

THE EPIDEMIOLOGY OF INFECTION WITH THE HUMAN HERPESVIRUSES IN NAVAJO CHILDREN

THOMAS M. BECKER,¹ LARRY MAGDER,¹ H. ROBERT HARRISON,¹
JOHN A. STEWART,² DORRETH D. HUMPHREY,² JOANNE HAULER,³ AND
ANDRE J. NAHMIAS⁴

Becker, T. M. (U. of New Mexico School of Medicine, Albuquerque, NM 87131), L. Magder, H. R. Harrison, J. A. Stewart, D. D. Humphrey, J. Hauler, and A. J. Nahmias. The epidemiology of infection with the human herpesviruses in Navajo children. *Am J Epidemiol* 1988;127:1071-8.

Investigations of serum antibody status to the five human herpesviruses—herpes simplex virus type 1, herpes simplex virus type 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster virus—were conducted on 197 Navajo children, aged 1-15 years, at a reservation pediatric outpatient clinic in Crownpoint, New Mexico, from 1981-1984. To determine the severity of infection with the human herpesviruses, the authors reviewed lifetime medical records of 166 of the children for evidence of herpesvirus-related diseases, and to illuminate potential modes of transmission of the viruses, they completed home interviews on the families of 87 of the children. The investigation showed that the children had a high prevalence of antibody to herpes simplex virus type 1 (73% of total sample), cytomegalovirus (78%), Epstein Barr virus (98%), and varicella-zoster virus (77%), and that prevalence tended to increase with age. None of the children demonstrated herpes simplex virus type 2 antibodies. The medical records showed that 30% of the children had suffered from gingivostomatitis prior to the study. When age was controlled for, the study showed herpes simplex virus type 1 seropositivity to be associated with children who slept in the same bed as their parents during infancy ($p = 0.003$) and with frequent attendance at community events ($p = 0.02$); cytomegalovirus seropositivity was shown to be associated with female sex ($p = 0.007$) and with living in a traditional Navajo dwelling ($p = 0.007$). The Navajo children also demonstrated a greater frequency of symptomatic oral herpes simplex virus type 1 infection than is usually recorded. The findings suggest a relation between certain patterns of cultural behavior and transmission of herpesvirus infections.

herpesvirus infections; Indians, North American; serology

Infections with the human herpesviruses are common in human populations studied

to date (1). Little is known, however, about the epidemiology of these viruses—herpes

Received for publication March 18, 1987, and in final form July 9, 1987.

¹ Division of Sexually Transmitted Diseases, Center for Prevention Services, Centers for Disease Control, Atlanta, GA.

² Division of Viral Diseases, Center for Infectious Diseases, Centers for Disease Control, Atlanta, GA.

³ Crownpoint Indian Health Service Hospital, Crownpoint, NM.

⁴ Department of Pediatrics, Division of Infectious Diseases and Immunology, Emory University, Atlanta, GA.

Reprint requests to Thomas M. Becker, New Mex-

ico Tumor Registry, Cancer Center, University of New Mexico School of Medicine, 900 Camino de Salud N.E., Albuquerque, NM 87131.

This work was supported in part by Grant AI-PO1-19554 from the National Institute of Allergy and Infectious Diseases.

The authors thank Garrett Mallory, Dorothy Warner and Rita Elliott for technical assistance; Francis Lee, Paula Bailey, and Carla Griffin for laboratory assistance; Dr. Robert Williams for his advice; and the Crownpoint Indian Health Service Unit's Community Health Representatives for their assistance in locating families for interviews.

