Hantavirus Infection in Children in Argentina

Clinical hantavirus infection was diagnosed in five Argentine children ages 5 to 11 years by immunoglobulin M (IgM)- capture enzyme-linked immunosorbent assay using Sin Nombre virus (SNV) antigens. Death in three of the children was associated with absence of detectable IgG to SNV antigens. An additional two cases in healthy children were studied: one, a breast-fed 15-month-old whose mother died of suspected hantavirus pulmonary syndrome (HPS) 8 months previously, had hantavirus IgG ($\geq$ 1:6400); a second, whose mother survived HPS during month three of pregnancy, apparently had maternal antibodies no longer detectable 1 year after birth.

In May 1993, a new hantaviral illness, hantavirus pulmonary syndrome (HPS), was recognized in the southwestern region of the United States (1). HPS is a viral zoonosis characterized by a febrile prodrome in young, healthy adults; the disease progresses to respiratory failure with the clinical picture of adult respiratory distress syndrome (ARDS). The striking pulmonary involvement differentiates HPS from a previously described hantaviral disease known as hemorrhagic fever with renal syndrome.

In the first 100 HPS cases in the United States, the average age was 34.9 years (range 11 to 69); eight cases were in children or adolescents under 16 years of age (2). In Argentina, from 1987 to July 1997, 114 cases were diagnosed in three areas of the country where several strains of new world hantaviruses are known to cause HPS diseases (3,4). Before 1995, no cases were detected in Argentine children under 12 years of age. Ten cases were reported among adolescents (13 to 19 years) with a case-fatality rate of 30% (Instituto Nacional de Enfermedades Virales Humanas, [INEVH], unpub. data).

The initial case definition referred to ARDS and included adults and young adults (5) as the affected population. The lack of HPS cases among children in the original outbreaks led to a circulating hypothesis that children were not at risk or were at a very low risk for HPS. Another hypothesis was that children were protected from pulmonary involvement, perhaps by immune system immaturity or a lack of other risk factors (such as cigarette smoking) for lung injury.

In this report we describe five cases in children; in all of them the etiologic diagnosis was established by the presence of immunoglobulin M (IgM) antibody to Sin Nombre virus (SNV) antigens. Serologic results for two of the children were also positive for SNV IgG antibody. Serum samples were tested for IgM and IgG antibodies to SNV by enzyme-linked immunosorbent assay (ELISA) (6). An ELISA titer greater than or equal to 1:400 was considered positive (Table 1).

Patient 1 was identified during the study of the first outbreak in southern Argentina in 1995 (5). Four patients in this outbreak were from the same family. During interviews of the family members, we found that a 9-year-old boy had a febrile disease without respiratory involvement, beginning on April 19. Serology performed on May 3, 14 days after the onset of symptoms, demonstrated IgM and IgG antibodies to SNV antigens.

Table 1. Hantavirus infection in children, Argentina, 1995–1997

Case	Sex	Age (yrs)	Date of onset	Serology[a] Date IgM IgG	Area[b]	Outcome
1	M	9	4-19-95	5-3-95 >6400 1600	South	Alive
2	F	5	3-21-97	3-23-97 >6400 Neg	North	Dead
3	M	9	3-30-97	4-3-97 1600 400	North	Alive
4	F	11	4-14-97	4-16-97 1600 Neg	North	Dead
5	M	5	4-27-97	4-28-97 1600 Neg	Central	Dead

[a]Titer expressed as the reciprocal of the serum dilution reactive in enzyme-linked immunosorbent assay.
[b]Area of origin in Argentina.

The other four cases in children were identified during routine surveillance. From 1995 to 1997, samples from 25 children (ages 3 months to 12 years; mean = 5.8 years) were sent to INEVH for diagnosis. Table 2 summarizes the main clinical and laboratory findings. None of the children had renal failure; patient 2 had uremia of 0.30 g/l, and patient 4 had a serum creatinine level of 1.40 g/l. All patients who later died received supplemental oxygen as part of their treatment.

