Cambodia Journal of Public Health

Case Report

Severe Dengue Infection and Coinfection with Human Parainfluenza Virus-3

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Received January 09, 2024; revised March 04, 2024; accepted March 11, 2024

ABSTRACT

Introduction

Dengue infection is an endemic disease in Southeast Asia. Cambodia is located in Southeast Asia and has a belt of disease distribution. According to the Cambodia National Dengue Control Program, thousands of cases are reported annually, and the mortality rate significantly decreased from 1.19% to 0.9% between 2002 and 2020. Human parainfluenza virus (HPIV) is the second most common respiratory virus infection in children followed by respiratory syncytial virus. In the past, there has had no case reports of dengue virus and HPIV co-detection, which makes it challenging for clinicians to comprehend this mixed infection. Therefore, we present our first confirmed case, which we were able to share with other physicians to enhance their knowledge and experience.

Case Presentation

A 4-year-old girl was initially diagnosed with Dengue infection (Ns1 Ag+) upon her admission to the National Pediatric Hospital. She arrived complaining of malaise, coughing, and a high fever for 2 days. In the following days, she presented with a severe form of dengue (dengue hemorrhagic fever) with plasma leakage, bleeding, electrolyte imbalance and organ compromise. After passing the critical phase of dengue, which is usually the patient's recovery period, she did not. She required prolonged oxygen therapy sessions and exclusively supportive care, as her respiratory system continued to worsen. Additionally, her extremely elevated liver enzymes raised concerns regarding her liver function. This could lead to liver failure and death. Later, her conditions were found to be associated with HPIV-3 coinfection. Significantly, she managed to recover completely despite having a prolonged fever for ten days and eleven days after being admitted.

Conclusion

Dengue and HPIV-3 coinfection can cause serious health problems. The clinical manifestations of the patient were persistent, complicated, deterioration, and prolonged hospitalization. Any unusual presentation of dengue infection should be suspected of comorbidity or coinfections. However, further observations and the collection of other future data are needed for more evidence.

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Keywords DHF: Dengue hemorrhagic fever, HPIV-3; Human parainfluenza virus-3, Ns 1 Ag+; Ns1 antigen positive

Introduction

Dengue infection is an endemic disease in Southeast Asia, including Cambodia. This tropical disease remains a health burden to the general population. From 2002–2020, 353 270 dengue incidences were reported via Cambodia National Dengue Surveillance. Notably, the mortality rate decreased to 0.9% from 2014–2020 [1]. The severity of dengue depends on known risk factors, including infancy, obesity, and coinfections. Currently. Different microorganisms are co-detected with dengue infection. This factor of disease severity also relies on the type of species, such as bacteria, viruses, or parasites. To our knowledge, coinfection between dengue virus and human para-influenza virus 3 (HPIV-3), a common virus of lower respiratory tract infection, has not been reported as a practice clinician. Therefore, it is difficult for physicians to understand these mixed infections, and patient prognosis is unpredictable.

In this report, we present a case of severe dengue infection with comorbidities of HPIV-3. The patient presented many complications such as plasma leakage, bleeding, electrolyte imbalances, and vital organ dysfunctions. Additionally, patient clinical signs and symptoms continued to deteriorate despite the recovery stage of dengue. She experienced prolonged fever with respiratory distress. We also reported the case management and posthospital follow-up information with an overview of other literature.

Case Presentation

A 4-year-old girl was referred to our National Pediatric Hospital (NPH) due to high fever (39 °C) for two days, poor appetite, dry cough, and weakness. Her mother also bought some medications at a nearby pharmacy to treat her illness, but her conditions did not improve. Therefore, the mother took her to the NPH for further care and management.

The patient completed her childhood vaccination according to the National Immunization Program. She had no history of any allergy or contact with other patients. Her mother reported the child started to feel unwell on 18 July 2023 and was less physically active. She had a high fever of 39°C, was chilled, and refused her daily appetite. In the outpatient department (OPD) of the NPH, physical examination revealed that her temperature was 37.7°C with mild dyspnea and malaise, and her pharynx was mildly red. Therefore, she was admitted to the In-Patient Department, Infectious Disease Unit of the NPH, for further investigations, clinical follow-up, and management.

On the first day of admission, she was clinically diagnosed with acute pharyngitis and possibly sepsis. Blood tests for septic patients, such as complete blood count, C-reactive protein (CRP), blood culture, and the dengue Ns1 Ag test, were subsequently performed. Then, she was prescribed ceftriaxone and other supportive care, such as intravenous fluid and antipyretic drugs. During her first two days, her condition did not improve, and she continued to experience fever, poor intake, and mild dyspnea. Additionally, the results of her blood test showed that she was contracting dengue infection, as her serum NS1 Ag was positive for leukopenia and hypokalemia. Other blood test results, such as hemoglobin and platelets, were still within the normal limits.

