Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.64, No.4(2024). p.363-8; DOI: https://doi.org/10.14238/pi64.4.2024.363-8

Case Report

H1N1pdm09 infection in children: a case report of reemerging disease in COVID-19 pandemic

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An outbreak of H1N1 infection was first declared by the *World Health Organizatio*n in 2009 and confirmed in the post-pandemic phase in 2010. Amid the COVID-19 pandemic, we found a confirmed case of H1N1pdm09 in Bunda Women and Children Hospital Jakarta. A 13-year-old boy was referred to our hospital after four days of hospitalization due to worsening tachypnea following a productive cough and fever. The patient had severe dyspnea with inspiratory effort and oxygen desaturation to 80%, therefore admitted to our pediatric intensive care unit. On physical examination, the patient had increased work of breathing, looked irritable, had a respiratory rate of about 40x/minute with non-rebreathing mask support, and crackles were heard in both lungs. Chest X-ray showed right bronchopneumonia. There was a history of a generalized seizure for less than 1 minute, which stopped spontaneously in previous hospital care. The patient was diagnosed with mucopolysaccharidosis at age six years old and has never received enzyme replacement therapy. Laboratory results revealed thrombocytopenia, leukopenia, neutrophilia, monocytosis, high c-reactive protein and procalcitonin, and elevated liver enzymes. The investigation of etiology was performed using the respiratory panel test and showed a positive real-time polymerase chain reaction for H1N1pdm09 and Influenza A. The patient was given oxygen therapy with a high-flow nasal cannula with an oxygen fraction of 40% and a flow of 20 liters per minute, fluid maintenance while fasting, antibiotics, inhaled β-2 agonists, and a neuraminidase inhibitor (oseltamivir). The patient's clinical and laboratory markers improved on the third day of treatment, and he was discharged two days later. **[Paediatr Indones. 2024;64:363-8; DOI: 10.14238/pi64.4.2024.363-8**].

Keywords: *H1N1pdm09; influenza A; COVID-19 pandemic*

The H1N1pdm09 influenza pandemic was first declared by the *World Health Organization* (WHO) on June 11, 2009, and ended on August 10, 2010. During this pandemic, it was estimated that H1N1pdm09 infected around 100 million people and caused 75,000 deaths worldwide.[1] In Indonesia, the first case of H1N1pdm09 was announced by the Minister of Health of the Republic of Indonesia on June 24, 2009.[2] Influenza A virus is a pathogen that can modify its main surface proteins, named hemagglutinin (HA), which allows the virus to attach to epithelial cells in the upper respiratory tract, and neuraminidase (NA), which acts in the replication and spread of the virus into respiratory tract mucosa.[3] Influenza A virus antigenic variability can occur as antigenic drift (nucleotide replacement, deletion, and insertion of HA and NA genes) or antigenic shift (changes in HA and/or NA genes), potentially leading to a pandemic source.[4] The most significant change is the genetic recombination of swine and avian influenza

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Submitted October 5, 2022. Accepted September 3, 2024.

viruses with viruses that infected humans, such as those that caused the pandemics in 1918 (H1N1), 1957 (H2N2), and 1968 (H3N2). The H1N1 virus reappeared in 1977, and continues to be transmitted amongst humans.[5,6]

Although H1N1pdm09 influenza infection has been considered a seasonal flu, this infection may result in significant morbidity and mortality in vulnerable individuals, such as patients with neurodevelopmental disorders, neuromuscular diseases, chronic lung disease, heart failure, immunosuppression, chronic kidney failure, and metabolic disorders.[7] Identification of H1N1pdm09 infection during the COVID-19 pandemic posed a challenge, considering the similarity of its symptoms to other respiratory tract infections. The real-time polymerase chain reaction (RT-PCR) respiratory infection panel examination can detect several pathogens that cause respiratory tract infections and is the gold standard in establishing the etiology. However, as its availability is still limited in Indonesia, suspected cases of H1N1pdm09 infection rarely obtain a definitive etiologic diagnosis. Therefore, we present a case of H1N1pdm09 in Jakarta to illustrate the clinical manifestations of the infection in Indonesia.

The case

A 13-year-old boy with a body weight of 45 kg and height of 155 cm had been hospitalized for four days prior with shortness of breath preceded by non-productive cough and fever. On the fifth day of hospitalization, the patient's condition worsened as he had severe shortness of breath, increased inspiratory effort, and oxygen desaturation up to 80%. He was referred to the pediatric intensive care unit (PICU) at Bunda Women and Children Hospital, Jakarta. Upon arrival, the patient had severe dyspnea, chest retractions, and nasal flaring, looked irritable, and coughed frequently. On physical examination, his respiratory rate was 40 breaths per minute on 10 liters per minute (lpm) of oxygen with a non-rebreathing mask (NRM), and crackles were heard on both lungs. Despite using NRM, the oxygen saturation only reached up to 92%. Chest X-ray showed an appearance of perihilar infiltrates in the right lung, suggesting bronchopneumonia.