simplex virus type 1, herpes simplex virus type 2, cytomegalovirus, Epstein-Barr virus, and varicella-zoster virus—in Native Americans (American Indians). There are indications that among Navajo Indians, these infections are common and may be of public health importance. In an earlier study, Montgomery et al. (2) found high rates of cervical cytomegalovirus infection in pregnant Navajo women; he also found the prevalence of antibody to cytomegalovirus in Navajo women to be twice as high as that in blacks and whites living in New Mexico. Other workers have observed that the prevalence of cytologic changes due to genital herpesvirus infection, as seen in Papanicolaou smears, is similar in Navajo women and in whites in New Mexico (3). No studies of Epstein-Barr virus or varicella-zoster virus infections in Navajos have been reported; however, Epstein-Barr virus antibodies have been studied in Eskimos and Alaskan Indians in relation to nasopharyngeal carcinoma (4). There are no reports on human herpesvirus infections in Native American children, although Navajo Area Indian Health Service physicians have observed a high frequency of severe oral herpes simplex virus infection in Navajo children (Robert Williams, Crownpoint Indian Health Service Hospital, personal communication, 1983).

This investigation was conducted to determine the age-specific prevalence of antibodies to the five human herpesviruses in Navajo children; to define the proportion of symptomatic disease and asymptomatic acquisition of infection as determined by medical chart review; and to investigate cultural, behavioral, and environmental variables that might affect transmission of the herpesvirus in Navajo children.

METHODS

Patient population and medical facility

The study was performed at Crownpoint, New Mexico, located near the eastern border of the Navajo reservation. The population of the Crownpoint chapter (comparable to a census tract) in 1984 was 1,449

people. Patients visiting the Crownpoint Indian Medical Center come primarily from this chapter and from chapters immediately surrounding Crownpoint.

The Crownpoint Indian Medical Center is supported by the Indian Health Service. The hospital has inpatient and outpatient facilities and is equipped with a laboratory that provides most routine laboratory services. We selected a sample of all children presenting to the clinic, for any reason, who had blood drawn as part of their clinical care. The sample included children who presented for medical and surgical conditions and children who presented for routine physical examination for well-child care. An attempt was made to enroll equal numbers of children of each age from 1–15 years. The study subjects were initially selected as part of a chlamydia serologic study by researchers at the University of Arizona (5). The chlamydia studies were performed in Tucson, Arizona, and the serum samples were then shipped to Atlanta, Georgia, where the herpesvirus serologic assays were performed. The serum was stored at -20°C prior to shipment and remained frozen at -20°C until the assays were carried out.

Antibody assays

Epstein-Barr virus. We employed the viral capsid antibody test to detect immunoglobulin G (IgG) antibodies—an indirect immunofluorescent test using cells derived from Burkitt's lymphoma (6)—to measure remote infection with Epstein-Barr virus. A titer of $\geq 1:10$ was defined as positive.

Cytomegalovirus. We employed an indirect hemagglutination assay to detect all immunoglobulin classes of cytomegalovirus antibody (7). A titer of $\geq 1:8$ was defined as positive.

Varicella-zoster virus. We employed an indirect immunofluorescent assay which detects IgG antibodies to surface antigens of varicella-zoster virus-infected cells (8). A titer of $\geq 1:2$ was considered positive.

Herpes simplex viruses type 1 and type 2. Antibodies to herpes simplex viruses were first detected by enzyme-linked immuno-

sorbent assay using extracts of herpes simplex viruses type 1 and type 2 infected HEP-2 cells (9). If the test was positive, the serum was further tested for herpes simplex virus type-specific antibodies using recently described glycoproteins gG-1 and gG-2 (10, 11). We used the immunoaffinity purified antigens in immunodot enzymatic assays on nitrocellulose discs. A high sensitivity and specificity of the tests for herpes simplex viruses type 1 and type 2 antibodies was clearly established (12), and the reproducibility of the tests remained greater than 96 per cent.

Chart reviews

We abstracted medical records of all children in the sample. We collected data on all clinic and hospital visits, abstracting the date of visit, age at visit, diagnosis generated from visit, whether the patient was febrile (>38.3 C), need for hospitalization, and, if applicable, period of hospitalization. Supporting laboratory data were examined when available.