On the following day of her illness, her condition worsened. On the third day after admission, she presented with a severe form of dengue infection, dengue hemorrhagic fever (DHF). She complained of repeated vomiting and abdominal pain and was unable to eat her meal. She had plasma leakage, and her blood concentration increased with increasing hematocrit (Hct 37%-43%) and decreasing the platelet count (290,000/ml to 56,000/ml). The critical phase of dengue is generally in the afebrile phase, but patients continue to have a high fever and malaise. The patient was managed for severe dengue or DHF by intravenous isotonic fluid solution. Her fluid resuscitation ranged from 3 ml/kg/h to 8 ml/kg/h based on the Cambodia guidelines for dengue infection, with plasma leakage lasting approximately 48 hours [2]. Significantly, the patient did not need any hypertonic solutions, such as Dextran or Voluven, and demonstrated major bleeding. The following investigations were also performed to verify her clinical presentations, including complete blood count, electrolyte, albumin, liver function, coagulation factor, etc. The results showed that she had problems with many serum abnormalities, including electrolyte imbalances (hypokalemia, hypocalcemia), hypoalbuminemia, and prolonged coagulation (PT/APTT) factors, which need to be corrected. Additionally, she exhibited substantial fluid accumulation in both the abdominal and pleural cavities **(Figure 01 and 02)**, which compromised her respiratory compliance and gastrointestinal tract. She also needed oxygen support and a diuretic (furosemide) to increase fluid excretion the following day.

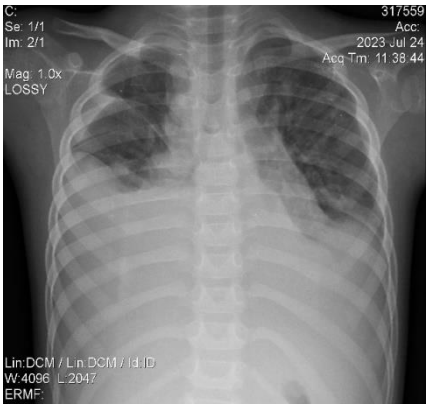

Figure 01: Both Pleural effusion and predominantly at right side

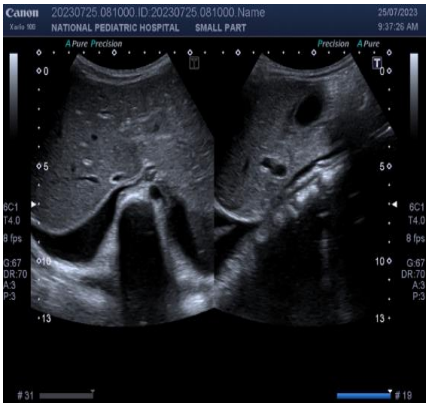

Figure 02: Abdominal ultrasound showed both pleural effusion and ascites

Another serious symptom was fever during the entire critical phase as well as the recovery phase. Normally, fever disappears during the severe dengue phase, which is why it is called the afebrile phase. This presentation made her in general condition unwell. She was tired, had cough, a runny nose, dyspnea, and refused meals. Physical examination revealed lung cracking, chest retraction, and abdominal distention. She preferred to rest in an upright position, as she was worse and had difficulty breathing when changing her position. The patient was clinically diagnosed with concurrent pneumonia with dengue infection and clinical sepsis. Therefore, septic investigations, including blood culture, were repeated. Board spectrum antibiotics such as meropenem were also prescribed because her clinical signs and symptoms progressively worsened, although she was treated with a first-line antibiotic (ceftriaxone) beginning on the first day after admission. Moreover, nasal and throat swabs were also collected and sent for molecular diagnostic (PCR) at the same time to assess for respiratory virus infection. Her PCR result was reported on 26 July 2023, with HPIV-3 **(Figure 03**), a subtype of HPIV. Her blood test results also indicated that she was suffering from liver failure with very high transaminase levels (ALT/AST; 3680/1967 U/L). Therefore, oral lactulose was also added to prevent hepatic encephalopathy by increasing the amount of ammonia eliminated.

Nine days after admission, the patient was diagnosed with severe dengue infection with many complications, and clinical complications were associated with mixed respiratory system infections. Other cultures, including urine and blood, were also released the following day, and there was no bacterial growth.

