Encephalitis-Associated Hospitalizations among American Indians and Alaska Natives

Jason M. Mehal,* Robert C. Holman, Neil M. Vora, Jesse Blanton, Paul H. Gordon, and James E. Cheek

Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, and Epidemic Intelligence Service, Centers for Disease Control and Prevention, Atlanta, Georgia; Public Health Program, Department of Family and Community Medicine, University of New Mexico Health Sciences Center, Albuquerque, New Mexico; Northern Navajo Medical Center, Indian Health Service, Shiprock, New Mexico

Abstract. Encephalitis produces considerable morbidity in the United States, but morbidity rates among American Indian/Alaska Native (AI/AN) people have not been described. Hospitalization records listing an encephalitis diagnosis were analyzed by using Indian Health Service direct/contract inpatient data. For 1998–2010, there were 436 encephalitis-associated hospitalizations among AI/AN people, an average annual age-adjusted hospitalization rate of 3.1/100,000 population. The rate for infants (11.9) was more than double that for any other age group. Death occurred for 4.1% of hospitalizations. Consistent with reports for the general U.S. population, the rate was high among infants and most (53.9%) hospitalizations were of unexplained etiology. The average annual rate during the study period appeared lower than for the general U.S. population, due particularly to lower rates in the elderly. Future community-based surveillance and mortality studies are needed to confirm these findings and examine reasons underlying the low rates of encephalitis in AI/AN people.

INTRODUCTION

Encephalitis is characterized by inflammation in the brain that leads to widespread cerebral symptoms, including seizures, impaired cognition, impaired movements, and cranial nerve disorders.^{1–3} Illness is severe, leading to death in 4–30% of persons affected^{4–9} and disability in a high proportion of survivors.⁷ Prompt diagnosis and initiation of treatment can improve outcome.^{7,10,11}

Patient history and laboratory testing aid in diagnosis, but the etiology of encephalitis goes undiagnosed in 40–80% of cases.^{3,6,7,12} Infections, such as those with herpes simplex virus and varicella zoster viruses, have historically been the most commonly identified etiologies.^{3–5,7} However, there are now more than 100 recognized infectious causes of encephalitis,^{3,5,10} and noninfectious, including immune-mediated, processes are increasingly recognized as important and potentially treatable explanations.^{13,14} The clinical presentations of infectious and noninfectious encephalitides are often indistinguishable.^{1,10,15} Driven by factors such as climate change, population migration, and globalization of food production, new infectious causes such as West Nile virus (WNV) might emerge with regularity and pose an ongoing challenge to clinical and public health professionals.^{11,16}

In the United States, an estimated average of more than 20,000 encephalitis-associated hospitalizations occur annually; in 2010, charges from encephalitis-associated hospitalizations approximated \$2.0 billion.¹⁷ Recent nationwide analyses did not include hospitalizations for American Indian and Alaska Native (AI/AN) people admitted to Indian Health Service (IHS)/tribal facilities, where most AI/AN people living on or near reservations seek medical care.¹⁸ Because many AI/AN persons on reservations live in remote rural settings, they may also be at greater risk of exposure to some infectious causes of encephalitis. Higher rates of some zoonotic diseases, such as Rocky Mountain spotted fever and hantavirus infections, have been observed for AI/AN people.^{19,20} In this study, we

analyzed IHS inpatient data to evaluate the burden of encephalitis-associated hospitalizations for AI/AN people.

METHODS

Encephalitis-associated hospitalizations among AI/AN people during 1998–2010 were analyzed by using the IHS direct and contract health service inpatient visit data from the IHS National Patient Information Reporting System. These data consist of all hospital discharge records from IHS-operated, tribally operated, and community hospitals and facilities that contract with the IHS to provide healthcare services to eligible AI/AN people.^{18,21} The IHS is comprised of 12 regional administrative units (area offices) that are grouped into geographic regions: East (Nashville area), Northern Plains East (Bemidji area), Northern Plains West (Aberdeen and Billings areas), Southern Plains (Oklahoma area), Southwest (Albuquerque, Navajo, Phoenix, and Tucson areas), Alaska, and West (California and Portland areas). The IHS California and Portland administrative areas in the West region were excluded from the analysis because neither had IHS-operated or tribally operated hospitals, California did not report contract health service inpatient data by diagnosis, and Portland had limited contract health services for inpatient care.²¹

