Eye Banking and Screening for Creutzfeldt-Jakob Disease

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Objectives: To quantify the risk of Creutzfeldt-Jakob disease (CJD) among cornea donors, evaluate supplemental screening strategies, and address concerns about the adequacy of current methods of screening tissue donors in the United States.

Methods: Reported data on deaths due to CJD and from all causes were used to estimate the rate of CJD among cornea donors. The impact of increased screening on risk of CJD and donor supply was evaluated.

Results: Only 1.3 of the approximately 45,000 cornea donors in the United States each year might be expected to have CJD. Most of the estimated risk (91%) is due to preclinical (asymptomatic) disease and therefore could not be eliminated by screening for signs or symptoms. If only the highest-risk age group (60 to 69 years) were screened and specificity were 90%, more than 21,000 otherwise acceptable donors would incorrectly be excluded over a period of 17.5 years to correctly exclude a single donor with symptomatic CJD.

Conclusions: Currently, the risk of CJD transmission following cornea transplantation is remarkably low. Screening for symptoms of CJD would have minimal impact on safety, but would reduce donor supply and likely result in many patients not receiving needed treatment.


IT HAS BEEN KNOWN since 1974 that Creutzfeldt-Jakob disease (CJD), a transmissible spongiform encephalopathy, can be transmitted from person to person through cornea transplantation.1 This led to the establishment of screening criteria to prevent those with a known diagnosis of CJD (and more recently those with a family history of CJD) from being selected as cornea donors.2 Since 1974, more than 600,000 cornea transplantations have been performed in the United States without any additional reported cases of transmission of CJD. Recently, however, several factors have raised concerns about the adequacy of current screening methods.

In the United Kingdom, a new variant of CJD characterized by a relatively young age of onset has been identified and linked to the occurrence of bovine spongiform encephalopathy (mad cow disease).3-8 Because a large number of persons in the United Kingdom had likely been exposed to the causative agent (prion protein) from ingestion of affected beef or contact with products from the rendering industry during the 1980s and early 1990s, the possibility could not be dismissed that CJD would occur with increasing frequency among potential cornea donors. Thus far, no cases of variant CJD have been reported in the United States. Another factor that has focused attention on donor screening criteria has been the occurrence of 2 additional possible cases of transmission of CJD through cornea transplantation. One was reported from Japan in 1994 and the other from Germany in 1997.9,10 Also, 2 corneas and sclera were transplanted to 3 recipients in the United Kingdom from a woman who was found at autopsy to have had CJD.11 All 3 recipients underwent surgical removal of the donor tissue several months after placement, and none has yet developed CJD (approximately 2 years after removal).

In 1999, Hogan and associates11 suggested that collection of additional information concerning previous neurologic findings among potential donors would reduce the risk of transmitting CJD. Also, the Food and Drug Administration12 has issued a proposed rule that would require a “donor medical history interview” to identify cognitive, behavioral, and other possible indications of underlying disease that would preclude tissue dona-
METHODS

DIAGNOSED CJD

The frequency of occurrence of CJD among potential cornea donors in the United States was estimated from reported information on death rates of CJD, all-cause death rates, and population figures by age. Holman and associates examined US death records from 1979 through 1994 and reported no statistically significant trend in death rates of CJD over time. Consequently, we used the average annual age-specific death rates to calculate expected numbers of deaths due to CJD for the 1997 US population. The total numbers of deaths by age due to all causes were obtained from the National Vital Statistics Reports for 1997.

Currently, potential cornea donors with a known diagnosis or family history of CJD are excluded. Also, the Eye Bank Association of America medical standards for documentation of cause of death require exclusion of tissue from potential donors who died of unknown causes or of neurologic disease of unestablished diagnosis. Even with those safeguards, the possibility exists that a series of errors could potentially lead to transplantation of tissue from a donor who had the clinical diagnosis of CJD established before death. However, we are not aware that this has ever occurred. An additional threat is posed by persons who die of CJD without ever having had their disease correctly diagnosed. A consensus view of the authors is that no more than 1% of persons who die of CJD (approximately 2.6 cases per year) are not excluded by current screening criteria. This figure was used to estimate the frequency among cornea donors of CJD due to persons who had the diagnosis or died of the disease.