Family interviews

Interviews were always conducted by the same research team member, although translators varied depending on the community location where subject families resided. All translators were bilingual Navajo community health representatives employed by the Navajo tribe. The questionnaire used in the interviews focused on several factors that had either been suggested by other researchers to have some effect on herpesvirus transmission or that we believed warranted testing. These included family population density; community population density; intensity of contact with family, friends, and community; sharing of fomites; breastfeeding; and other child-rearing practices. Questions that were not answered by the respondent because of lack of adequate information about the particular questions were coded as "unknown." All families who were contacted participated in the interviews. Figure 1 gives a

summary of those subjects enrolled, tested, and interviewed.

Statistical methods

We employed Fisher's exact test (two-tailed) to examine associations between observed variables (13). To assess the significance of observed increases in seroprevalence of antibody by age group, we used a chi-square for slope (13). We used logistic regression analyses to control for age while testing for associations between variables (14).

RESULTS

Demographic variables

Serum samples from 197 Navajo children were tested for antibody status. Originally, 216 children were entered into the study, but 19 of the serum samples were destroyed during shipping. Of the 197 children tested, 166 had complete recorded medical histories, and 87 were the subjects of family interviews (figure 1). Demographic characteristics of the sample of children whose families were interviewed were comparable to those of the larger sample of children with serum specimens (table 1).

Serologic assays

Results of serologic assays show that increasing age was significantly associated with higher rates of seropositive antibody status for herpes simplex type 1 and varicella-zoster viruses (χ^2 , $p = 0.003$, $p = 0.001$, respectively) (table 2). Cytomegalovirus and Epstein-Barr virus seropositivity remained high in all age groups; herpes simplex virus type 2 antibody was not observed. All individuals tested were seropositive for at least two agents; 81 per cent of children aged 11–15 years had antibodies to both cytomegalovirus and Epstein-Barr virus (data not shown).

Cytomegalovirus seropositivity was higher in females than in males when the data were controlled for age (82/96 females (85 per cent) vs. 67/94 males (71 per cent),