An encephalitis-associated hospitalization was defined as a hospitalization for which an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for encephalitis was listed among up to 15 discharge diagnoses (Table 1).²² The encephalitis definition and the ICD-9-CM codes were based on a recent study of encephalitis-associated hospitalizations in the United States.¹⁷

Encephalitis-associated hospitalizations were classified as having a specified etiology if at least one diagnosis belonged to one of the following cause-specific encephalitis disease categories: viral, other infectious, postimmunization, post-infectious, toxic, or other specified (Table 1). Unspecified encephalitis-associated hospitalizations, those for which the etiology was not specified, lacked a cause-specific encephalitis code. A hospitalization was considered human immunodeficiency virus (HIV)–associated if the ICD-9-CM codes 042 (HIV disease), V08 (asymptomatic HIV infection status) or 079.53 (HIV, type 2) were listed among the discharge diagnoses.

*Address correspondence to Jason M. Mehal, Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333. E-mail: jmechal@cdc.gov

TABLE 1

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Codes for Encephalitis*

Encephalitis disease category; diagnosis description	ICD-9-CM code (new code(s) with year)
Specified etiology	
Viral	
Acute bulbar poliomyelitis	045.0
Other specified non-arthropodborne viral encephalitis	049.8
Herpetic meningoencephalitis	054.3 (2007: 058.21, 058.29)
Encephalitis due to rubella	056.01
Japanese encephalitis	062.0
Western equine encephalitis	062.1
Eastern equine encephalitis	062.2
St. Louis encephalitis	062.3
Australian encephalitis	062.4
California virus encephalitis	062.5
Other specified mosquito-borne viral encephalitis	062.8
Russian spring-summer encephalitis	063.0
Louping ill	063.1
Central European encephalitis	063.2
Other specified tickborne encephalitis	063.8
Venezuelan equine encephalitis	066.2
West Nile fever with encephalitis	066.41
Rabies	071
Mumps encephalitis	072.2
Encephalitis in viral diseases classified elsewhere	323.0 (2006: 323.01)
Other infectious diseases	
Tuberculous encephalitis	013.6
Meningococcal encephalitis	036.1
Congenital syphilitic encephalitis	090.41
Syphilitic encephalitis	094.81
Toxoplasmic encephalitis	130.0
Meningoencephalitis caused by <i>Naegleria</i>	136.2 (2008: 136.29)
Encephalitis in rickettsial diseases classified elsewhere	323.1
Encephalitis in protozoal diseases classified elsewhere	323.2
Other encephalitis due to infection classified elsewhere	323.4 (2006: 323.41)
Postimmunization	
Encephalitis after immunization procedures	323.5 (2006: 323.51)
Postinfectious	
Postvaricella encephalitis	052.0
Postmeasles encephalitis	055.0
Postinfectious encephalitis (including infectious ADEM)	323.6 (2006: 323.61, 323.62)
Toxic	
Toxic encephalitis	323.7 (2006: 323.71)
Other specified	
Other causes of encephalitis (including noninfectious ADEM)	323.8 (2006: 323.81)
Unspecified etiology	
Unspecified cause of encephalitis	323.9
Unspecified viral encephalitis	049.9
Unspecified mosquito-borne encephalitis	062.9
Unspecified tickborne viral encephalitis	063.9
Viral encephalitis transmitted by other and unspecified arthropods	064

*ADEM = acute disseminated encephalomyelitis.

Annual and average annual hospitalization rates were calculated by sex, region, and age group (< 1, 1–4, 5–19, 20–44, 45–64, and ≥ 65 years) as the number of hospitalizations per 100,000 of the corresponding population. The annual IHS AI/AN population denominators for 2001–2010 were the fiscal year 2001–2010 IHS annual user populations. Because user

populations for 1998–2000 were unavailable, corresponding population denominators were estimated by subtracting the difference in annual service populations from the 2001 user population.¹⁷ The annual user population includes all AI/AN people who received IHS-funded healthcare services at least once during the previous three years.¹⁸ Annual and average annual age-adjusted hospitalization rates were calculated overall and by sex and region using the direct method with the 2000 projected U.S. population as the standard.²³

Age-specific rates were compared by using Poisson regression whereas other rate comparisons were performed using Poisson regression while controlling for age group.²⁴ Hospital length of stay was computed and was compared between groups using the Wilcoxon rank-sum test.²⁵ The most common diagnoses listed with encephalitis on hospital discharge records were examined. Chi-square tests were used to compare the proportions of hospitalizations with specified etiology as well as the proportions of hospitalizations who died. A *P* value < 0.05 was considered statistically significant.