Two special situations involving children arose during the study of the first cases of HPS in El Bolsón in 1995. 1) A woman belonging to the family of patient 1 contracted HPS during the first quarter of pregnancy. She had a febrile syndrome, without respiratory failure; chest X-rays showed bilateral interstitial infiltrates. Serologic tests showed both SNV IgM ($\geq$ 1:6400) and IgG ($\geq$ 1:6400) on April 22, 1995, 8 days after the onset of symptoms. She delivered a healthy infant in October 1995. A sample of the newborn's cord blood was positive for SNV IgG ($\geq$ 1:6400) and negative for SNV IgM. A serum sample drawn from the mother at the same time had a SNV IgG titer $\geq$ 1:6400 and was negative for SNV IgM. A second serum sample, taken from the baby a year later during November 1996, had no detectable SNV IgG or IgM. 2) During a retrospective search for cases fulfilling the HPS case definition, a woman who died of ARDS in September 1994 was considered to have a possible case. No serum samples or autopsy tissues were available to make an etiologic diagnosis. Before dying, this woman breast-fed a 7-month-old baby; when tested for antibodies 8 months later in May 1995 at 15 months of age, the baby had SNV IgG ($\geq$ 1:6400) and no detectable SNV IgM antibodies. A second serologic sample, collected 18 months later in November 1996, still had SNV IgG antibodies, with a similar titer. Both babies have continued to develop normally as of October 1997.

A case similar to that of patient 1 was detected in New Mexico in June 1993 (7) in the course of the investigation of a fatal HPS case. In this case, the patient also had a mild clinical course that did not meet the surveillance case definition for HPS. This case definition (revised 9/96) is as follows: "a febrile illness characterized by bilateral diffuse interstitial edema that may radiographically resemble ARDS, with respiratory compromise requiring supplemental oxygen, developing within 72 hours of hospitalization, and occurring in a previously healthy person; or an unexplained respiratory illness resulting in death, with an autopsy examination demonstrating noncardiogenic pulmonary edema without an identifiable cause" (8).

Our remaining four cases were sporadic, in persons without previous contact with other HPS patients, and were suspected because their clinical symptoms were typical of HPS. Results of serologic testing with SNV antigens of the household contacts in cases 2 and 5 (five persons

Table 2. Laboratory results and clinical features of children with hantavirus infection, Argentina, 1995–1997

Tests and features	Case				
	1	2	3	4	5
Leukocytes (/mm^3)	9,200	27,000	12,800	10,600	69,200
Hematocrit (%)	44	66	43	55	53
Thrombocytes (/mm^3)	ND[a]	266,000	200,000	97,000	ND
Sedimentation rate (mm/hr)	ND	4	28	8	1
GOT/GPT[b]	ND	Increased	Increased	Increased	Increased (mild)
Chest X-ray	HI[c]	DII[d]	DII	DII	DII
Respiratory symptoms	None	Distress	Slight dyspnea	Tachypnea, clinical and X-ray disassociation, hypoventilation	Acute respiratory insufficiency

[a]ND: Not done.
[b]GOT/GPT: Glutamic oxalacetic transaminase/Glutamic pyruvic transaminase.
[c]HI: Hilar indistinctness.
[d]DII: Diffuse interstitial infiltrate.

each) were negative. The clinical, radiologic, and laboratory findings were similar in children and in adults; severely ill patients had greater variation in laboratory values than mild cases, and in fatal cases, only SNV IgM was present.

The case-fatality rate in this series was 60%, but the small number of cases does not permit conclusions. In previously reported cases in adolescents 13 to 19 years of age, the case-fatality rate was 30%.

These cases originated in the three areas where the illness is endemic in Argentina. This is an important point because an unusual case of HPS in southern Argentina, with the possibility of person-to-person transmission, had been reported (9,10). Patient 1 and the baby that was breast-feeding when the mother died of suspected HPS could be further instances of person-to-person transmission.

