

SEVERE COINFECTIONS OF DENGUE AND PANDEMIC INFLUENZA A H1N1 VIRUSES

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Abstract: Here we report on 4 hospitalized patients with dengue-influenza virus coinfections. All patients were RT-PCR positive for dengue virus and pandemic influenza A H1N1. Clinical findings at presentation ranged from influenza-like illness to severe dengue. Clinical progression of the infections varied, but all developed dengue symptoms and had interstitial infiltrates. Three cases required intensive care management and 1 case was fatal.

Key Words: dengue, influenza, coinfection, Nicaragua, children

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In April 2009, a new influenza A virus, pandemic H1N1, caused a severe outbreak in Mexico.¹ The virus quickly spread throughout the world, and the World Health Organization declared a pandemic in June 2009.² In Nicaragua, pandemic H1N1 was first detected on June 1, and high levels of influenza transmission occurred from June to October. The influenza and dengue seasons in Nicaragua do not normally overlap, with epidemics of influenza in May to July and dengue epidemics in August to December.³ High transmission of pandemic influenza outside the normal season resulted in an overlap of influenza and dengue transmission in Nicaragua.

Dengue virus infection can be asymptomatic or produce a range of clinical presentations, from undifferentiated fever to dengue fever, characterized by abrupt-onset fever with headache, malaise, retro-orbital pain, arthralgias, and/or myalgias, to severe dengue, characterized by plasma leakage that may lead to shock and death. Currently, there is no antiviral therapy for dengue; thus, treatment relies on supportive care, primarily fluid and electrolyte management.⁴

Here we report on the clinical and epidemiological characteristics and laboratory findings from 4 patients with dengue virus serotype 3 (DENV-3) and influenza A H1N1 coinfections. All patients were hospitalized at the National Pediatric Reference Hospital, Hospital Infantil Manuel Jesús Rivera (HIMJR), in Managua, Nicaragua. A summary of clinical characteristics is presented in Table 1.

CASE REPORTS

Case 1

A 5-year-old boy with a history of asthma and recent household exposure to H1N1 presented at a local health center in Boaco, Nicaragua, on September 2 with fever >40°C and pain on

swallowing of 2 days duration, headache, arthralgias, myalgias, prostration, and loss of appetite. He was hospitalized 1 day later with a diagnosis of probable influenza in a local hospital and treated with Oseltamivir (75 mg BID) for 2 days. The patient was transferred to HIMJR in critical condition 5 days postsymptom onset, and respiratory and blood samples were collected for RT-PCR, which subsequently revealed H1N1 and DENV-3 infection, respectively. Despite treatment, the patient's condition deteriorated and he was reclassified as a suspected severe dengue case because of decreasing platelet counts and increasing hematocrit, radiologic evidence of bilateral pleural effusions, and hepatomegaly, ascites, and enlarged gallbladder as evidenced by abdominal ultrasound. The patient developed shock and was transferred to the intensive care unit (ICU), where he was given IV saline solution followed by dextran, albumin, and then norepinephrine. Mechanical ventilation was begun, and norepinephrine and oseltamivir (150 mg BID) were administered. A chest radiograph showed bilateral interstitial infiltrates. After 3 days in the ICU, the patient continued to be febrile and present leukocytosis, a predominance of segmented neutrophils, and clinical evidence of severe acute respiratory distress, together with consistent radiographic changes. Antibiotic treatment was changed to imipenem and vancomycin. Over the course of the following days, bronchospasms were treated with bronchodilators and corticosteroids. The patient improved clinically and radiographically. He was extubated after 12 days of mechanical ventilation, and vasopressure therapy was discontinued; he received a total of 14 days of double antibiotic therapy and 18 days of oseltamivir. Following 21 days of hospitalization (14 days ICU), the patient was discharged in stable condition.

Case 2

A 10-year-old girl presented at a primary care health center on September 3, the day of symptom onset, with a temperature of 39.5°C, headache, sore throat, arthralgias, and myalgias. She was suspected of having influenza, and a respiratory sample was collected. Additionally, a blood sample was collected for dengue RT-PCR testing and complete blood count. The patient was instructed to return for follow-up visits for each of the following 4 days, during which time she complained of pain on swallowing and loss of appetite, and laboratory results confirmed a dengue infection. On the fifth day, she had a capillary refill ≥ 3 seconds, was confirmed as a case of H1N1, given an IV of saline solution (0.9%), and transferred to the HIMJR. She was admitted to HIMJR in hemodynamically stable condition with a positive tourniquet test, skin rash, and crepitations at both lung bases. Treatment was initiated with oral fluids, acetaminophen, oseltamivir (75 mg BID), and continual monitoring of hemodynamic state. The following day, a complete blood count revealed thrombocytopenia and leukocytopenia, and a chest radiograph showed bilateral interstitial infiltrates. The patient continued in a stable state and was discharged after 4 days of hospitalization.