SYMPTOMATIC BUT UNDIAGNOSED CJD

Separate estimates were made of the risk posed by potential donors who died of causes unrelated to CJD but who had either preclinical disease (the phase before symptoms of CJD have developed) or symptomatic disease that had not yet been diagnosed. Survival following onset of symptoms of CJD is generally no longer than a few months. In a recent review of iatrogenic CJD, Gibbs had previously observed a range of 16 months to 30 years from exposure to onset of CJD among 267 patients. Johnson and colleagues reported a range of 16 months to 17 years among more than 80 patients who had received dura mater grafts. The interval from onset of preclinical disease to onset of symptoms (estimated to be 10 years), age-specific death rates of CJD, US population figures, and age-specific death rates based on all causes of death were used to estimate the annual numbers of potential donors who had preclinical CJD. It was assumed that none of those potential donors would be identified and excluded by current screening criteria.

CORNEA DONOR DATA

Data from the Eye Bank Association of America concerning the age distribution of cornea donors in 1998 (the most recent data available) were used to estimate the proportions of all deceased individuals (potential donors) by age who meet the selection criteria and become donors. Those proportions (cornea donor fractions) were multiplied by the estimated numbers of deceased individuals who either died of CJD and were not excluded by the screening criteria or who had preclinical or symptomatic disease. This provided estimates of the annual numbers of donors by age that could potentially transmit CJD to cornea recipients.

RESULTS

DIAGNOSED CJD

The average annual age-specific death rates of CJD based on a study of US death records from 1979 through 1994 selected as a cornea donor. The mean duration of symptoms before diagnosis (estimated to be 6 months), age-specific death rates of CJD, US population figures, and age-specific death rates based on all causes of death were used to estimate the annual numbers of potential donors with symptomatic (but not yet diagnosed) CJD. It was assumed that none of those potential donors would be identified and excluded by current screening criteria.

PRECLINICAL (ASYMPTOMATIC) CJD

There is only limited information concerning the intervals from onset of preclinical disease to development of symptoms of CJD. In a recent review of iatrogenic CJD from all causes, including use of contaminated neurosurgical instruments or intracerebral electroencephalogram electrodes, placement of human dura mater grafts, treatment with cadaveric human growth hormone or gonadotropin, and cornea transplantation, Brown and associates reported a range of 16 months to 30 years from exposure to onset of CJD among 267 patients. Johnson and colleagues had previously observed a range of 16 months to 17 years among more than 80 patients who had received dura mater grafts. The interval from onset of preclinical disease to onset of symptoms (estimated to be 10 years), age-specific death rates of CJD, US population figures, and age-specific death rates based on all causes of death were used to estimate the annual numbers of potential donors who had preclinical CJD. It was assumed that none of those potential donors would be identified and excluded by current screening criteria.

SYMPOMATIC AND PRECLINICAL CJD

The numbers of persons by age who at any given time would be expected to be symptomatic but not diag-
nosed as having CJD are shown in Table 2. Death rates based on all causes of death were used to calculate the numbers of such persons who would be expected to die each year. Because of the much longer assumed duration of the incubation period (10 years) than the symptomatic period (6 months), the estimated frequencies of potential donors with preclinical disease (incubating CJD) are much greater.

TOTAL CJD RISK AMONG CORNEA DONORS

Although the Eye Bank Association of America does not provide data on age by 5-year intervals, the estimated proportions of all deceased individuals who become cornea donors are similar in the age range of 21 to 70 years (Table 3). The age-specific proportions were used to estimate the annual numbers of cornea donors who might be expected to have had preclinical or symptomatic disease or to have had the diagnosis or died of CJD (Table 4). The overall estimate of 1.3 cornea donors with CJD among the annual total of approximately 45000 donors in the United States is equivalent to a rate of approximately 1 per 35000 cornea donors. Most of the estimated risk (approximately 91% of total risk) is due to preclinical disease.