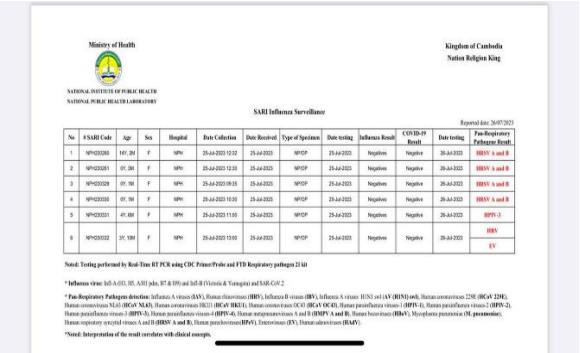

Figure 03: PCR test showed HPIV-03 infection (Number 05)

On day 11 after admission, the patient's clinical presentation started to recover. Her fever decreased, her appetite increased, and she had less dyspnea. All her serum electrolytes returned to normal levels, stabilized her cell count, and improved her transaminitis and elevated her liver enzymes. The patient's condition progressively improved, and there were no complications or illnesses. The patient was discharged on 29th July 2023, with at-home follow-up. Two follow-ups after discharge were performed for clinical re-evaluation, and essential blood tests, such as liver enzymes, were monitored. During her follow-up on August 4th and August 25th, 2023, she recovered well. All blood tests were normal. Therefore, her final diagnosis was severe dengue and respiratory compromise by dengue virus and HPIV-3 infection.

Discussion and conclusions

Cambodia is in a belt of endemic dengue infection. From 2002 to 2020, the mortality rate decreased from 1.19% to 0.9% [1]. However, severe forms of dengue can cause death. Disease severity is generally known to be triggered by several factors, including secondary dengue infection, dengue serotypes and preexisting conditions (i.e., infancy, obesity) [2]. Currently, different organisms, such as parasites, bacteria, and viruses, have been reported to play additional roles in mixed infections, such as malaria, typhoid,

chikungunya, COVID-19, Zika, HIV, and hepatitis A [3].

HPIV is commonly co-detected with other respiratory viruses, such as rhinovirus, enterovirus, or influenza. HPIV is generally a respiratory infection in younger children, especially those younger than 2 years. There are four antigenically distinct HPIVs that can be divided into HPIV-1 to HPIV-4, and HPIV-3 is often associated with bronchiolitis or pneumonia in children [4]. HPIV is the second leading cause of acute respiratory illness-related hospitalizations in children under five years of age after RSV infection [4].

Dengue infection can be divided into 3 phases: the febrile phase, the afebrile or critical phase, and the recovery phase. The afebrile or critical phase is a severe stage of dengue infection and can cause death due to plasma leakage and bleeding. The afebrile stage is characterized by the transition from febrile to afebrile [5]. This patient still had fever despite plasma leakage. Hence, afebrile symptoms alone should not be used to determine the critical phase of dengue, as coinfection can cause dengue patients to continue having fever. Additionally, clinical diagnosis in our patient was challenging, as severe dengue could also cause respiratory symptoms as HPIV does.

The treatments for dengue and HPIV-3 are only supportive care. Most HPIV-3 strains recover on their own since there is no licensed antiviral agent [6]. However, supportive care for dengue infection, especially DHF, is different since it is crucial for preventing mortality. IV fluid correction is a cornerstone treatment for severe dengue to appropriately maintain vascular circulation and urine output. Furthermore, other aspects of severe dengue, such as electrolyte abnormalities, coagulation disorders, organ dysfunctions, and bleeding, also need to be critically evaluated and properly managed [5].

In short, we describe a never-reported case of severe dengue infection with HPIV-3 coinfection. The patient's condition continued to deteriorate after admission, and she needed many days in the hospital to receive supportive care and curative treatment. Fever and respiratory distress were also unusually prolonged due to the coinfection. She suffered many consequences, such as plasma leakage, bleeding, electrolyte disorders, and organ dysfunctions. Without the use of PCR to identify respiratory viruses, management and treatment are challenging due to the unidentified causes of coinfections and unpredictable prognoses.

Abbreviations

APTT: Partial thromboplastin time, ALT: Alanine transaminase, AST: Aspartate transferase, CRP: C-Reactive protein, DHF: Dengue haemorrhagic fever, HCT: Haematocrit, HPIV: Human para-influenza virus, NS1 Ag: NS1 Receptor antigen, NPH: National Paediatric Hospital, PT: Prothrombin time, RSV: Respiratory syncytial virus

Author contributions

CN wrote the manuscript. THP was the treating physician and revised the manuscript. All the authors have read and approved the final manuscript.

Funding

Not applicable.

Declarations

The consent was obtained directly from the patient's mother for the publication.

Competing interests

The authors declare that they have no competing interests.

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