Creutzfeldt-Jakob disease among American Indians and Alaska Natives in the United States

Abstract—The occurrence of Creutzfeldt-Jakob disease (CJD) among American Indians and Alaska Natives in the United States was evaluated using national multiple cause-of-death data and medical information obtained from state health departments. Twelve CJD deaths were identified for 1981 through 2002, and the average annual age-adjusted death rate was 0.47 per million population. This rate was significantly lower than that for whites and similar to the rate for African Americans.

R.A. Maddox, MPH; R.C. Holman, MS; E.D. Belay, MD; J.E. Cheek, MD; K.L. Yorita, MPH; and L.B. Schonberger, MD, MPH

Creutzfeldt-Jakob disease (CJD) has a reported US annual rate of about one case per million. The Centers for Disease Control and Prevention (CDC) conducts surveillance for CJD through several mechanisms including review of national multiple cause-of-death data. Because CJD is fatal generally within a year of diagnosis, death certificate data are useful for CJD surveillance. The National Prion Disease Pathology Surveillance Center (NPDPSC), which was established in 1997 by CDC in collaboration with the American Association of Neuropathologists, augments US surveillance by performing diagnostic testing of suspected CJD patients.

The CJD death rate for whites is higher than for African Americans in the United States, but no reports have examined the occurrence of CJD among the American Indian and Alaska Native (AI/AN) population. This study describes the occurrence of CJD among AI/ANs and compares it with the incidence among whites and African Americans in the United States.

Methods. To identify CJD decedents by race, we reviewed the multiple cause-of-death data from the National Center for Health Statistics, CDC, for 1981 through 2002. The data include all deaths occurring in the United States as obtained from death certificates filed by each state. Persons with CJD (sporadic, familial, or iatrogenic) listed as a cause of death anywhere on the record were identified by searching for the International Classification of Diseases (ICD), Ninth Revision code 046.1 for 1981 through 1998 and the ICD-Tenth Revision code A81.0 for 1999 through 2002. Demographic variables such as age, sex, and state of occurrence were analyzed for AI/ANs who had these codes listed. This information was then shared with the appropriate state health departments to obtain death certificates and portions of the medical records for review. Death certificates were used to confirm coding for race and CJD diagnosis, and medical records were evaluated to classify CJD case status based on the World Health Organization (WHO) CJD case definition. To determine whether additional AI/AN CJD cases existed, we reviewed data on patients with available race information who were evaluated at NPDPSC.

CJD death rates and age-specific death rates for AI/ANs, whites, and African Americans were calculated using US census estimates for 1981 through 2002. Age-adjusted death rates were standardized by the direct method, using the standard 2000 US population age-group distribution. Poisson regression analysis was used to compare the CJD death rate for AI/ANs with that for whites and for African Americans, taking into account the age distribution of the populations.

Results. Twelve CJD deaths were identified among AI/ANs for 1981 through 2002. Thirteen CJD deaths among AI/ANs were reported; however, we excluded one death that a review of medical records revealed had been coded incorrectly. No additional deaths among AI/ANs were identified through review of NPDPSC data. As determined based on the 12 identified decedents, the average annual age-adjusted CJD death rate during the study period was 0.47 deaths per million population. This rate was lower than the age-adjusted rate for whites (p < 0.01) and similar to the rate for African Americans (table 1). Age-specific death rates for AI/ANs, particularly for the 50 to 69-year age group (p < 0.01), were consistently lower than those for whites.

CJD was listed as the primary cause of death for 10 (83%) of the 12 decedents, and cerebral vascular accident and congestive heart failure were listed as the cause of death for the remaining two decedents. Four decedents (33%) were younger than 55 years of age, and seven (58%) of the decedents were men. The decedents’ ages ranged from 39 to 85 years (median 65 years, mean 64.3 years). The 12 deaths occurred in nine states and the District of Columbia.

Death certificate, medical records, or both were obtained for 10 decedents (83%) (table 2). Seven decedents had portions of their medical records available for review. One decedent had an unusually long illness duration (6 years) but met the WHO case definition for probable CJD because of the presence of consistent clinical signs, typical EEG findings, and elevated CSF 14-3-3 protein; no brain tissue or genetic test results were available. All seven decedents had dementia, with typical EEG findings noted for five (71%). In addition, five (71%) had ataxia, four (57%) had myoclonus, and three (43%) had visual disturbances. The median illness duration for seven patients with available information was 7 months (range 2 to 72 months).
A study conducted in Washington State found that the median age at death for AI/AN CJD patients (65 years) was similar to that previously reported for the general US population (68 years).1

The life expectancy of AI/ANs is almost 4 years less than that for the general US population.9 This difference may result, at least in part, from barriers to accessing health care services,9 which could lead to the diagnosis of fewer AI/AN CJD cases. Because CJD is primarily a disease of the elderly, the lower life expectancy could potentially lower the number of CJD deaths that occur among AI/ANs. However, the age-specific CJD death rates were consistently lower among AI/ANs compared to whites, particularly for persons 50 to 69 years of age, indicating that lower life expectancy may not fully explain the difference in CJD death rates.