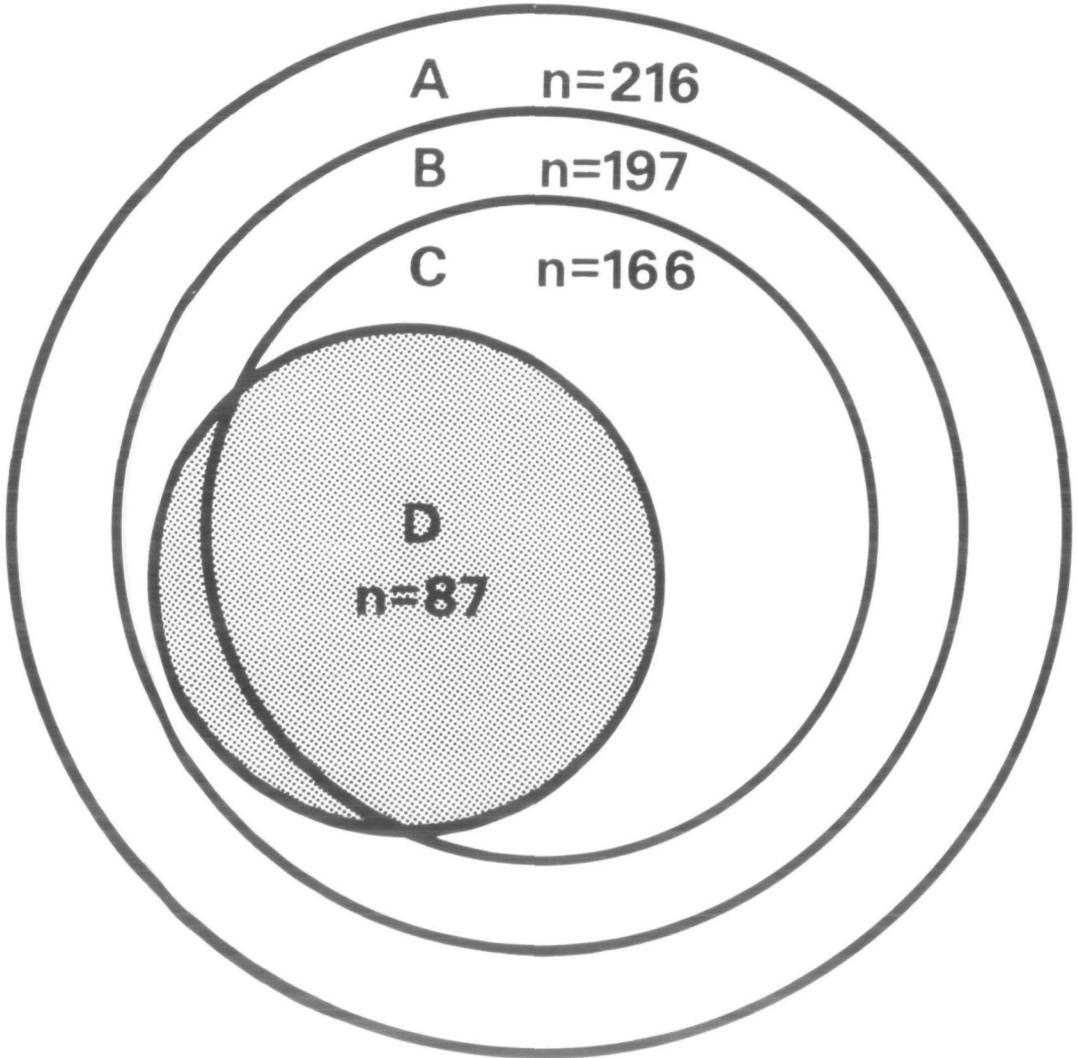


FIGURE 1. Samples and subsamples of Navajo children. Circles refer to children entered into the study (A); those who had serum specimens (B); those with complete medical records and a serum specimen to match (C); and those with completed interviews (D). Seven children with interview data had no matching lifetime medical records. Nineteen serum specimens were destroyed during shipping.

$p = 0.018$), but no other significant differences in serologic status by sex were noted.

Herpes-related disease profiles

Chart reviews on 166 children with complete medical records revealed numerous cases of clinically diagnosed, herpesvirus-related diseases. Gingivostomatitis was recorded in 52 cases (31 per cent of total), with 90 per cent of the cases occurring before age four years; chickenpox was recorded in 44 cases (27 per cent of total);

genital herpes was recorded in three cases (1.8 per cent of total); and cold sores were recorded in four cases (2.4 per cent of total). Zoster was recorded on one chart (0.6 per cent), and mononucleosis was not recorded on any charts.

Associations between serologic status and charted diseases

The relation between human herpesvirus antibody status and disease history was shown to be statistically significant in only

a few cases: gingivostomatitis was associated with herpes virus simplex type 1 seropositivity (46 cases/123 seropositives (37 per cent) vs. six cases/44 seronegatives (14

per cent), $p = 0.004$); pneumonia was associated with herpes simplex virus type 1 seropositivity (61 cases/123 seropositives (50 per cent) vs. 11 cases/44 seronegatives (25 per cent), $p = 0.005$); chickenpox was associated with varicella-zoster virus seropositivity (37 cases/123 seropositives (30 per cent) vs. five cases/36 seronegatives (14 per cent), $p = 0.056$); urinary tract infection was also associated with varicella-zoster virus antibody status (17 cases/123 seropositives (14 per cent) vs. zero cases/36 seronegatives (0 per cent), $p = 0.014$).

