trauma caused by a motor vehicle accident. This donor had no evidence of neurologic disease or dysfunction, and there was no history of human growth hormone administration. His other cornea was implanted in a 45-year-old woman who was also lost to follow-up.

Case 2

A 59-year-old woman became ill in August 2002 and was admitted to a hospital in Japan in October for a neurologic disorder. She experienced progressive dementia, myoclonus, cerebellar signs, extrapyramidal signs, and akinetic mutism. MRI findings were typical, and an EEG showed periodic synchronous discharges. She died in December 2002, ~4 months after illness onset. The Japanese Surveillance Committee classified this case as probable sporadic CJD. Consent for autopsy was refused by the family.

To treat corneal opacity in her right eye because of leukoma, the patient had received a cornea procured from a US eye bank in September 1999, 2 years, 11 months before CJD onset. The donor was a 73-year-old woman who died of lung cancer. No neurologic symptoms were reported in the donor, no family history of degenerative neurologic disease was noted, and the donor never received any organ or tissue transplant. She had a history of travel to France, England, Ireland, and Germany for an unknown length of time. The other

cornea recipient was a 20-year-old man treated for keratoconus. As of early 2007, this recipient was in good health.

Case 3

A 56-year-old man became forgetful and depressed in 2003 and had difficulty using appliances and equipment at home and work. In April 2004, he quit his job because of trouble remembering details. In August of that year, he was diagnosed with a transient ischemic attack associated with monocular vision loss, and he was treated with Coumadin for a left atrial thrombus. Short-term memory problems became much more prominent, and he became increasingly disorganized. By late 2004, his gait was slower, and significant language problems had developed. Beginning in 2005, the patient suffered from hallucinations and delusions. Cerebrospinal fluid 14–3-3 protein analysis performed at the NPDPSC was reported as ambiguous. However, the MRI and EEG results were suggestive of a diagnosis of CJD. The patient died in April 2006 at the age of 58 years after an illness duration of ~3 years. A diagnosis of prion disease by Western blot and immunohistochemical analyses of autopsy brain tissue was confirmed at the NPDPSC. PrP gene sequencing was used to further characterize the disease as being consistent with sporadic CJD type MV2. No family history of CJD or PrP gene mutations were identified.

Because of advanced keratoconus in his right eye, the patient had received a corneal transplant in July 1985, ~18 years before the onset of symptoms. The donor was a 17-year-old boy who committed suicide by hanging; further records on the donor and the status of his other cornea are unavailable.

Case 4

In April 2006, a 66-year-old man presented to the emergency department with confusion and a 3-week history of gait instability and trouble walking. The patient’s wife reported that he had been experiencing dizziness for the past 8–10 weeks and was evaluated for this condition a few weeks prior. The patient also reported that he had experienced some shakiness. MRI of the brain showed evidence of small vessel ischemic changes of the periventricular white matter and centrum semiovale. An EEG showed no epileptiform abnormalities or asymmetries. The patient’s workup did show severe cervical spine stenosis at C3–C4, and a cervical laminectomy was therefore performed. The patient did poorly postoperatively, developing a significant encephalopathy and tremor. Abnormal EEG readings were indicative of generalized encephalopathy. Cerebrospinal fluid protein 14–3-3 was positive, and a diagnosis of CJD was considered. The patient died in July 2006 after an illness duration of 4.5 months. Western blot and immunohistochemical analyses of autopsy brain tissue at the NPDPSC confirmed a prion disease diagnosis which PrP gene sequencing further characterized as being consistent with sporadic CJD type VV2.

The patient had undergone penetrating keratoplasty for corneal edema in his left eye in August 1998, 7.5 years before CJD onset. The donor of the cornea was a 59-year-old man who died of myocardial infarction. Although no autopsy was performed, no neurologic symptoms were reported. There was no family history of CJD or history of travel by the donor outside of the United States. His other cornea was implanted in an 87-year-old woman

who died <2 years later of atherosclerotic heart disease, with no mention of prion disease on the death certificate.

Statistical Analysis

During 1990 through 2006, an average of 34,145 corneal transplantations were performed annually in the United States.[7] The average annual CJD mortality rates for 1990–2003 by age group were 0.142 (<55 years old), 2.900 (55–64 years old), 5.327 (65–74 years old), and 4.198 (≥75 years old) per million person-years, and the average annual mortality rates for all causes excluding CJD by age group were 1716, 10,599, 24,918, and 80,751 per million person-years, respectively. Statistical analyses suggest that, for the period 1990–2006, ~11 cases (95% confidence interval: 5, 20) of coincidental sporadic CJD in corneal transplant recipients would be expected to occur, or ~1 case every 1.5 years. Most of these cases (87.0%) would be expected to be among patients ≥65 years old.