A case of hemorrhagic fever with renal syndrome and pregnancy was reported in 1992 (11); the dynamics of serum antibody persistence were similar to those found in the one instance where we believe antibody was passively transferred from mother to baby. These results indicate that HPS should be considered in the differential diagnosis of respiratory distress or atypical bilateral pneumonia in children, at least in areas where these diseases have been confirmed. Mild disease should be considered too, especially in contacts of HPS patients and in younger age groups.

Our findings also suggest the transfer of passive antibodies from mother to fetus (without fetal infection) and the possibility of transmission of infection by maternal breast feeding.

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Reemergence of Dengue in Cuba: A 1997 Epidemic in Santiago de Cuba

After 15 years of absence, dengue reemerged in the municipality of Santiago de Cuba because of increasing migration to the area by people from disease-endemic regions, a high level of vector infestation, and the breakdown of eradication measures. The 1997 epidemic was detected early through an active surveillance system. Of 2,946 laboratory-confirmed cases, 205 were dengue hemorrhagic fever, and 12 were fatal. No deaths were reported in persons under 16 years of age. Now the epidemic is fully controlled.

Cuba had its first dengue epidemic of modern times in 1977; transmission continued probably until 1981, and more than 500,000 mild cases were reported. A 1978 serologic survey for flavivirus antibody indicated that 44.6% of the Cuban population had been infected with dengue-1 virus, whereas before 1977 only 2.6% had antibodies (1,2).

A second dengue epidemic in 1981, caused by dengue-2 virus (2), was unusually severe and widespread. Of 344,203 cases, 10,312 were clinically classified as dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), and 158 persons (101 children and 57 adults) died (3). Before 1981, only 60 suspected or confirmed DHF sporadic cases had been reported in the region (4). Dengue-2 virus isolated during the 1981 epidemic was classified in the same genotype as New Guinea 1944 (5). Not previously known to circulate in the Americas, this genotype was not isolated again in the region until 1994 in Venezuela and in 1995 in Mexico (6). Retrospective studies show that although the 1981 epidemic was detected in May, the first cases occurred in December 1980. After the epidemic ended on October 10, 1981, a campaign to improve mosquito control and eradicate *Aedes aegypti* was immediately launched. Eradication was not achieved, but most of the 169 Cuban municipalities were free of the vector.

Passive Surveillance—1981

A passive dengue surveillance system was established at the end of the 1981 epidemic. Of 9,543 paired sera (acute- and convalescent-phase) from all suspected dengue patients, only 14 showed seroconversion to immunoglobulin G (IgG) by enzyme-linked immunosorbent assay (ELISA) (7); none developed IgM antibodies to dengue virus by capture IgM ELISA (8). Dengue virus infection was excluded on the basis of clinical and epidemiologic investigation. No *Ae. aegypti* mosquitoes were found in the residence localities of these patients. The surveillance system detected cases, imported from other Latin American countries, that had no evidence of indigenous transmission. Since 1987, 4,983 samples received through the surveillance system for measles and rubella, as well as paired sera of patients with rash, were studied for dengue antibodies [María Guzmán, World Health Organization (WHO)/Pan American Health Organization (PAHO) Collaborating Center for the Study of Viral Diseases, unpub. info.]. No dengue cases were identified. The low *Ae. aegypti* premise indexes and the results of the passive surveillance system indicate no dengue transmission in Cuba between 1981 and the end of 1996. However, reinfestation has occurred in some areas; the municipality of Santiago de Cuba was reinfested in 1992 by *Ae. aegypti* transported in imported tires (9).

Active Surveillance—1997

In January 1997, the Institute of Tropical Medicine "Pedro Kourí" of the Cuban Ministry of Health (a WHO/PAHO Collaborating Center for the Study of Viral Diseases) established an active surveillance system for dengue in Santiago de Cuba municipality. The municipality is located in Santiago de Cuba province, in the eastern part of the country, and has several risk factors for the reemergence of dengue: limited water supply, inadequate eradication efforts, high vector infestation, and increasing migration of people from Latin American and Caribbean disease-endemic countries to the municipality. Following the Guidelines for the Prevention and Control of Dengue and Dengue Hemorrhagic Fever in the Americas (4), this surveillance system actively

searched for febrile patients in the primary health-care subsystem whose clinical picture was compatible with dengue fever and whose sera collected 5 to 6 days after onset of the disease contained dengue IgM antibodies. As a result of this system, dengue cases were detected on January 28, 1997, in one area of the municipality. In three of the first seven cases, dengue-2 virus was detected by polymerase chain reaction (10) and was confirmed by viral isolation and identification using C6/36 cell line and monoclonal antibodies to the four dengue serotypes.

