Case Report

Co-Infection of Tuberculosis and COVID-19 in Children: A Case Report

Madeleine Ramdhani Jasin, Talitha Rahma Ayuningtyas, Achmad Rafli, Irawan Mangunatmadja, Wahyuni Indawati, Nastiti Kaswandani

Department of Pediatrics, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia

Abstract

Background: Coinfection of TB and COVID-19 might occur, yet few evidence has been reported. Current COVID-19 pandemic also results in disruption at TB management in the community.

Case: A 5-month-old boy came with recurrent seizure, with history of persistent cough and fever for 1 month prior, also positive possible TB contact. He was diagnosed with disseminated TB, involving miliary appearance in chest Xray also meningitis, coinfected with COVID-19.

Discussion: During COVID-19 pandemic, TB service in the community is disrupted, resulting in delay in TB diagnosis, as observed in this patient, leading to severe manifestation. Coinfection of TB and COVID-19 can occur and may lead to more severe symptoms in either both diseases. Management of TB COVID-19 coinfected children is similar to those without COVID-19. Our patient received treatment consisting of 2 RHZE then 10 RH. Monitoring of symptoms and possible sequelae is necessary.

Conclusion: Coinfection TB and COVID-19 may occur in children, and both can lead to more severe manifestation of each condition, particularly if diagnosis is delayed. Strengthening TB care in the community is essential so that there will be no delay in diagnosis, also no disruption in treatment and monitoring.

Keywords: children, coinfection, COVID-19, tuberculosis

Corresponding Author:
Madeleine Ramdhani Jasin | Department of Pediatrics, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo General Hospital, Jakarta, Indonesia | madeleine.ramdhani@ui.ac.id

Submitted: June 6th, 2022
Accepted: October 30th, 2023
Published: January 30th, 2024

J Respirol Indones. 2024
Vol. 44 No. 1: 82–88
https://doi.org/10.36497/jri.v44i1.323

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic since March 2020 has led to various global health and economic problems.[1] The first case of COVID-19 in Indonesia was declared on 21st March 2020, indicating the rapid spread of COVID-19 between countries.[2] Three years have passed, the number of cases in Indonesia is still increasing, until August 2023 there were 6,813,981 confirmed cases and 161,916 mortality cases.[3]

As of April 2022, COVID-19 cases in children had reached more than 2 million cases, cumulatively there were more than 700 cases or 0.6% of mortality in children age 0-5 years and 6–18 years in Indonesia.[4] Similar data was observed in a study in Indonesia's tertiary referral hospital which showed out of 490 subjects who were treated and diagnosed with suspected and probable COVID-19, 50 (10.2%) subjects were diagnosed as confirmed COVID-19, and 20 (40%) subjects had fatal outcome.[5]

Prior to COVID-19 pandemic, tuberculosis (TB) has been one of the leading cause of mortality due to infectious diseases in developing countries.6 Estimated TB cases in 2021 were 845,000 cases per year, while childhood TB was accounted for 74,000 cases. Data from Global TB Reports shows that in 2021 the TB incidence rate is 354 per 100,000 populations with TB mortality rate of 52 per 100,000 populations.[6,7] During the COVID-19 pandemic, health services, including TB services, was disrupted as it was influenced by policies to adapt with the pandemic, such as restrictions on community activities, health workers transfer, lack of medical devices and diagnostic tools as well as the reduction of outpatient care patients.[8]

Studies in Asia, Africa, and Europe showed that COVID-19 pandemic resulted problems in TB reporting and TB care. Notification of TB cases experienced a decrease during the pandemic, especially pulmonary TB.[9,10] From Directorate

General of Prevention and Diseases data reported that in Indonesia the decrease number of case findings during the pandemic has led to a fairly high increase in estimated incidents from 2020 of 824,000 to 969,000 in 2021. Until October 2022, there were 503,712 TB case detections that indicates an increase in case detection of 60,477 compared to 2021.[7] Although TB is not a major contributor to death in COVID-19 patients, TB conditions accompanied by COVID-19 result in poorer prognosis and even death.[11] At this time, there have not been many reported studies on TB and COVID-19 coinfection in children.

CASE

A 5-month-old boy came to the hospital with chief complaint of recurrent seizures in the last 4 hours before hospital admission. During the seizure, the patient's eyes squinted to the left, as he had tonic type of seizure and was unconscious thereafter. Seizures were not accompanied by fever, and no noticeable precipitating factors. There was no history of seizures with or without fever, also no complaints of vomiting and diarrhoea.

A week before admission, the patient was experiencing seizures with the same pattern, accompany by fever. At hospital, he was diagnosed with COVID-19, and treated with remdesivir along with anti-seizure medication. After six days of treatment, he experienced no fever and seizures then he was discharged for self-isolation. PCR test was not repeated upon discharge.