TABLE 1

Demographic characteristics of Navajo children, Crownpoint, New Mexico, 1981-1984

Characteristic	No. (%) of total serologically tested (n = 197)	No. (%) of total interviewed (n = 87)
Age (years)		
1-5	66 (34)	31 (36)
6-10	72 (36)	29 (33)
11-15	59 (30)	27 (31)
Sex		
Male	97 (49)	47 (54)
Female	100 (51)	40 (46)
Reason for phlebotomy		
Acute illness	119 (60)	55 (63)
Well-child care	53 (27)	22 (25)
Trauma, other	25 (13)	10 (12)

Associations between human herpesvirus antibody status and behavioral/environmental factors

Several associations of behavioral/environmental variables with human herpesvirus antibody status were statistically significant ($p < 0.05$) when data were analyzed controlled for age (table 3). Numerous

TABLE 2

Seroprevalence of antibody to the human herpesviruses in Navajo children, by age group, Crownpoint, New Mexico, 1981-1984

Antibody*	1-5	6-10	11-15	1-15
HSV-1	39/66 (59)†	57/72 (79)	48/59 (81)	144/197 (73)
HSV-2	0/66 (0)	0/72 (0)	0/59 (0)	0/197 (0)
CMV	50/65 (77)	55/72 (76)	48/59 (81)	153/196 (78)
EBV	60/64 (94)	68/70 (97)	59/59 (100)	187/193 (97)
VZV	37/61 (61)	55/68 (81)	51/58 (88)	143/187 (76)

* HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; CMV, cytomegalovirus; EBV, Epstein-Barr virus; VZV, varicella-zoster virus.

† Number positive/number tested (per cent).

TABLE 3

*Significant associations between antibody status and behavioral/environmental factors among Crownpoint, New Mexico, Navajo children (n = 87), 1981-1984**

Antibody† and trait	p value	RR†	(95% CI)‡
HSV-1			
Sleeping with parents in infancy	0.003	5.7	1.2-15.8
Attendance at community events within the month prior to interview	0.020	5.0	1.3-19.1
CMV			
Having parent or guardian who speaks only Navajo	0.021	10.1	1.3-79.8
Living in multiple-room dwelling§	0.007	0.73	0.59-0.90
Having outhouse vs. indoor bathroom	0.010	4.2	1.4-12.2

* Data analyzed controlled for age.

† HSV-1, herpes simplex virus type 1; CMV, cytomegalovirus.

‡ RR, point estimates for relative risk values.

§ CI, confidence interval boundaries of point estimates for relative risk values.

¶ Protective effect of living in a multiple-room house; relative risk expressed for room increments.

attributes of Navajo lifestyle were examined and were not shown to be statistically significant in relation to human herpesvirus antibody status. These characteristics included family size and density, relative isolation of the family, hygienic practices (such as sharing of eating utensils), breastfeeding, cradleboard use, and attendance at pre-school and boarding school.

Associations between disease histories and behavioral/environmental factors

When age was controlled for, a history of gingivostomatitis was significantly associated only with attendance at community events within the prior month ($p = 0.045$). Chickenpox was not significantly associated with any of the variables defined in the questionnaire.

DISCUSSION

The most important conclusions from this study are that Navajo children show a high prevalence of infection to all the human herpesviruses except herpes simplex virus type 2, with antibodies to the four viruses present early in life; they have a remarkably high degree of symptomatic oral herpes simplex virus type 1 infection; and they demonstrate certain patterns of cultural behavior that are statistically associated with acquisition of herpesvirus infection and/or disease. While previous work has shown a high prevalence of a variety of infections in the Navajo (15–24), our study provides a detailed investigation of the epidemiology of the human herpesviruses in this population.