Although retrospective seroepidemiologic studies indicated that the initial transmission occurred during the second half of December 1996, it is highly probable that the cases detected on January 28 were the first. Of 60,000 cases reported from the emergency rooms of Santiago de Cuba hospitals from November 1 to January 28, 592 were clinically compatible with dengue fever. Home interviews of these 592 patients reduced the figure to 154. Blood samples from 143 of 154 patients were examined for IgM antibodies, but no positive cases were detected.

The breakdown of the vector control campaign in this municipality interfered with our efforts to abort the epidemic, despite the early detection of the first dengue cases; however, the partial vector control measures implemented once the outbreak was detected prevented its extension to the other 30 Cuban municipalities infested with the *Ae. aegypti* mosquito.

Active surveillance continued from January to July 1997. Serologic confirmation of cases was carried out by IgM capture ELISA, confirming recent infection. The serologic diagnosis was decentralized to the Provincial Laboratory in Santiago de Cuba, which used an ultramicro-ELISA for dengue IgM detection (11). The Institute of Tropical Medicine served as the national reference laboratory for serology, viral isolation, and strain identification and characterization.

During the epidemic, 17,114 febrile patients were initially considered to have dengue, but serologic testing of 10,024 of these patients confirmed dengue in only 2,946; 46 dengue-2 isolates from 160 serum samples were obtained. The nucleotide sequence of the E\NS1 gene junction of the first isolated strain (12) indicated that it belonged to the Jamaica genotype, which during recent years is being transmitted extensively throughout Latin American and Caribbean countries and is associated with DHF/DSS in some countries (6,13).

Epidemiology

After the end of the 1981 Cuban DHF epidemic, seroepidemiologic studies in Palmira, Cienfuegos, and Cerro municipalities examined dengue-1 and dengue-2 seroprevalence in these populations (14,15). Taking into consideration these data and the total population of the Santiago de Cuba municipality, we estimated the prevalence of dengue-1 and dengue-2 antibodies. The estimated total population at risk for dengue-2 infection was 301,986 adults and children susceptible to a primary infection by any dengue virus serotype (63.5% of the population) and 88,108 adults with antibodies to dengue-1 virus acquired during the epidemic of 1977 to 1980, now susceptible to a secondary infection with dengue-2 and at increased risk for DHF/DSS (18.5% of the population).

The earlier Cuban experience (3) confirms other reports of secondary infection (dengue-1 and dengue-2) as the main risk factor for DHF/DSS. During the 1997 dengue outbreak, secondary infection was again confirmed as a risk factor for DHF/DSS. Of the 2,946 confirmed cases, 205 (including 12 fatal adult cases) were classified as DHF/DSS cases according to the criteria established by PAHO (4). DHF/DSS was observed mostly in adults, the only age group in whom secondary infection was possible. DHF/DSS-compatible symptoms were seen only in one child with primary infection. Preliminary studies indicated that secondary infection was present in 100 (98%) of 102 DHF/DSS cases. In fatal cases, secondary infection could be documented in 11 (92%) of 12 cases. In Thailand the greatest risk appeared when the secondary infection occurred 6 months to 5 years after the primary one (16). For that reason, an epidemic of DHF/DSS was not expected in Santiago de Cuba, perhaps only sporadic cases. However, DHF/DSS in adults who contracted a secondary infection at least 16 years after the primary infection was not previously reported.