For the past one month before being admitted to the hospital, patient complained of fever and phlegmy cough which were worsening. Complaint of weight loss and loss of appetite was denied. Contact with TB patients was unknown, however his father and grandfather had complaint of chronic cough for more than two weeks and had never been examined or treated. The reason for not seeking treatment was declared to be fear of hospital visit during pandemic.

Physical examination performed upon hospital admission showed a compos mentis patient with no signs of respiratory or circulatory distress. He was weighing 5.6 kg, with height 59.2 cm, head circumference 41 cm, flat fontanelle size of 2.5x2 cm. He had good nutritional status, yet short stature. He had no enlargement of the lymph nodes in the coli region, normal chest movement symmetrically, vesicular lung sounds, no crackles nor wheeze, and normal heart sounds without murmur nor gallop. On neurological examination, physiological reflexes were found to be increased. There was no cranial nerve paresis, no signs of increased intracranial pressure, and Babinski reflex was positive.

Table 1. Blood laboratory test result

Variables	Result	Unit	Normal Range
Complete Blood Count			
Haemoglobin	10.8	g/dL	11.1-14.1
Haematocrit	32.3	%	30.0-40.0
Erythrose	4.27	10^6/µL	4.10-5.30
MCV/VER	75.6	fL	68.0-84.0
MCH/HER	25.3	pg	24.0-30.0
MCHC/KHER	33.4	g/dL	30.0-36.0
Platelet count	1.144*	10^3/µL	200-500
Leukocyte count	32.580*	10^3/µL	6.00-18.00
Differential WBC Count			
Basophil	0.1	%	0-2
Eosinophil	0.0	%	1-6
Neutrophil	69.7	%	40.0-80.0
Lymphocyte	20.6	%	20-40
Monocyte	9.6	%	2-10
Liver test			
SGOT	48	U/L	15-60
SGPT	101*	U/L	8.7-39
CRP Quantitative	4.7	mg/L	<5.0
Procalcitonin	0.6*	ng/mL	<0.05
d-Dimer Quantitative	1,010*	µg/L	<440

Note: *values below or above the normal range

The laboratory tests result (Table 1) showed the presence of thrombocytosis and leucocytosis accompanied by an increase in procalcitonin and d-dimer quantitative. There was an increase in liver transaminase, as might be accounted due to anti-seizure medication given. The results of the SARS Cov-2 PCR swab were positive with CT Value ORF1ab Cq = 24.38 and N Gene Cq = 22.61.

Cerebrospinal fluid was examined, resulting in increased cell counts predominantly lymphocyte, and low glucose, suggesting for TB infection (Table 2). GenExpert of cerebrospinal fluid had resulted *in Mycobacterium tuberculosis* was detected, though

resistance to rifampicin was not detected. Tuberculin skin test was performed and leading to positive result.

Table 2. Cerebrospinal Fluid Analysis

Variables	Result	Unit	Normal Range
Macroscopic			
Colour	Colourless		Colourless
Clarity	Clear		Clear
Clotting	Negative		Negative
Microscopic			
Cell counts	70*	cell/µL	0-30
PMN (segment)	28	/µL (%)	MRR
MN (lymphocyte)	42*	/µL (%)	MRR
Indian ink colouring	Cryptococcus not found		
Chemistry			
CSF Protein	165*	mg/dL	15-45
CSF Glucose	20*	mg/dL	50-80
Glucose serum	152.1*	mg/dL	60-100
Chloride (Cl)	104	mEq/L	115-130
Impression	Infection		

Note: *values below or above the normal range

Brain CT scan was performed and showing multiple post-contrast iso-hypodense lesions in the cortical subcortical left frontoparietal lobes and left thalamus and leptomeningeal enhancement in the left parietal region and bilateral basal cisterns, with communicating hydrocephalus, suggesting a brain infection and supporting the diagnosis of TB meningitis.

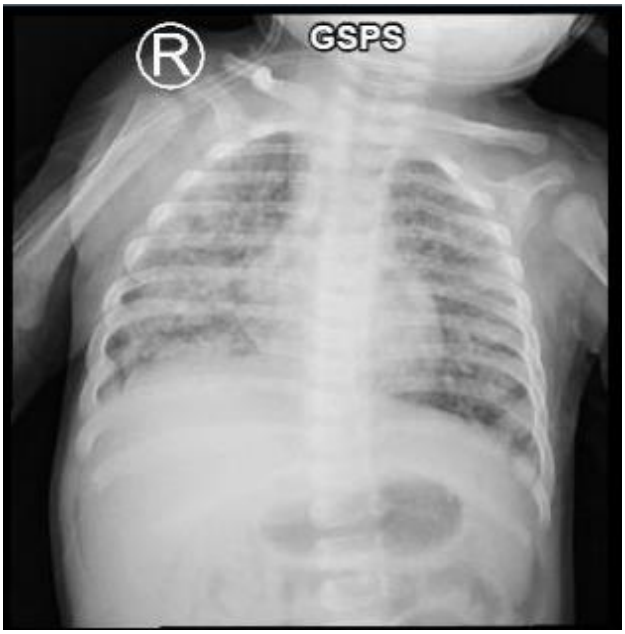

Figure 1. Chest x-ray shown miliary lesion on both lungs

Chest X-ray was also performed and resuting in miliary lesions filled both lung fields, suggesting miliary TB (Figure 1). Xpert from gastric lavage resulted to be negative.