Case 3

A 5-year-old girl with a history of asthma presented with a temperature of 39.2°C, sore throat, cough, runny nose, swollen cervical lymph nodes, vomiting, and a positive tourniquet test, on September 15, 2 days postonset of illness. Specimens were collected for influenza and dengue testing. The family was provided oseltamivir; however, the parents chose not to administer it to the child. The patient returned the following day with continuing symptoms and loss of appetite, retro-orbital pain, headache, myalgias, arthralgias, and back pain. On the fifth day postonset, she was given IV saline solution and transferred to HIMJR. Upon admission, the patient was well-hydrated with

TABLE 1. Clinical Characteristics of 4 Children With Dengue-Influenza Virus Coinfections*

	Case 1	Case 2	Case 3	Case 4
Underlying conditions	Asthma	None	Asthma	Asthma, obesity
Clinical findings				
Maximum temperature (°C)	40.0	39.5	38.5	38.4
Headache	Yes	No	Yes	Yes
Myalgias	Yes	Yes	Yes	Yes
Arthralgias	Yes	Yes	Yes	Yes
Cough	No	Yes	Yes	No
Sore throat	Yes	Yes	No	Yes
Rhinorrhea	No	No	Yes	No
Abdominal pain or tenderness	Yes	No	No	Yes
Vomiting	Yes	No	No	No
Diarrhea	No	No	No	No
Rash	Yes	Yes	Yes	No
Loss of consciousness	No	No	Yes	Yes
Cold extremities	Yes	No	Yes	Yes
Weak pulse	No	No	Yes	Yes
Hypotension	Yes	No	Yes	Yes
Tourniquet test	Positive	Positive	Positive	Positive
Laboratory results				
Minimum leukocytes ($\times 10,000$ cells/mm ³)	11.3	3.2	2.2	6
Maximum lymphocytes (%)	50	82	73	10
Maximum hematocrit (%)	45.0	36.2	35.0	31.9
Minimum platelets ($\times 10,000$ cells/mm ³)	75	92	129	211
Maximum creatinine (mg/dL)	1.96	NP	0.50	0.75
Minimum albumin (mg/dL)	2.95	NP	4.39	4.43
Maximum AST (IU)	278	92	60	38
Maximum ALT (IU)	62	32	26	22
Hospitalization data				
Days hospitalized	21	4	21	1 (11 h)
Mechanical ventilation	Yes	No	Yes	Yes
Intensive care unit	Yes	No	Yes	Yes
Outcome	Full recovery	Full recovery	Full recovery	Death

*NP indicates not performed; AST, aspartate amino transferase; ALT, alanine amino transferase; IU, international units.

the following signs, symptoms, and findings on physical examination: malaise, somnolence, hepatomegaly, cold extremities, diaphoresis, capillary refill >3 seconds, and a weak pulse. She was given IV saline solution and admitted to the ICU. Chest radiograph revealed bilateral interstitial infiltrates. Laboratory results confirmed H1N1 infection, and oseltamivir treatment (120 mg BID) was started. Ampicillin was initiated for a possible bacterial coinfection.

The patient continued in stable condition, and was confirmed to have DENV-3 infection by RT-PCR. On the eighth day of illness, she developed hypotension, which initially responded to administration of saline solution; however, 6 hours later, her diastolic blood pressure (BP) decreased rapidly; dextran and dopamine were administered, and a central venous catheter was inserted. BP improved and dopamine was reduced, but then somnolence and hypotension were noted, and endotracheal intubation was performed. On the ninth day of illness, norepinephrine was substituted for dopamine, which stabilized BP. A second chest radiograph revealed increased bilateral infiltrates, and antibiotic therapy was changed to ceftriaxone. Over the following 24 hours, the patient's hemodynamic indices and respiration status improved, which was reflected in a third chest radiograph. Norepinephrine was decreased, and the patient was extubated after 65 hours of assisted ventilation in stable condition. She recovered fully and was discharged after 21 days in the hospital.