Multiple cause-of-death data are useful for CJD surveillance in the United States, detecting more than 80% of deaths attributable to CJD.1 For AI/AN persons identified in the database who died of CJD, we examined available medical records to verify the CJD diagnosis and the patient’s race. In these national data, race is determined by the person completing the death certificate, and correct classification of the death certificate, and correct classification of AI/AN race was more likely for decedents older than 40 years of age and for persons who did not die of cancer.10

Although clinical symptoms and disease progression can lead to a probable diagnosis, CJD cannot be confirmed without brain biopsy or autopsy. The autopsy rate of 40% reported in this study highlights the need for increasing awareness of the importance of diagnostic testing. NPDPSC provides state-of-the-art testing without charge for suspect TSE cases reported in the United States.2

This study is the first to examine and describe the occurrence of CJD among AI/ANs in the United States. Although the CJD death rate for AI/ANs was low during the study period, it is important to continue monitoring CJD occurrence among AI/ANs and to submit tissue samples for testing to confirm the diagnosis.

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References
Fascicular hypoglossus nerve lesion

Ingo Nolte, MD; Carsten Wessig, MD; and Bendszus Martin, MD, Würzburg, Germany

A 43-year-old woman had undergone left-sided hypoglossus-facialis nerve anastomosis after vestibular schwannoma surgery.

Fourteen years later MRI of the cerebellopontine angle showed normal postoperative findings. However, the left base of the tongue revealed isointense enlargement suggestive of a mass lesion whereas there was left hemiatrophy and fatty degeneration of the proximal tongue.1 These findings were compatible with fascic-ular denervation of the proximal tongue (figure, arrow) after hypoglossus-facialis anastomosis and compensatory hypertrophy of the residually innervated base of the tongue (figure, dotted arrow). This was confirmed by EMG showing spontaneous activity in the proximal left tongue and normal findings in the tongue base.

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Address correspondence and reprint requests to Priv.-Doz. Dr. M. Bendszus, Department of Neuroradiology, University of Würzburg, Josef-Schneider-Str.11, D-97080 Würzburg, Germany; e-mail: bendszus@neuroradiologie.uni-wuerzburg.de

Figure. T1-weighted image at the level of the mandible. The tongue displays signs of fatty degeneration (A, arrow). The left base of the tongue reveals isointense enlargement (A, dotted arrow). In the degenerated part of the tongue, there is no voluntary activity (B, activated units stem from the posterior part) but pathologic spontaneous activity (C, activated units stem from the posterior part). The enlarged part of the tongue shows a burst of spontaneous activity (D).

Variable benefit in neuropsychological function in HIV-infected HAART-treated patients

Lucette A.J. Cysique, PhD; Paul Maruff, PhD; and Bruce J. Brew, MBBS, MD, FRACP

In the highly active antiretroviral therapy (HAART) era, AIDS dementia complex (ADC)
still occurs, but prospective studies addressing illness activity and stability have had shortcomings:
entry has been restricted to those already with impairment, and the observation period has been relatively short.

Therefore, we sought to prospectively examine the neuropsychological performance in individuals at risk of HIV-related cognitive change and treated with HAART for 5 years.

Methods. Subjects. One hundred HIV+ individuals with stage C3 HIV disease were randomly invited to participate from the outpatient clinics at St. Vincent's Hospital. Eighty-one individuals came for a second visit at 6 months, 51 for a third visit at 15 months, and 38 for a fourth visit at 27 months. Demographic, clinical, and laboratory data are presented in table 1. Thirtyseven negative controls matched for age and education were recruited to develop norms for change and assessed at one follow-up session.

Procedure. The neuropsychological battery included the assessment of attention, learning, memory, motor coordination, complex attention/psychomotor speed, language, visuoconstruction (see Cysique et al. for additional details).

Data analysis. Decline was classified using the within SD (WSD)–based reliable change index (RCI). The control group WSD was used as the statistical reference of stability over time to compute the RCI in all individuals in the short term (6 months) and long term (27 months). To identify HIV+ individuals with significant cognitive decline over the first 6 months, we defined it as an RCI of less than –1.96 on two or more of the 10 tests. To identify which of the neuropsychological tests was most sensitive to HIV-related cognitive change, we compared performance on each of the 10 measures between the HIV+ with cognitive decline and HIV+ without (nondecliners) using t tests. Six tests sensitive to HIV-related cognitive decline over the short term were used to compute a composite change score (composite RCI) to identify decline over the long term. Standardized composite RCIs of –1.96 and –1.5 were classified as abnormal (i.e., significant decline).