DISCUSSION

Our review of the scientific literature found 6 previously reported corneal graft-associated cases of CJD (Table 1). The risks of CJD transmission in 5 of these cases were characterized as definite (1 case), probable (1 case), or possible (3 cases).[3] The definite case, reported in the United States in 1974, involved a 56-year-old woman who died of autopsy-confirmed CJD after an 8-month illness. She had received a corneal graft 18 months before illness onset from a donor with autopsy-confirmed CJD.[3,8,9] The probable case of transmission of CJD through corneal transplantation was reported in Germany in 1997. This case involved a 46-year-old woman who died of clinically typical, but not autopsy-confirmed, CJD after an 8-month illness. She had received 2 corneal transplants, 1 of which was from a donor with autopsy-confirmed CJD 30 years earlier.[3,9,10] All 3 possible cases of CJD transmission through corneal transplantation died of confirmed CJD; however, information to confirm CJD in the cornea donors was unavailable.[3,11,12] The sixth reported corneal graft–associated CJD case died of autopsy-confirmed CJD[4]; the donor died of heart disease with no apparent neurologic symptoms, and information on the recipient of the other cornea was not available (U. Heinemann, personal communication, 2007).

Although the 4 patients in this report had a diagnosis of CJD, 3 of which were confirmed by autopsy, it is unlikely that their CJD deaths were related to the corneal transplantations. Interestingly, although VV2 and MV2 are not the most common subtypes of sporadic CJD, all 3 CJD cases with tissue examined by Western blotting and immunohistochemical analysis were characterized as sporadic CJD type 2 carrying at least 1 allele with valine residue at codon 129. However, there is no evidence in the available eye bank records to suggest that any of the cornea donors had CJD, and the young age of 3 of the donors argues against their incubating this disease. Although 2 recipients of paired corneas were unfortunately lost to follow-up, their corneas came from 2 of these young donors, 16 and 44 years of age, respectively. About 80% of CJD deaths reported to the CDC annually are 60 years of age or older.[1]

From our analyses, in the United States for the period 1990–2006, ~11 coincidental cases of CJD would be expected to occur in corneal transplant recipients. This number may be a

slight overestimate because no adjustment was made in the analysis for multiple corneal transplantations (in 2006, 14.1% of transplants[13]); however, any overestimate may be offset somewhat because those persons who received corneas before 1990 were not accounted for in the analysis. Because our expected number of 11 cases is higher than the number of cases actually observed, there are probably additional unidentified CJD cases among corneal transplant recipients that have occurred in the United States. Among these unidentified cases, a definite case of transmission may have occurred. However, donor screening procedures instituted to minimize the risk of CJD transmission are likely to have markedly reduced the probability of such a transmission. The EBAA has produced guidelines for the screening of cornea donors that specify exclusion of potential donors who have a TSE diagnosis.[14] A donation is also contraindicated if it is from a donor with a family history of CJD, unknown cause of death, dementia (with exceptions), or neurologic disease of unestablished diagnosis.[14] New EBAA standards for record maintenance developed after the reporting of a corneal graft–associated CJD case in 2002, which specify the perpetual retention of certain cornea donor and recipient data, will also make it easier to identify any CJD link between donor and recipient when future CJD cases with a history of corneal transplantation are identified.[3] As shown by the potential incubation period of 30 years in the probable case of CJD transmission, a history of corneal transplantation in CJD cases should not be dismissed as a risk factor because of the date of transplantation alone.

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TABLE 1.

Corneal Transplantation–associated CJD Cases

Reference	Year of Death/Report	Country of Report	Recipient Age at Death/CJD Onset (y)*	Possible Incubation Periods	Donor Information	
					Age (y)	Cause of Death
Duffy et al[8]	1974†	United States	56	1 y, 6 mo	55	Autopsy-confirmed CJD
Uchiyama et al[11]	1992	Japan	63	1 y, 3 mo	NA	NA
Heckmann et al[10]	1996	Germany	46	30 y	63	Autopsy-confirmed CJD
				12 y	NA	NA
Rabinstein et al[12]	2002†	United States	56‡	6 y; 4 y; 2 y	NA	NA
Hammersmith et al[3]	2002	United States	80	23 y, 8 mo	NA	NA
				14 y, 6 mo	40	NA
Heinemann et al[4]	2005	Germany	62‡	13 y	NA	Heart disease
Case 1	2000	United States	68	11 y, 5 mo	44	Myocardial infarction and respiratory failure
				9 y, 10 mo	16	Trauma (motor vehicle accident)
Case 2	2002	Japan	60	2 y, 11 mo	73	Lung cancer
Case 3	2006	United States	58	18 y	17	Suicide
Case 4	2006	United States	66	7 y, 6 mo	59	Myocardial infarction

*All recipients' CJD diagnoses confirmed by autopsy except patient reported by Heckmann et al and case 2.

†Year of case report.

‡Patient's age at illness onset.

NA, not available.