Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.64, No.3(2024). p.281-6 ; DOI: https://doi.org/10.14238/pi64.3.2024.281-6

Case Report

Comparison between COVID-19 with DHF co- infection and COVID-19 alone in two pediatric siblings

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We report herein the difference between Corona virus disease-19 (COVID-19) and dengue hemorrhagic fever (DHF) co-infection compared with COVID-19 alone in two pediatric sibling patients. This case report highlights a 10-year-old boy with both COVID-19 and DHF who had less severe coagulation disorder than his sister with COVID-19 alone. In a patient with a dual infection, the presence of dengue antibodies may induce immunological protection against COVID-19. We found reports of milder symptoms in patients who had dengue prior to SARS- CoV-2 infection; however, the opposite occured when SARS-CoV-2 infection precedes dengue.**[Paediatr Indones. 2024;64:281-6; DOI: 10.14238/pi64.3.2024.281-6**].

Keywords: *coronavirus; dengue; antibody; DENV; SARS-CoV-2*

Indonesia has the highest rate of dengue fever case in Asia and the second highest worldwide.[1] In the COVID-19 pandemic, it was a challenge to distinguish between the two infections due to similar clinical and laboratory features. Several studies have shown COVID-19 and dengue co-infection virus (DENV) serotypes 1 and 2. [2,3] Before the COVID-19 pandemic, there was a severe dengue outbreak of 2019 in North Sulawesi that was dominated by the DENV-3 serotype.[4] Interestingly, a study in Brazil showed an increase incidence of dengue fever, followed by a decrease incidence of COVID-19,[5] and another study demonstrated the possibility of mimicry between DENV and SARS-CoV-2 antibodies.[6]

This case report describes the differences between a patient with COVID-19 and dengue hemorrhagic fever (DHF) co-infection and the other with only COVID 19. We also review the literature on prior dengue disease with severity of COVID-19 and vice versa.

The cases

Case 1

A previously healthy 10-year-old boy admitted to Wolter Monginsidi Army Hospital Manado, developed fever 4 days before admission. He had productive cough for 3 days before admission, as well as experienced spontaneous epistaxis and abdominal pain 1 day before admission. Both of his parents were confirmed to have COVID-19 and were hospitalized during his admission. On admission, his vital signs were normal. His physical examination revealed

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Submitted January 11, 2023. Accepted May 28, 2024.

hyperemic tonsils and pharynx as well as liver enlargement.

Laboratory findings were as follows: hemoglobin 15.3 g/dL, hematocrit 42.9%, white blood cell count 2,770/μL, platelet count 115,000/μL, eosinophil count 0%, lymphocyte count 60.7%, neutrophil count 31%, neutrophil lymphocyte ratio (NLR) 0.51, absolute lymphocyte count (ALC) 1,681/μL, serum glutamic oxaloacetic transaminase (SGOT) 89 U/L, serum glutamic pyruvic transaminase (SGPT) 102 U/L, prothrombin time (PT) 12.9 seconds (control 11.5-15 seconds), activated partial thromboplastin time (aPTT) 27.7 seconds (control 28-38.6 seconds), international normalized ratio (INR) 0.97 (control 0.5-0.8), and D-dimer 1,053 ng/mL. Dengue serology testing was positive for anti-DENV immunoglobulin M (IgM) and negative for anti-DENV immunoglobulin G (IgG). Both rapid antibody testing and reverse-transcription polymerase chain reaction (RT-PCR) were positive for SARS-CoV-2. Chest X-ray (CXR) examination revealed infiltrate in both lungs, suggestive of pneumonia. On the second day of care, the patient developed generalized macular erythematous rash (**Figure 1**). On the third day, his platelet count decreased to 82,000/mm^3.

The boy was diagnosed with dengue hemorrhagic fever grade 2 and COVID-19. He was given intravenous fluid, cefixime (200 mg per 12 hours orally), paracetamol (500 mg t.i.d.), vitamin B complex twice a day, and vitamin C (500 mg b.i.d.). The patient was discharged after 10 days of isolation, without any sequelae.