A fair comparison of antibody seroprevalence figures among different populations is hindered by differences in sampling techniques and in the varying sensitivity and specificity of antibody assays. Given these differences, however, the present study shows that Navajo children have a prevalence of herpes simplex virus type 1 antibody that is among the highest of any population yet reported, the figures comparing with the high prevalence figures reported from Amazonian Brazil (25–27), the Faroe

Islands (28), Delhi, India (29), and an urban population in Atlanta, Georgia (30). Navajo acquisition of herpes simplex virus type 1 antibodies also follows that of other populations of lower economic standing, with approximately 90 per cent of young Navajo adults infected with herpes simplex virus type 1. The strongest correlate of herpes simplex virus type 1 seropositivity in Navajo children was the common practice of sleeping in the same bed as the parents during infancy. The resulting prolonged face-to-face contact with herpes simplex virus type 1-positive parents may be an important viral transmission opportunity. Herpes simplex virus type 1 antibody status was also associated with attendance at a high number of community events, at which increased risk of exposure to infected individuals, particularly other children, may occur.

Our study showed no acquisition of herpes simplex virus type 2 infection in Navajo children, a finding consistent with reports from a sample of urban children in Atlanta, Georgia (30). Studies in Delhi, India (29), in Nigeria (31, 32), and of Indian tribes in Brazil (25) reported acquisition of these antibodies in children, suggesting routes of nonsexual transmission in these populations. However, the antibody assays employed in these earlier studies (complement fixation or microneutralization) were not adequately specific to the herpes simplex virus antibodies, leaving the findings in doubt. The high sensitivity and specificity of the antibody assay in our study have been established, and while we have no serologic data on the parents of our study subjects, our test results suggest that nonsexual transmission of herpes simplex virus type 2 is uncommon.

Both cytomegalovirus and Epstein-Barr virus infections were common, and present early in life, among the Navajo children. Cytomegalovirus seropositivity was associated with more traditional Navajo lifestyles, but precise factors of cytomegalovirus transmission were not illuminated in our study. Female children were more likely

than male children to be cytomegalovirus antibody-positive, possibly because as infants they are kissed and handled more and are later given more child-rearing responsibilities, all resulting in increased exposure opportunities. As with herpes simplex virus type 1, cytomegalovirus and Epstein-Barr virus acquisition patterns compare closely with those of other economically disadvantaged groups (25-28, 33-37). In addition, 81 per cent of the Navajo children in the oldest age group were seropositive to both cytomegalovirus and Epstein-Barr virus, agents that cause mononucleosis in previously unexposed teenagers and young adults. The infrequent occurrence of cases of mononucleosis among the Navajo may be explained by the high proportion of children who have experienced cytomegalovirus and Epstein-Barr virus infection prior to adulthood and thus have developed protective antibodies. Mononucleosis was not charted in the sample of children studied in this series.

We observed significant correlations between gingivostomatitis and herpes simplex virus type 1 seropositivity, and between chickenpox and varicella-zoster seropositivity. Less biologically plausible, however, is the association between pneumonia and herpes simplex virus type 1 seropositivity, since herpesvirus pneumonia is usually a severe infection in an immunocompromised host, and none of the children in this series were immunocompromised or diagnosed as having herpesvirus pneumonia. Also difficult to explain biologically is the relation between varicella-zoster virus antibody and urinary tract infections in the children, since varicella has never been shown to be related to urinary tract infections. These observations warrant further study.

Gingivostomatitis occurred in 31 per cent of the children in this study, a remarkably high proportion since it is estimated to occur as a consequence of herpes simplex virus type 1 infection in only 1 to 10 per cent of infected individuals (1, 38). Chart reviews indicated that most children who manifested this disease did so during the

first three years of life. The diagnoses of genital herpes, noted in three study subjects, were not supported by viral cultures, observed clinical recurrences, or charted indications of sexual activity by the patients and, therefore, remain doubtful.

Limitations of our study include lack of viral culture support for diagnoses, lack of a priori defined and standardized diagnoses, confinement to a sample of subjects seen at a clinic rather than drawn from the general population, and recall bias resulting from parents' or guardians' inability to accurately remember the early histories of their children. Other potential problems with the study include small sample size, inability to locate a large proportion of families for interviews, and the use of different translators for interviews. Despite these limitations, however, our study still provides insights into the epidemiology of human herpesvirus infections among Navajo children. Similar studies in other cultures would offer interesting comparative data.

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