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Severe co-infections of dengue and pandemic influenza A H1N1 viruses

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Keywords

Dengue; Influenza; Co-infection; Nicaragua; children

Introduction

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 through October. The influenza and dengue seasons in Nicaragua do not normally overlap, with epidemics of influenza in May–July and dengue epidemics in August–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

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Conflict of Interests

We declare that we do not have any conflict of interests.

anti-viral 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 four patients with dengue virus serotype 3 (DENV-3) and influenza A H1N1 co-infections. 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 H1N1presented 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 one day later with a diagnosis of probable influenza in a local hospital and treated with Oseltamivir (75mg BID) for 2 days. The patient was transferred to HIMJR in critical condition 5 days post-symptom onset, and respiratory and blood samples were collected for RT-PCR. 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 (150mg 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 imipenen and vancomycin. Over the course of the following days, bronchospasms were treated with bronchodilators and corticosteriods. The patient improved clinically and radiographically. He was extubated following 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 (CBC). 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 5th 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 (75mg BID), and continual monitoring of hemodynamic state. The following day, a CBC 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 on September 15, 2 days post-onset of illness, with a temperature of 39.2°C, sore throat, cough, runny nose, swollen cervical lymph nodes, vomiting, and a positive tourniquet test. 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 5th day post-onset, she was given IV saline solution and transferred to HIMJR. Upon admission, the patient was well-hydrated with 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 (120mg BID) was started. Ampicillin was initiated for a possible bacterial co-infection.

The patient continued in stable condition, and was confirmed to have DENV-3 infection by RT-PCR. On the 8th day of illness, she developed hypotension, which initially responded to administration of saline solution; however, 6 hours later, her diastolic 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 performedOn the 9th day of illness, norepinephrine was substituted for dopamine which stabilized blood pressure. 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, 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 unremarkable 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. Afterwards, her pulse was 110 and BP was 130/50 mmHg; 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 blood pressure (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 (2mm), 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 (DSS). 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 four documented DENV-influenza A H1N1 co-infections in children; all four were RT-PCR positive for both viruses. In three cases, samples for influenza and dengue RT-PCR testing were taken on the same day; in Case 4, the influenza sample was taken post-mortem, one day after the sample for dengue. While bilateral interstitial and/or alveolar infiltrates were present in all four cases, the clinical presentation of the four 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 one of the four 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 4–6 days post-symptom onset is unusual for dengue, as is a markedly reduced diastolic blood pressure (as in Case 3).

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

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Table 1

Clinical characteristics of four children with dengue-influenza virus co-infections*

	Case 1	Case 2	Case 3	Case 4
Underlying conditions	Asthma	None	Asthma	Asthma, obesity
Clinical findings				
Max. temperature (°C)	40.0	39.0	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	No
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				
Min. leukocytes (x10,000cells/mm^3)	11.3	3.2	2.2	6
Max. lymphocytes (%)	50	82	73	10
Max. hematocrit (%)	45.0	36.2	35.0	31.9
Min. platelets (x10,000cells/mm^3)	75	92	129	211
Max. creatinine (mg/dl)	1.96	NP	0.50	0.75
Min. albumin (mg/dl)	2.95	NP	4.39	4.43
Max. AST (IU)	278	92	60	38
Max. ALT (IU)	62	32	26	22
Hospitalization data				
Days hospitalized	21	4	21	1 (11 hours)
Mechanical ventilation	Yes	No	Yes	Yes
Intensive Care Unit	Yes	No	Yes	Yes
Outcome	Full recovery	Full recovery	Full recovery	Death

*NP denotes not performed, AST aspartate amino transferase, ALT alanine amino transferase, IU international units