Case 2

A 7-year-old girl was admitted to Wolter Monginsidi Army Hospital Manado with complaints of abdominal discomfort. She was the younger sister of patient in case 1. She had no fever, cough, or shortness of breath. The parents and brother of this girl were confirmed to have COVID-19 with negative dengue serologic test and were still hospitalized when she was admitted. On admission, her vital signs were normal, with other physical examinations within normal limits.

Laboratory findings showed hemoglobin 13.2 g/dL, hematocrit 36.3%, white blood cell count 10,000/μL, platelet count 539,000/μL, eosinophil count 0%, lymphocyte count 49.4%, neutrophil count 42.1%, NLR 0.85, ALC 4,210/μL, SGOT 21 U/L, and SGPT 15U/L, PT 13.2 seconds (control 11.5-15 seconds), aPTT 40.4 seconds (28-38.6 seconds), INR 1.00 (control 0.5- 0.8), and D-dimer 13,551 ng/mL. Rapid antibody testing and RT-PCR were positive for SARS-CoV-2. As with her brother, CXR examination showed infiltrate in both lungs, suggestive of pneumonia.

Diagnosed with COVID-19, this girl was given paracetamol (350 mg t.i.d.), vitamin B complex twice a day, vitamin C (200 mg t.i.d.), zinc 20 mg once a day, and vitamin D 1000 U once day. The patient was discharged after 10 days of isolation, without any symptoms.

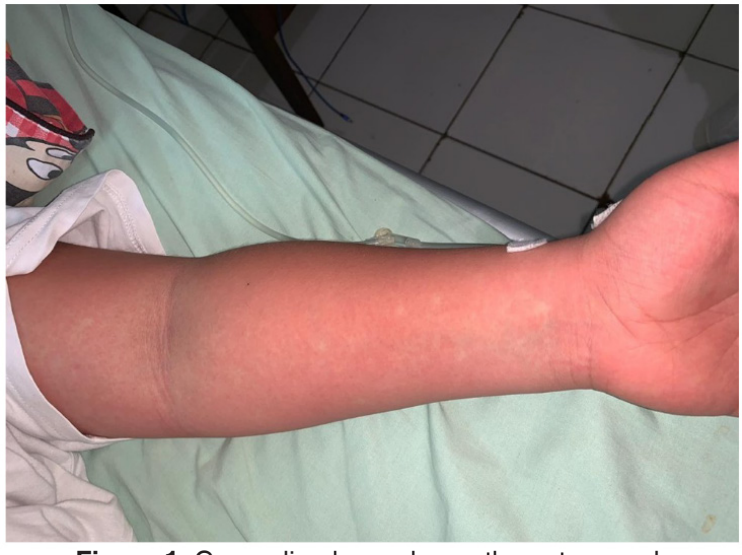

Figure 1. Generalized macular erythematous rash

Discussion

Our cases provide evidence that dengue and COVID co-infection may occur in dengue endemic areas. The disease course of COVID-19 with DHF co-infection compared to COVID-19 alone is illustrated in **Figure 2**.

Abdominal pain or discomfort is a common symptom in both COVID-19 and DHF whose pathophysiology are different. Abdominal pain in DHF is known to be caused by lymphoid follicle hyperplasia and plasma leakage[7] where possible subserous fluid collection and thickened gallbladder occur with dengue fever.[8] The dominant symptom in the 2nd case was abdominal pain, without fever. Common symptoms of COVID-19 are fever and gastrointestinal symptoms, including diarrhea, vomiting, and abdominal pain.[9] A meta-analysis concluded that COVID-19 patients with severe disease are seven times more likely to have abdominal pain than patients with non-severe disease. This may be due to the degree of viral replication, and histopathology has confirmed ischemic conditions with patchy necrosis in the bowel. Bowel ischemia is suggested to be due to the formation of tiny blood clots (hypercoagulable state), marked by increases in D-dimer and fibrinogen levels.[10,11] The gastrointestinal tract is one of the main extrapulmonary targets of SARS-CoV-2, most likely due to the presence of angiotensin-converting enzyme 2 (ACE2) receptors.[12] In the 2nd case, patient had abdominal pain and a marked increase in D-dimer. These results are in line with recent systematic review reporting significantly elevated D-dimer levels in severe COVID-19.[13] Several studies have reported COVID-19 severity with the degree of both extravascular and intravascular fibrinolysis. Severe COVID-19 increase more pro-inflammatory cytokines, leading to the increased of formation and degradation of plasmin. The interplay between the inflammation and coagulation pathways results severe coagulation disorders in patients with COVID-19.[13]