RESULTS

Overall perspective. During 1998–2010, there were 436 encephalitis-associated hospitalizations among AI/AN people within the IHS/tribal healthcare system, resulting in an age-adjusted average annual hospitalization rate of 3.1 per 100,000 population (Table 2). The rate was similar by sex (*P* = 0.65), ranged annually from 2.1 in 2009 to 4.1 in 2003 (Figure 1), and varied by region from 1.4 in the Northern Plains East region to 6.2 in the East region (Table 2). Infants (< 1 year of age) experienced the highest age-specific rate of encephalitis-associated hospitalization (Table 2). Death occurred in 4.1% (*n* = 17) of hospitalizations overall and

TABLE 2

Average annual age-adjusted and age-specific encephalitis-associated hospitalization rate and number of encephalitis-associated hospitalizations by disease category among American Indian and Alaska Native people, IHS/tribal, United States, 1998–2010*

Characteristic	All encephalitis		Unspecified etiology		Specified etiology	
	Rate	Total no.	Rate	Total no.	Rate	Total no.
Overall	3.14	436	1.69	235	1.45	201
Sex						
M	3.14	205	1.69	110	1.45	95
F	3.14	231	1.70	125	1.45	106
Age group (years)						
< 1	11.93	29	6.17	15	5.76	14
1–4	2.75	36	1.07	14	1.68	22
5–19	1.31	63	0.93	45	0.37	18
20–44	2.02	117	1.12	65	0.90	52
45–64	5.37	142	2.46	65	2.91	77
≥ 65	4.83	49	3.06	31	1.77	18
Region						
Alaska	6.17	100	3.47	56	2.71	44
East	6.19	34	4.37	24	1.82	10
Northern Plains	1.39	14	0.55	6	0.84	8
East						
Northern Plains	3.64	73	1.99	39	1.64	34
West						
Southern Plains	1.85	64	0.99	35	0.86	29
Southwest	3.05	151	1.55	75	1.49	76

*Indian Health Service (IHS) direct and contract health service inpatient data were used. The IHS West region was excluded from the analysis because the region does not have IHS-operated or tribally operated hospitals. Average annual hospitalization rates are presented per 100,000 corresponding population, with age-adjusted rates overall and by sex and region.

FIGURE 1. Annual age-adjusted encephalitis-associated hospitalization rate by disease category and proportion of encephalitis-associated hospitalizations with specified etiology among American Indian and Alaska Native people, Indian Health Service (IHS)/tribal, United States, 1998–2010. IHS direct and contract health service inpatient data were used. Hospitalization rates are presented per 100,000 corresponding population.

10.2% of hospitalizations among those ≥ 65 years of age; there were no deaths reported for infants. The median length of hospital stay was 6 days (interquartile range [IQR] = 3–12 days) and was longer for males (median = 7 days, IQR = 4–15 days) than for females (median = 5 days, IQR = 3–11 days) ($P = 0.01$).

Specific etiologies. A viral cause of encephalitis was listed for 23.2% ($n = 101$) of encephalitis-associated hospitalizations, making this the most common cause-specific category (Table 3). Infants had the highest age-specific rate for viral etiology (5.8 per 100,000), which was nearly four times the next highest rate (persons 45–64 years of age = 1.5), and a viral etiology was listed for all infant hospitalizations of specified cause. The age-adjusted rate of viral encephalitis-associated hospitalizations was similar among males and females (0.85 and 0.64, respectively; $P = 0.26$). Herpetic menin-

goencephalitis (63.4%, $n = 64$) and WNV infection (15.8%, $n = 16$) were the most common specified causes of viral encephalitis, and all of the WNV hospitalizations occurred during 2005–2010. Most (81.2%) hospitalizations for WNV infection occurred during August and September, and hospitalizations with herpetic meningoencephalitis occurred year-round.