At the age of 6 years, the patient was diagnosed with mucopolysaccharidosis type 3 (MPS III), but had never undergone enzyme replacement therapy. During the previous hospitalization, the patient had a history of a single generalized seizure that lasted for one minute and ceased spontaneously. A non-contrast brain CT scan revealed ventriculomegaly and brain atrophy, leading to the temporary working diagnosis of bronchopneumonia and mucopolysaccharidosis.

Laboratory findings in the PICU revealed a hemoglobin level of 12.6 g/dL, a white blood cell count of 3.660/μL, a platelet count of 71,000/μL, a segmented neutrophil count of 52.4%, lymphocyte count of 35.5%, and monocyte count of 11.5%, giving the impression of monocytosis suggestive of a viral infection. C-reactive protein level was 22.26, procalcitonin level was 0.19, and electrolyte levels (sodium, potassium, and chloride) were within normal limits. Blood gases, taken when the patient received high-flow nasal cannula (HFNC) oxygenation with an oxygen fraction (FiO_2) of 45% and a flow of 25 lpm, showed a pH of 7.43, PCO_2 of 29.4 mmHg, PO_2 of 138.2 mmHg, HCO_3 of 19.1, and base excess (BE) of -3.8. Random blood glucose was 125 mg/dL. Subsequently, a respiratory infection panel examination (*QIAstat-Dx Respiratory SARS-Cov2*, *QIAGEN*, Venlo, The Netherlands) using a PCR method was performed on the patient. The panel detected influenza A (29.5/215,589) and influenza A H1N1 pdm09 (29.3/54,115) viruses. The SARS-Cov2 virus was not detected in the current respiratory infection panel test or previous SARS-CoV-2 PCR examination at the time of admission.

While in the PICU, the patient was given oxygen support with HFNC 25 lpm, FiO_2 45%. He was fasted and a nasogastric tube (NGT) was placed. Treatment consisted of maintenance intravenous fluids, intravenous antibiotics of 25 mg/kg cefoperazone-sulbactam every 8 hours, inhalation with beta-2 agonists every 8 hours, 10 mg/kg of acetaminophen if needed, 20 mg of zinc once daily, and 75 mg of oseltamivir twice a day for five days. As the patient seemed agitated and difficult to console during monitoring, he was given a low dose of dexmedetomidine 0.04 mcg/kg/hour and monitored for vital signs periodically, considering its risk for bradycardia.

By the third day of treatment in the PICU, the

patient's clinical appearance had improved. Fever and seizures were not found throughout treatment. Cough still occurred occasionally, but there was no shortness of breath. Crackles were still found on physical examination, but we were able to gradually wean the oxygen therapy with his improved oxygen saturation. The patient was able to tolerate 8x50 mL of enteral feeding via NGT. Antibiotics and antivirals were continued, with the addition of oral N-acetylcysteine and esomeprazole. On the fourth day of treatment, the patient's oxygen saturation reached 100% using a nasal cannula and he was able to take oral feeding. His laboratory parameters such as platelets and CRP showed improvement (**Table 1**). He was transferred to the hospital ward and discharged the following day.

Discussion

The main symptoms experienced by patients with H1N1pdm09 infection are fever and cough, followed by other symptoms such as runny nose, fatigue, sore throat, dizziness, shortness of breath, and gastrointestinal problems such as diarrhea and vomiting. A retrospective analytical study in Austria reported that fever and respiratory symptoms were the most common symptoms in patients under 18-year-old.[8] Similar findings were found in a retrospective descriptive study in Indonesia.[9] The patient experienced the same symptoms as in our case; the complaint of shortness of breath was felt after being preceded by cough and fever. Our patient's history of MPS III posed a challenge in assessing other symptoms because his delayed behavioral development prevented effective communication of subjective complaints. MPS III is caused by abnormalities in lysosomal storage due to a deficiency in the breakdown

Table 1. Summary of laboratory findings during treatment

Laboratory markers	Before admission to the PICU	First day of care (PICU)	Second day of care (PICU)	Third day of care (PICU)	Fifth day of care (non-PICU)
Haemoglobin	12.8	12.6		13.6	13.9
Haematocrit	39.2	38.7		41	42.2
White blood cells	3,380	3,660		5,510	7,040
Platelets	64,000	71,000		105,000	216,000
Differential count					
Basophil	0.3			0.4	0.6
Eosinophil	0.3			0.9	2.6
Neutrophil	52.4			46.1	32.8
Lymphocyte	35.5			41.2	48.4
Monocyte	11.5			11.4	15.6
C-reactive protein	38.88	22.26		12.74	
Procalcitonin	0.78	0.19		0.08	0.07
Sodium	146	141			
Potassium	3.65	3.84			
Chloride	106	97			
AST	81				
ALT	51				
NS1 Dengue antigen	Negative				
Lactate			2.1	1.5	
Blood gas analysis					
pH		7.43	7.38		
pCO_2		29.4	38.8		
pO_2		138.2	25.4		
HCO_3		19.1	22.7		
Base excess		-3.8	-2		

of glycosaminoglycans (GAGs). This disease is inherited by an autosomal recessive pattern and is characterized by progressive neurodegeneration.[10,11] In this case, the patient has not received treatment for MPS III.