A study in Brazil showed a significant negative correlation between COVID-19 mortality rates and the percentage of the state population with positive anti-DENV IgM. Moreover, a state with a higher prevalence of dengue fever cases for 2019-2020 reported fewer COVID-19 cases and deaths.[6] These results were in line with data from the Brazilian Ministry of Health and previous studies in Asia, Latin America, and islands in the Pacific and Indian Oceans.[5,6] Overall, a region with a higher incidence of dengue had a lower number of COVID-19 cases and lower COVID-19-related mortality. It was proposed to be related to cellular and humoral cross-reactivity between one or more DENV and SARS-CoV-2 serotypes.[5,6] Moreover, the B cells, T cells, and antibodies produced due to dengue infection that provide specific protection against dengue may also lead to clinically significant immunity to COVID-19.[6] Cross-reactivity between dengue virus and SARS-CoV-2 antibodies has revealed some antigenic similarities, as reported in Singapore, India, and Latin America.[14,15] A study in Brazil involving 2,351 participants showed that symptoms of COVID-19 were more pronounced in patients with a history of dengue due to an enhanced inflammatory response, despite the lower mortality. The study reported COVID-19 patients with previous dengue infection showed a lower risk of mortality at the 60-day follow-up.[16] These results suggest that prior dengue infection might induce immunological protection against COVID-19.

The pathophysiology of dengue, which is often more severe during the second infection, is caused

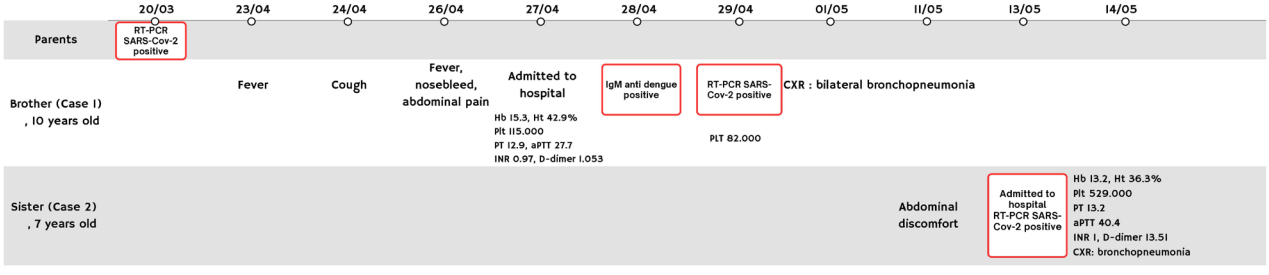

Figure 2. Timeline of disease and examination results of the family

by antibody-dependent enhancement (ADE). Neutralization of DENV occurs when DENV-specific antibodies prevent binding between virions and receptors on the host cell wall or endosome membrane fusion. In the case of ADE, DENV-specific antibody levels are too low to occupy all binding sites for virions to prevent the virus from entering host cells. This is especially true due to non-neutralizing antibodies, as in a second DENV infection, as the causal agents are a different serotype from the previous infection. As a result, the virion-antibody complex enters the host cell by attaching to the Fc receptor of immune cells, such as B lymphocytes, NK cells, macrophages, neutrophils, and mast cells. Activation of these immune cells results in a cytotoxic and proinflammatory state in the body, which aggravates clinical symptoms.[17] Furthermore, Nath et al. showed a positive correlation between the amount of neutralizing antibody and the degree of pathological injury in COVID-19. They also reported that SARS-CoV-2 can enter macrophages with the help of the Fc receptor during ADE.[18]