Relationships between demographic, treatment-related, and clinical variables were explored with the composite RCI and multiple regression as well as Pearson correlations when appropriate. To explore a potential attrition effect, HIV+ individuals who dropped out were compared at baseline with the patients who remained in the study on all variables, and no differences were found. The rate of decline between dropout cases and remaining participants was also explored and no differences were found.

Results. Over the short term, the prevalence of neuropsychological decline was higher in the HIV+ group than in controls (30% vs 13%, p < 0.05). HIV+ decliners and nondecliners differed on six neuropsychological measures (effect sizes >0.4): domains of verbal learning, memory, motor coordination, psychomotor speed, and complex attention (these were retained to compute the composite RCI). When decline was defined as an RCI of less than –1.5 SD and based on the six measures to develop the composite RCI, we found that 13 individuals were classified as decliners. When the 10 initial measures were used to develop a composite RCI, we also found that 13 individuals were classified as decliners. Therefore, fewer tests did not alter significantly the frequency of classification of decline. Moreover, of the 13 decliners, nine individuals were identical in both composite RCI representing a 70% agreement in the classification of decline.

Based on the composite RCI, the prevalence of decline varied between 5.88% and 13.72% at session III and remained static at 5.26% at session IV. The profile of change for individual cases is illustrated in the figure.

Cognitive decline over the long term was related to lower nadir CD4 cell counts, past depressive episode, past HIV-related brain diseases, and initial number of AIDS-defining illnesses. Individuals with a longer disease duration, older individuals, and individuals with lower level of education showed improvements in cognitive performance over time. Self-reported anxiety and depressive symptoms were also associated with decline in cognitive functioning. Complex attention was positively associated with the presence of at least three neuroactive antiretrovirals composing HAART (neuroactive was defined as a HAART regimen including at least three neuroactive antiretrovirals). Current CD4 cell count and plasma viral load were not associated with cognitive performance overtime (table 2).

Discussion. In this study, we examined the extent to which cognitive function changed overtime in HAART-treated individuals with advanced HIV infection. First, we found that 30% of HIV+ participants showed reliable cognitive decline over the short term, but the majority improved over the long term, albeit with considerable variability. Second, change in cognitive performance was not related to...
HAART optimization, at least when plasma viral load was considered. Third, cognitive deterioration over the study period was as frequent in participants with an undetectable or detectable plasma viral load. Fourth, a three-neuroactive drug regimen was associated with better complex attentional function. Finally, lower nadir CD4 cell counts were associated with cognitive impairment in the long term.

When the stability of cognitive function was considered over the longer term, it became evident that the initial cognitive decline was generally not sustained. The illustration of individual profiles shows six cases of sustained cognitive decline over the study period. Another pattern observed in the data was an abrupt decline from one session to another with a mild improvement afterward, but incomplete recovery (three cases). The attrition rate may have only partially altered the ability to detect more decliners because the proportion of decliners and non-decliners was not different in the patients who remained and those who dropped out.

Some factors may render long-term analyses complex in HAART-treated advanced HIV+ patients. We found that the course of HIV-associated cognitive impairment may vary in individuals according to age and education in a counterintuitive way. Performance on neuropsychological tests was more likely to improve over the study period in older and less educated individuals. This has been observed in other studies and interpreted to reflect the combined effects of regression toward the mean and task familiarization.9

The reason that performance stabilized in the majority of participants over time may reflect the efficacy of HAART.3 This may be a consequence of the nature of the drugs used in the HAART regimen, but importantly it is not related to control of the plasma viral load. It also means that an undetectable viral load is no guarantee against cognitive deterioration. Across the study period, between 8% and 34% of individuals with undetectable viral load declined. It is therefore important to search for new HIV illness markers that are associated with cognitive change (such as host susceptibility to cognitive impairment10). We also found that factors such as past depressive episode and the presence of past HIV-related brain diseases play a role in the occurrence of decline.

Our finding that the majority of patients showed improved neuropsychological performance argues...
strongly against the possibility that burn-out or inactive HIV-related brain disease is common. Indeed, it argues against the possibility of stable disease. Previously, we found no change in the prevalence of neuropsychological impairment in neurologically asymptomatic patients between the pre-HAART and HAART eras. This was despite the known efficacy of HAART in improving HIV-related brain disease. There are at least two possible explanations. First, HAART was ineffective because the deficits were "old," representing inactive or burnt-out disease, or HAART was variably effective with some improving and others deteriorating, leading to no net change. Given the current results, it appears that HIV-related brain disease in most patients is still dynamic. The net lack of change seen in our previous study may be explained by a bidirectional flow: net improvement in neuropsychological performance in asymptomatic patients counterbalanced by net improvement in dementia patients to an asymptomatic but still impaired state.

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Correction

Fascicular hypoglossus nerve lesion

In the NeuroImage, “Fascicular hypoglossus nerve lesion” (Neurology 2006;66:441) by Ingo Nolte, Carsten Wessig, and Martin Bendszus, the author Martin Bendszus was incorrectly listed as Bendszus Martin. The publisher regrets this error.