IMPACT OF INCREASED SCREENING FOR CJD

The numbers of otherwise suitable donors who might incorrectly be excluded to correctly exclude a single donor with symptomatic or diagnosed disease (who without screening based on symptoms would remain in the donor pool) were calculated for various levels of speci-

Table 2. Expected Annual Deaths Among Patients With Preclinical or Symptomatic Creutzfeldt-Jakob Disease in the United States

<table>
<thead>
<tr>
<th>Age, y</th>
<th>All-Cause Death Rate*</th>
<th>Living Preclinical Patients†</th>
<th>Living Symptomatic Patients‡</th>
<th>Expected Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-9</td>
<td>957</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10-14</td>
<td>232</td>
<td>0.6</td>
<td>0</td>
<td>0</td>
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<tr>
<td>15-19</td>
<td>748</td>
<td>1.6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20-24</td>
<td>986</td>
<td>3.8</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>25-29</td>
<td>1021</td>
<td>9.8</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>30-34</td>
<td>1266</td>
<td>20.8</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>35-39</td>
<td>1687</td>
<td>45.5</td>
<td>0.9</td>
<td>0</td>
</tr>
<tr>
<td>40-44</td>
<td>2397</td>
<td>93.3</td>
<td>1.7</td>
<td>0.1</td>
</tr>
<tr>
<td>45-49</td>
<td>3524</td>
<td>167.2</td>
<td>4.2</td>
<td>0.6</td>
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<tr>
<td>50-54</td>
<td>5262</td>
<td>263.1</td>
<td>7.5</td>
<td>1.4</td>
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<tr>
<td>55-59</td>
<td>8346</td>
<td>376.5</td>
<td>12.6</td>
<td>3.1</td>
</tr>
<tr>
<td>60-64</td>
<td>13 312</td>
<td>468.3</td>
<td>17.9</td>
<td>6.2</td>
</tr>
<tr>
<td>65-69</td>
<td>19 951</td>
<td>469.0</td>
<td>24.6</td>
<td>9.4</td>
</tr>
<tr>
<td>70-74</td>
<td>30 849</td>
<td>354.3</td>
<td>25.2</td>
<td>10.9</td>
</tr>
<tr>
<td>75-79</td>
<td>46 125</td>
<td>199.9</td>
<td>19.9</td>
<td>9.2</td>
</tr>
<tr>
<td>80-84</td>
<td>74 259</td>
<td>112.8</td>
<td>9.2</td>
<td>8.4</td>
</tr>
<tr>
<td>≥85</td>
<td>153 452</td>
<td>95.0</td>
<td>4.8</td>
<td>14.6</td>
</tr>
<tr>
<td>Total</td>
<td>...</td>
<td>2681.5</td>
<td>129.1</td>
<td>64.1</td>
</tr>
</tbody>
</table>

* Data are from National Vital Statistics Reports. Deaths per 1 million population, 1997.
† Estimated numbers of living preclinical patients at any point in time were derived from age-specific death rates of Creutzfeldt-Jakob disease, estimated duration of preclinical disease (10 years), and US population estimates.
‡ Estimated numbers of living symptomatic patients at any point in time were derived from age-specific death rates of Creutzfeldt-Jakob disease, estimated duration of the interval from onset of symptoms to diagnosis (6 months), and US population estimates.
60 to 69 years were screened and specificity was as high as 90%, tissue from approximately 21,580 donors would incorrectly be discarded over a period of 17.5 years to exclude 1 donor with symptomatic or diagnosed disease. The numbers of otherwise suitable donors not selected (per donor with disease appropriately excluded) would be much greater if screening were applied to a broader age range of donors or if the sensitivity of screening were less than 100%. Moreover, donor exclusion based on age alone would not be an attractive strategy. If all donors aged 60 to 69 years were excluded, more than 19,000 donors would be eliminated for each case of CJD removed from the donor pool.

**Table 5. Estimated Numbers of Otherwise Suitable Donors Incorrectly Excluded by Screening for Symptoms Suggestive of Creutzfeldt-Jakob Disease (CJD) per Donor With Disease Correctly Excluded**

<table>
<thead>
<tr>
<th>Age Range (y)</th>
<th>% of All CJD Deaths Screened, Donors Screened</th>
<th>Required No. of Years Screening</th>
<th>% of CJD Died of CJD</th>
<th>% of Donors Incorrectly Excluded by Specificity of Screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>100</td>
<td>100</td>
<td>8.1</td>
<td>18,415</td>
</tr>
<tr>
<td>≥60</td>
<td>79</td>
<td>98</td>
<td>8.3</td>
<td>14,882</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>33</td>
<td>17.5</td>
<td>10,790</td>
</tr>
</tbody>
</table>