A high viral load in COVID-19 has the potential to cause ADE to develop with severe symptoms because the neutralizing antibodies formed are not sufficient to mask all binding sites. The duration of viremia is longer in COVID-19 than in dengue (up to 10 days, rather than 7 days).[19,20] Thus, in the case of COVID-19 and dengue co-infection with dengue occurring first, the chance for ADE to occur is lower due to the shorter viremia duration of DENV.[21,22] Additionally, the DENV antibodies produced may help to neutralize SARS-CoV-2, hence explaining the milder clinical manifestations.[21] Conversely, in the case in which COVID-19 precedes dengue, or in the case of overlapping infection of COVID-19 and dengue infection, there are insufficient antibody levels to overcome or neutralize both viruses due to the longer viremia duration of SARS-CoV-2, in combination with DENV viremia thereafter. Thus, there is a higher chance of ADE due to ineffective binding of sub-neutralizing concentrations of antibodies to the virion, resulting in cytokine storms and worse clinical manifestations. We found reports of milder symptoms in patients who had dengue prior to SARS-CoV-2 infection;[2,3] however, symptom aggravation occurred with the opposite (SARS-CoV-2 infection prior to dengue).[23-26] The disease timeline from all reported cases is depicted in **Figure 3**.

In conclusion, in DHF endemic countries, COVID-19 and DHF co-infection may occur. This report describes that coagulation disorders may be more severe in COVID-19 alone than in COVID-19 and DHF co-infection. These results also suggest that some immunological protection against subsequent COVID-19 may occur in COVID-19 with DHF when DHF occurs first, resulting in a milder disease course.

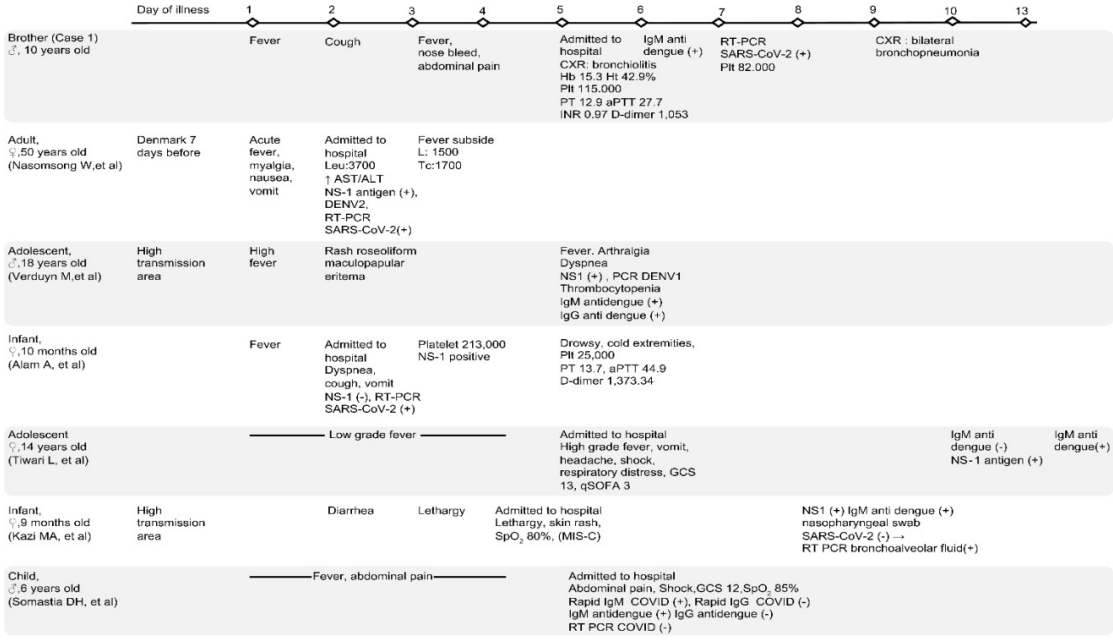

Figure 3. Timeline of illness in cases of co-infection

Conflict of interest

None declared.

Acknowledgement

We thank the pediatricians, health workers and COVID-19 team of Robert Wolter Mongisidi Army Hospital and pediatric residents of Sam Ratulangi University.

Funding acknowledgement

The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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