Several retrospective studies and a multicenter study in Spain in the pediatric population showed that central nervous system disorders were one of the predictors of H1N1 infection cases for worsening and admission to the intensive care unit.[8,12,13] Having a history of seizures followed by severe shortness of breath led the patient to be referred to our hospital to be monitored in the PICU. A retrospective study in Colorado of 307 pediatric patients with confirmed H1N1pdm09 showed seizures, impaired consciousness, dyspnea, and hypoxia significantly associated with the indication for intensive care admission.[13]

As the clinical manifestation and radiological findings led to the possibility of pathogens causing pneumonia, the respiratory infection panel test was conducted to investigate the etiology. In this case, the respiratory infection panel test used a real-time PCR multiplex nucleic acid test for qualitative detection and differentiation of nucleic acids from several respiratory viruses and bacteria. The procedure was carried out by performing a nose and throat swab.[14] In a population-based study on pediatric pneumonia patients in the United States, the most frequently detected pathogens were respiratory syncytial virus (28%), human rhinoviruses (27%), adenovirus (11%), mycoplasma pneumonia (8%), and influenza (7%).[15] However, our patient's respiratory panel yielded H1N1pdm09 and influenza A.

Influenza A H1N1pdm09 virus is a new strain of H1N1 influenza virus that was easily transmitted from human to human and caused a pandemic in 2009. Influenza A and B viruses have different types of proteins on their surfaces, named haemagglutinin (HA) and neuraminidase (NA), which was the main reason for mutation, antigenic shift, and antigenic drift in virus evolution.[4] Influenza transmission can be affected by several factors, including the potential for infection, population susceptibility, and the risk of contact between susceptible and infected individuals. The H1N1 virus is transmitted from person to person mainly via droplets when an infected person coughs or sneezes.[16]

Influenza infection can cause mild to severe manifestations, even fatal, particularly in high-risk populations, such as children, pregnant women, the elderly, immunocompromised patients, and people with chronic or other comorbid medical conditions. A study by involving neonatal to elderly patients showed that H1N1pdm09 had the highest detection rate in children aged 5-11 years.[17] Children in their growth period and adolescence are the most vulnerable groups, where every 2 out of 5 infected children are under the age of 14 years.[18] Another study in Indonesia also reported that most cases of H1N1 were found in the age group of 12-18 years.[9] Our patient belonged to this age group of high susceptibility.

Laboratory parameters in our patient revealed leukopenia, thrombocytopenia, elevated transaminase enzymes, and C-reactive protein (CRP). Significantly, elevated CRP was found more frequently in pediatric H1N1pdm09 cases than in adults.[8] This aligns with studies reporting a correlation between elevated CRP levels with the clinical course of illness and poor outcomes in influenza infection.[19] Thrombocytopenia is often found as a complication of influenza virus infection. A study reported an association between viral load and platelet count in patients with 2009 H1N1/A virus infection. The patients with high viral load were reported to have severe thrombocytopenia. This is due to the process of phagocytosis by platelets in vivo against the influenza virus. Thus, it is possible for platelet-mediated transport for the virus to circulate in the blood circulation. In addition, the uptake of viral particles by platelets requires binding to sialoglycals and causes the disposal of sialic acid by viral neuraminidase, which will trigger hepatic clearance of platelets.[20]

Oseltamivir is the most commonly used oral medication approved for seasonal influenza and swine flu (swine flu/H1N1) treatment. In general, two classes of antiviral drugs have been approved as therapy for both Influenza A and B, either by blocking protein pumps (rimantadine and amantadine) or by inhibiting NA (oseltamivir and zanamivir). The latter are preferred as antiviral therapy in influenza cases, due to the low rates of drug resistance against these agents.[18,21] Oseltamivir works as NA inhibitor that plays a role in blocking influenza virus proteins. Several studies have shown the benefits of taking oseltamivir for expediting clinical improvement and

reducing the length of stay. In the previous Indonesian study, oseltamivir was beneficial in preventing severe complications and mortality, also remained beneficial in cases with a delayed onset to the first dose of more than 48 hours.[9] A previous study also recommended early treatment with Oseltamivir for patients whenever an Influenza A H1N1pdm09 was suspected or diagnosed epidemiologically, regardless of age.[22] In our case, the patient showed significant clinical improvement following oseltamivir administration within the first 24 hours, even though the administration was more than 48 hours after symptom onset.

In conclusion, the findings of H1N1pdm09 infection and influenza A virus in this report can be a reference for continuing awareness in detecting reemerging infectious diseases amid the COVID-19 pandemic. Similar symptoms of acute respiratory infection may disguise the accuracy of diagnosis and management. Therefore, supporting qualified laboratory facilities must be appropriately utilized in establishing a diagnosis.

Conflict of interest

None declared.

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