Other specified causes of encephalitis, representing 15.4% ($n = 67$) of encephalitis-associated hospitalizations, comprised the second most common cause-specific disease category (Table 3). The most common associated diagnosis in this category was systemic lupus erythematosus (52.2%). The age-adjusted rate among females (0.6 per 100,000) in this category was similar to that among males (0.3 per 100,000; $P = 0.11$). Postinfectious causes of encephalitis accounted for 4.6% ($n = 20$) of hospitalizations. The diagnosis of postinfectious encephalitis (revised in 2006 to infectious acute disseminated

TABLE 3

Encephalitis-associated hospitalizations among American Indian and Alaska Native people by disease category, IHS/tribal, United States, 1998–2010*

Category of encephalitis, etiology	Overall No. (%)	Age (years)			
		< 1 No. (%)	1–19 No. (%)	20–64 No. (%)	≥ 65 No. (%)
Specified etiology	201 (46.1)	14 (48.3)	40 (40.4)	129 (49.8)	18 (36.7)
Viral	101 (23.2)	14 (48.3)	20 (20.2)	56 (21.6)	11 (22.4)
Other infectious	13 (3.0)	0 (0.0)	3 (3.0)	11 (4.4)	0 (0.0)
Postimmunization	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Postinfectious	20 (4.6)	0 (0.0)	10 (10.1)	8 (3.1)	2 (4.1)
Toxic	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
Other specified	67 (15.4)	0 (0.0)	7 (7.1)	55 (21.2)	5 (10.2)
Unspecified etiology	235 (53.9)	15 (51.8)	59 (59.6)	130 (50.2)	31 (63.3)
Total	436	29	99	259	49

*More than one International Classification of Diseases, Ninth Revision, Clinical Modification code for encephalitis may be listed on each Indian Health Service (IHS)/tribal hospital discharge record.

encephalomyelitis and other postinfectious encephalitis/encephalomyelitis) accounted for most (85.0%) hospitalizations having a post-infectious cause. Other infectious causes of encephalitis were listed for 3.0% ($n = 13$) of hospitalizations. Infection with HIV was recorded for 3.2% ($n = 14$) of hospitalizations.

Specified versus unspecified etiologies. Less than half (46.1%, $n = 201$) of hospitalizations had a specified etiology (Table 3). The proportion of hospitalizations of specified etiology varied yearly, from a low of 31.0% in 1998 to a high of 62.6% in 2006 (Figure 1) and was higher during 2006–2010 (53.8%) than in 1998–2005 (41.0%; $P = 0.01$).

The age-adjusted average annual rates of specified and unspecified encephalitis-associated hospitalizations were similar by sex ($P = 0.96$ and $P = 0.92$, respectively) (Table 2). Infants had the highest rates of specified and unspecified hospitalizations (Table 2). The proportion of hospitalizations resulting in death was similar for specified (4.5%) and unspecified (3.8%) hospitalizations ($P = 0.73$). Encephalitis-associated hospitalizations of specified etiology (median = 6, IQR = 3–14) and of unspecified etiology (median = 6, IQR = 3–11) had similar lengths of stay ($P = 0.37$).

DISCUSSION

To our knowledge, the rate of encephalitis-associated hospitalizations among AI/AN people has not been described. Examination of serious illnesses, including encephalitis, in unique populations is important because varying presentations could provide clues to prevention or treatment of people of different backgrounds.

The overall rate in the present study was 3.1 per 100,000 population. Similar to reports of encephalitis in other populations, infants had among the highest encephalitis-associated hospitalization rates,^{4,26,27} herpetic meningoencephalitis was the most common identifiable infectious cause,^{4,6,26,27} and most hospitalizations were for an unspecified etiology.^{4,26,27} Viral etiologies of encephalitis (23.2%), followed by other specified etiologies (15.4%), represented the largest proportions of cause-specific hospitalizations; these proportions were similar to those reported for the general U.S. population during the same time period (20.3%; 95% confidence interval [CI] = 19.8–20.9% and 18.4%; 95% CI = 17.7–19.1%, respectively).¹⁷ The proportion of hospitalizations resulting in death (4.1%) was also similar to that for the general U.S. population (5.8%; 95% CI = 5.5–6.0%).¹⁷ The overall rate and the rate for unspecified etiologies appeared to peak in approximately 2003, after which the ratio of unspecified to specified etiologies appeared to decrease. The increase in the proportion of hospitalizations for which an etiology of encephalitis was identified might be related to advances in diagnostic technologies or discovery of new forms of encephalitis in the United States. For example, WNV was first identified in the United States in 1999 and is now recognized as a common cause of encephalitis in almost every state.^{17,28}