Case 4

An 11-year-old girl with obesity and asthma presented at the emergency room of HIMJR on September 27 with a history of pain on swallowing for 1 day. The clinical examination was unremark-

able and the patient was released with instructions to return if symptoms worsened. The following morning she presented with the development of high fever, headache, arthralgias, and myalgias in the previous 12 hours. On examination, she was afebrile, breathing regularly, pale, had no hepatomegaly, and had pharyngeal hyperemia, tonsillar hypertrophy, abdominal tenderness, cold extremities, poor capillary refill, and a weak pulse. She was transferred immediately to the critical care area with a presumptive diagnosis of severe dengue. Saline solution was administered intravenously. Afterward, her pulse was 110 and BP was 130/50 mm Hg; she continued to have cold extremities, capillary refill of 4 seconds, and a weak pulse. Two additional boluses of saline solution and then dextran were administered, but the patient continued to have low diastolic BP (110/55). She was treated with dopamine, oxygen, and IV saline solution. Chest radiograph revealed bilateral interstitial and alveolar infiltrates. A diagnosis of pneumonia was made and cefotaxime treatment initiated. Ultrasound revealed a distended gallbladder with thin walls (2 mm), and an echocardiogram was normal. The patient continued in unstable condition with low diastolic pressure, so sepsis was suspected. Norepinephrine was substituted for dopamine. The patient was intubated and the dosing of norepinephrine was increased. Abundant blood-tinged mucous was removed through the endotracheal tube. Eleven hours after presenting at the hospital, the patient developed cardiac arrest and efforts to resuscitate her were unsuccessful. The cause of death was recorded as dengue shock syndrome. A respiratory sample collected immediately post mortem and a blood sample collected at admission were positive for influenza A H1N1 and DENV-3, respectively.

METHODS

A blood sample and nasal and throat swabs were collected for dengue and influenza testing, respectively. Cases were tested for DENV-1–4 by RT-PCR targeting the capsid gene.⁵ The Centers for Disease Control and Prevention's qRT-PCR protocol was followed for the detection of pandemic influenza A H1N1.⁶ Laboratory tests were performed at the Nicaraguan National Virology Laboratory, Ministry of Health.

Comment. We present 4 documented DENV-influenza A H1N1 coinfections in children; all 4 were RT-PCR positive for both viruses. In 3 cases, samples for influenza and dengue RT-PCR testing were taken on the same day; in case 4, the influenza sample was taken postmortem, 1 day after the sample for dengue. While bilateral interstitial and/or alveolar infiltrates were present in all 4 cases, the clinical presentation of the 4 cases varied and a single pattern was not observed. Three patients had a history of asthma, a known risk factor both for severe dengue and influenza.^{7–10}

In case 1, respiratory symptoms were absent. Due to asthma and close contact with a confirmed H1N1 case, the patient was given oseltamivir very early, which may have prevented respiratory symptoms and resulted in a predominately dengue-like clinical presentation, which evolved into shock, possibly aggravated by a bacterial infection. In contrast, case 2 presented with classic flu-like symptoms, including cough, as well as classic dengue symptoms. This patient, though hospitalized, had an illness of only mild-to-moderate severity, possibly due to early treatment with IV fluids when the patient began to display signs of hemodynamic instability. This patient is the only 1 of the 4 cases with no prior history of underlying conditions predisposing to severe influenza and dengue. In the third case, respiratory symptoms preceded the development of dengue symptoms. Oseltamivir treatment was not started until after the child was hospitalized and developing hemodynamic instability. Shock in this patient was different from case 1 and was atypical for dengue, in which the observed hypotension is usually limited to the systolic component. Initially, the patient was diagnosed with viral pneumonia, followed by bacterial pneumonia. The fourth case presented with classic dengue symptoms and rapidly went into shock. Onset of shock 2 days rather than 4 to 6 days postsymptom onset is unusual for dengue, as is a markedly reduced diastolic BP (as in case 3).

In conclusion, we present 4 children with laboratory-confirmed dengue-influenza virus coinfections with varying clinical presentations, and based on this experience, find that coinfections may be a risk factor for severe disease. Due to the range of clinical presentation and difficulties differentiating DENV-influenza coinfections from single infections, especially early on, it is advisable that testing for both viruses be performed when they are cocirculating.

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