Because in Cuba dengue-1 circulated from 1977 to 1980-81, the youngest patients expected to contract secondary infection should be older than 16 years of age; the youngest DHF/DSS patient with confirmed secondary infection was a 17-year-old, which indicates that the "enhancing" antibodies can circulate and be effective for at least 16 years and maybe for life.

A significant number of febrile patients with suspected dengue had respiratory signs and symptoms; therefore, simultaneous circulation of

respiratory or other pathogens was considered. Serologic screening for respiratory viruses using hemagglutination-inhibition and ELISA confirmed that 29.3% of 41 nonconfirmed dengue cases were influenza A, influenza B, or adenovirus infections. Additionally, some children had fever and rash clinically compatible with herpangina, and some had diarrheal disease with fever, as is common in Cuba during the summer. These febrile syndromes contributed to the high number of patients whose infections were provisionally considered suspect dengue cases. Suspect dengue cases were broadly defined to maximize sensitivity of detection and retain all possible dengue cases. This active surveillance excluded other febrile syndromes but recorded them as suspected cases. In practice, the risk perception by the population was very high, especially when the epidemic was officially declared and deaths were noted. Both the patients and the health providers appeared to think of dengue as the first diagnostic possibility. For this reason, the figure of 17,114 cases was considered the magnitude of the epidemic from the clinical management perspective. Since most cases were tested serologically, the incidence of clinical cases was probably close to the 2,946 serologically or virologically confirmed cases. Because asymptomatic and subclinical dengue cases are frequent, especially in children, the true rate of infection may be higher. In a separate and limited study on asymptomatic contacts of dengue cases, for every clinical case, 13.9 asymptomatic or subclinical cases were produced. Serologic studies of contacts in Santiago de Cuba are planned for a more in-depth study of this question.

Clinical Management

The health authorities established a liberal policy of hospitalization that varied with the availability of beds. Hospitalization permitted vector control of the human reservoir, more precise case classification, and close clinical surveillance.

When beds were available, all patients with suspected cases were hospitalized. When the numbers of patients surpassed the availability of beds, patients were treated at home under the supervision of the family doctor. The family doctor transferred the patient to the hospital if any medical complication appeared. Wards with specialized personnel were established where the patients were protected from vectors, and observation wards were organized for patients with complications. Intensive and intermediate care units, as well as an emergency subsystem for the transfer of patients from one unit to another, were available. As in 1981, some patients rapidly developed hypovolemic shock and died within hours of admission to the hospital (17).

An ad hoc task force followed the case definitions for dengue and DHF/DSS established by PAHO (4) for classifying the cases at the closure of the medical record. The accumulated experience of the Cuban scientists and doctors and the increased international knowledge about dengue and DHF/DSS in the last 15 years permitted a much deeper and more comprehensive study of this outbreak with more accurate classification and management of cases than in 1981. Nevertheless, the case-fatality rate was three times higher, mainly because of a much better classification of DHF/DSS cases. Other countries in the region with a very accurate case classification, such as Puerto Rico (13), also have a high case-fatality rate.

Vector Control

The campaign to control the vector started before the beginning of the 1997 dengue outbreak and is well established. Although the campaign required the mobilization of scarce financial resources and experts from all over the country, early intervention prevented spread of the outbreak to other potentially vulnerable municipalities. Of 169 municipalities in Cuba, 30 had *Ae. aegypti* mosquitoes. The epidemic was limited to the municipality of Santiago de Cuba; no autochthonous transmission to other municipalities of the province or country was detected.

An active search for cases detected transmission very early, before "fever alert" signaled an outbreak. In the Provincial Center for Hygiene, Epidemiology, and Microbiology of Santiago de Cuba, a special Unit for Analysis and Trends maintains a permanent fever alert system. For several years, this system has provided a weekly tabulation of febrile patients for every population. The tabulation allows us to evaluate fever alert (4) as applied to an active surveillance system. Because the fever alert did not appear in the epidemic area until May 1997, after the epidemic was already occurring, we consider fever alert an indicator with low sensitivity for the early and timely detection of dengue transmission, at least under the conditions of this study.