*Donors with CJD correctly excluded by increased screening are defined as those who without screening based on symptoms would remain in the donor pool. The estimated annual numbers of such donors are shown in the "symptomatic disease" and "died of CJD" columns in Table 4. For these calculations, it was assumed that the sensitivity of screening would be 100% (ie, all donors with "symptomatic disease" or "died of CJD" as estimated in Table 4 would be excluded by the screening process). The calculations are based on the volume and age distribution of cornea donors in the United States as reported by the Eye Bank Association of America for 1998.19

†The number of years of screening required to correctly exclude 1 donor with disease is the inverse of the sum of the estimated numbers of such donors as shown in the "symptomatic disease" and "died of CJD" columns in Table 4 for the age categories being screened. The number of years of screening were multiplied by the annual numbers of donors in the corresponding age categories. The indicated levels of specificity were applied to these figures to calculate the numbers of otherwise suitable donors who might incorrectly be excluded.

**COMMENT**

SCREENING FOR CJD

Currently, it is not possible to identify and exclude individual potential donors who had preclinical disease because no laboratory test suitable for widespread screening is available. Possible strategies to improve safety could be based on exclusion of potential donors in the age groups at highest risk or on more intensive efforts to identify the estimated small number of donors (approximately 1 case among every 368,000 donors) with a known diagnosis or symptoms of CJD who are missed by current screening methods. Hogan and associates11 previously suggested the latter approach. Also, the Food and Drug Administration included a requirement for a “donor medical history interview” to identify cognitive, behavioral, and other possible indicators of underlying disease in a recently proposed rule.12

Even if a supplemental screening approach were available that could identify all potential donors with a known diagnosis or symptoms of CJD (sensitivity of 100%), it might not be practical to use unless the specificity (proportion of those without disease who are correctly identified) were sufficiently high. Frequent clinical features of CJD include cognitive impairment (personality and behavioral changes, disorientation, and memory loss), myoclonus, cerebellar dysfunction, speech abnormalities, and visual impairment.11,16,17 The overlap of symptoms with common age-related findings among elderly people (eg, mental deterioration) would tend to limit the specificity of screening based on symptoms suggestive of CJD and lead to large losses of otherwise suit-
able cornea donors (Table 5). Also, the clinical information would not generally be collected by neurologists or other physicians but by technicians with limited medical training, and family members and other respondents might have considerable difficulty in judging and agreeing whether a potential donor had a particular symptom. If the percentage of persons who die of CJD and are not excluded by current screening criteria is actually much higher than has been assumed for our analyses (eg, 5% or 10% instead of 1%), it would imply that many patients have clinical findings and courses that are sufficiently atypical for the diagnosis of CJD not to be established. The effect of such an assumption would be to increase the number of donors with CJD, but expansion of screening criteria based on this possibility would likely further erode the specificity of screening and not have a favorable cost-to-benefit ratio.

DEMAND FOR DONOR CORNEAS

There are sufficient donor corneas to meet current demand in the United States, but worldwide demand will far exceed supply for the foreseeable future. Consequently, loss of donor corneas due to more intensive screening would have a direct impact on the number of persons who could have their vision restored by cornea transplantation and for others would likely lengthen the waiting time for surgical treatment. This view is supported by the recent initiation of a study sponsored by the National Eye Institute (the Cornea Donor Study; http://www.nei.nih.gov/neitrials_script/studydtl.asp?id=80) to evaluate outcomes following use of tissue from older cornea donors. If the results are favorable, the goal will be to increase the supply and acceptance of tissue from older donors. Also, concerns have been expressed that growth in the volume of refractive surgical procedures may constrain future availability of donor corneas. It is important, therefore, that consideration of new screening requirements take into account the likely impact on supply of donor corneas and that the supply not be limited unnecessarily.