The overall encephalitis-associated hospitalization rate in this study (3.1 per 100,000) appears to be lower than the rate in a comparable study of the general U.S. population (6.9) due in part to a lower rate among AI/AN people ≥ 65 years of age.¹⁷ An examination of age-specific rates showed that the distribution was similar for AI/AN people compared with the

U.S. population until the age of ≥ 65 years. For persons ≥ 65 years of age, the rate of encephalitis-associated hospitalizations increased for the general U.S. population but the rate for AI/AN people plateaued.¹⁷

The effect of race, including cultural, economic and social factors, on the occurrence of encephalitis is unexplored. Truly lower disease burden caused by reduced individual susceptibility or smaller susceptible population, or under-ascertainment are possible explanations for the lower rate for AI/AN people in our study compared with that for the general U.S. population.¹⁷ Compared with persons of other races, AI/AN people may have different susceptibility to some encephalides because of differences in genetic makeup or immune function.^{29,30} In addition, the life expectancy for AI/AN people is approximately five years less than for the general U.S. population¹⁸; competing causes of death could, in theory, reduce the size of the elderly population susceptible to encephalitis.³¹ The most likely explanation is that under-ascertainment contributes to lower recorded rates of encephalitis among AI/AN people. Low physician-to-patient ratios, few neurologists, and vast geographic areas suggest that some patients with encephalitis might not seek medical care or receive a correct diagnosis.³² Conversely, because there is no specific test for encephalitis, and the clinical presentation can be non-specific, it is also possible that some of the hospitalization records for the general U.S. population incorrectly list an encephalitis-associated ICD-9-CM code in patients with mental status changes of other cause, thus inflating the estimates. In other neurologic diseases, under-ascertainment affects elderly women most prominently^{33,34}; a pattern of lower rates in women was not found in this study, suggesting that there are other factors contributing to our findings.

Some limitations in the present study should be considered. Although the IHS database captures most patients residing on and near reservations, studies based on existing data might underestimate the number of hospitalizations. Miscoding or inaccurate hospital discharge diagnoses may have occurred and may have varied by region, and we were unable to conduct a chart review to confirm encephalitis diagnoses. Patients with mild disease or severe disease followed quickly by death might never have been treated in a hospital and will not be reflected by these data, thus resulting in an underestimation of hospitalizations. The unit of analysis was a hospitalization; multiple hospitalizations for the same patient or hospital transfers were included in the analysis. Also, the findings might not be generalizable to AI/AN people who do not use the IHS/tribal healthcare system. The AI/AN people within the IHS/tribal healthcare system may also seek care outside the system, which would result in an underestimate of rates. The denominator was estimated as the number of AI/AN people who used the IHS/tribal healthcare system in the previous three years, which may have slightly underestimated the size of the population at risk. Small numbers of hospitalizations limited our ability to fully describe differences among cause-specific disease categories.

The hospitalization rate for AI/AN people appears to be lower than for the general U.S. population because of particularly lower rates in the elderly. Similar to other reports, the bulk of identifiable etiologies were viral and many causes were elusive. Further research is needed to confirm our findings and examine reasons for the low encephalitis-associated hospitalization rate among AI/AN people. Community-based

surveillance studies and exploration of death certificate data, in combination with detailed assessment of competing causes of death, could further define the burden of encephalitis in AI/AN people. Ecologic studies could examine rates in comparison to environmental events, including the spread of existing causes and the appearance of new agents.

Received July 22, 2013. Accepted for publication December 19, 2013.

Published online February 10, 2014.

Acknowledgments: We thank the staff at the participating healthcare facilities, the IHS National Patient Information Reporting System, and Barbara Strzelczyk (IHS) for technical assistance.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the IHS.

Authors' addresses: Jason M. Mehal, Robert C. Holman, Neil M. Vora, and Jesse Blanton, Division of High-Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention Atlanta, GA, E-mails: jmechal@cdc.gov, rholman@cdc.gov, wii8@cdc.gov, and asi5@cdc.gov. Paul H. Gordon, Northern Navajo Medical Center, Indian Health Service, Shiprock, NM, E-mail: paul.gordon@ihs.gov. James E. Cheek, Public Health Program, Department of Family and Community Medicine, University of New Mexico Health Sciences Center, Albuquerque, NM, E-mail: jcheek@salud.unm.edu.

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