LEGISLATIVE CONSENT FOR DONOR CORNEA PROCUREMENT

In some states, the law allows for procurement of donor corneas by the medical examiner or coroner through a legislative consent process that does not require communication with the next of kin. Although current federal regulations require a “donor medical history interview,” there is an exception for corneas obtained through legislative consent. The recently proposed rule drafted by the Food and Drug Administration would eliminate this exception.12 If the donor’s next of kin, acquaintances, or primary treating physician must be interviewed about symptoms suggestive of CJD, the number of donors obtained through legislative consent will be substantially reduced (possibly by as much as 90%) because of the difficulty in locating appropriate individuals to interview during the short time available for procurement following the frequently sudden, unexpected, and traumatic deaths that are evaluated by medical examiners and coroners. At present, approximately 10% of all cornea donors in the United States are obtained through legislative consent. Data concerning the age distribution of those donors were collected from the Florida Lions Eye Bank, the Lions Eye Bank of Texas, and Tissue Banks International. The data show that in 1998 approximately 50% of cornea donors were 40 years or younger (compared with 15% among all donors). Based on those data, we estimate that the overall risk of preclinical, symptomatic, and diagnosed CJD in this subgroup is about 40% less than the estimated preclinical risk alone among all other donors. This should more than compensate for any potential increase in risk due to less complete ascertainment of information concerning family medical history because only about 13% of patients with CJD have a family history of the disease.16,17 Consequently, the data support the view that more intensive screening of donors obtained through legislative consent might actually reduce the level of safety rather than enhance it because of the loss of a large proportion of those donors. It should be noted that ethical concerns have been expressed about the process of obtaining legislative consent, but those concerns do not center on the issue of risk due to CJD.

TRANSMISSIBILITY OF CJD

For several reasons, our estimate of the annual number of cornea donors with CJD (Table 4) is greater than the number of cornea recipients who might be expected to develop the disease. Data from the Eye Bank Association of America indicate that more than one third of donated tissue is either not suitable for transplantation or is used for research or training purposes.19 Also, various biologic factors may influence the likelihood of transmission even if a recipient were to receive tissue from an affected donor. For example, genetic homozygosity for methionine at codon 129 (present in approximately 50% of the general population) is overrepresented (80%) in patients with iatrogenic CJD.18,20 In addition, attempts to transmit disease to experimental animals fail for 10% of patients with the most common form of CJD (sporadic disease).16

In the United States, more than 600,000 donor corneas have been transplanted without any additional reports of CJD transmission since 1974. This would require at least 300,000 donors (2 corneas per donor). Using our overall estimated rate of CJD among donors, it can be calculated that 8.6 of those donors (99% confidence interval, 8.3-9.0) would be expected to have had preclinical, symptomatic, or diagnosed CJD. Although CJD transmission to cornea recipients could potentially have occurred and not been identified or reported, biologic and other factors probably account for much of the lower than expected rate of disease among recipients. For this reason, we believe the estimates of otherwise suitable donors who would be excluded by screening (Table 3) understate the numbers who would be excluded per case of CJD transmission prevented among cornea recipients.

CONCLUSIONS

The risk of disease transmission following cornea transplantation is remarkably low with use of current prac-
tices for excluding potential donors with a known diagnosis or family history of CJD. Our analyses indicate that increased screening based on signs and symptoms would likely lead to minimal additional improvement in safety, but would reduce the supply of suitable cornea donors, particularly young donors obtained through legislative consent, and result in many patients not receiving needed treatment in a timely manner. Consequently, we would not recommend such screening. A limitation in addressing this issue, however, is the lack of data concerning actual experience with screening for symptoms of CJD, the precise number of cornea recipients who have received tissue from donors with CJD, the exact level of protection afforded by biologic and other factors, and the actual number of potential donors with CJD who are not eliminated by current screening methods. It is possible that variant CJD could be identified in the United States in the future and pose a new threat to cornea recipients. In the United Kingdom, variant CJD has occurred chiefly in adolescents and young adults (mean age, 28 years). However, preemptive screening or restriction of the supply of young donors before the occurrence of sufficient cases to document a risk from variant CJD would likely not be beneficial because the incidence rate of sporadic disease in the United States is currently much lower among donors younger than 40 years than among older donors.

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REFERENCES


From the Archives of the ARCHIVES

A look at the past . . .

A analyzing the causes of the generally known unsuitability of operations against wrong-standing eyelashes, two main points may be emphasized in this regard. Firstly, the operations are done without caring enough for the anatomical conditions. On the other hand the cicatrical shrinking does not stop even after operation, thus leading to recurrences.