Patient was diagnosis made was disseminated TB (TB miliary and TB meningitis), also COVID-19. He was treated with anti-tuberculosis drug therapy with regimen of rifampicin, isoniazid, pyrazinamide, ethambutol for 2 months, followed with rifampicin and isoniazid for 10 months. In addition, the patient also received prednisone 2 mg/kg/day for 4 weeks and then the dose will be lowered gradually over the next 4 weeks, as well as anti-seizure medication and vitamin B6. Anti-virus for COVID-19 was no longer given, because there was a history of previous administration of remdesivir. However, patient still received vitamin C, vitamin D, and zinc as part of COVID-19 treatment.

DISCUSSION

Children and adolescents are accounted for vulnerable group in population for various infectious diseases, such as TB. Several case reports indicate that SARS-CoV-2 infection can exacerbate the existing TB infection to the point that it may be fatal.[11,12] However, there are still limited case reports and research on co-infection with COVID-19 and TB.[13,14]

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis, primarily affecting the lungs, but also various organs other than lungs, and it can occur at any age. From WHO data in 2018, Indonesia has the second highest incidence of TB in the world (312 per 100,000 population) and accounts for 8.5 per cent of global cases, with high rates of drug-sensitive TB, MDR-TB and TB/HIV coinfection.[15] TB cases for children aged 0-14 years were reported 29,153 to the National TB Program (NTP).[16] Nonetheless, endemicity variety may also depict the quality differences in TB diagnosis between regions. Based on age group, children aged less than 5 years old are the highest group with TB cases in children, accounted for 48% in proportion.[17,18]

Most common organs other than lungs involved in TB (extra-pulmonary TB) are lymph,

meninges, bones and joints. Meningitis TB is a severe manifestation of TB in the central nervous system, and is more common in children within the age group of younger than 1 year. In children with miliary TB, 20–40% of the population have meningitis TB. Miliary TB is a severe form of TB due to systemic lympho-hematogenous spread, and often found in children younger than 2 years of age.[19,20]

Gold standard of TB is mainly obtaining positive bacterial results, either from Xpert or PCR, acid fast bacilli, or TB culture in children with clinical manifestation suspected of TB. If bacterial result is negative or samples is unable to be obtained, tuberculin skin test and chest X-ray are needed to be performed and TB scoring system is counted. In this patient, TB is initially suspected from manifestation of fever and cough lasting for one month, contact with family members with chronic cough, though TB diagnosis in them was never made to confirm.[21,22]

Due to neurological symptoms of seizure, cerebrospinal fluid analysis was obtained and resulted in pleocytosis with predominantly lymphocytes, low glucose, both were suggestive of TB, then confirmed with positive TB bacterial by Xpert. Brain CT-scan showed leptomeningeal enhancement and basal cisterns with communicating hydrocephalus, which are commonly found in meningitis TB. Meningeal involvement in patients is associated with hematogenous spread in miliary TB. Pulmonary involvement with miliary features and meningitis in patients led to the diagnosis of disseminated TB, which is a TB condition involving two or more organs due to lymphohematogenous spread.[21,22]

This patient also had leukocytosis along with high procalcitonin level than can be seen also in severe tuberculosis case. We did not find any other positive bacterial culture, thus this patient only treated as tuberculosis dan COVID-19 patient.

In this patient, tuberculin skin test was negative, and this is probably due to the immunocompromised condition in severe TB leading to inability to build competent immune response for tuberculin reaction. Gastric lavage for Xpert was also negative in this patient, as a study from Bates et al showed specificity and sensitivity for gastric lavage Xpert are 74.2% and 99.4%, respectively.[23]

Although, patient already had history of fever and cough since 1 month before coming to the hospital, with possible contact with father and grandfather who chronic cough but had never received diagnosis and treatment due to fear of COVID-19 pandemic, he was not brought to hospital for further examination due to similar reason as his father and grandfather. Delay in notifying TB cases, in both patients and family contacts, is often associated with fear of COVID-19 pandemic. This plays a role in the severity of the manifestations that this patient had during hospital admission.[6,24,25]

The COVID-19 pandemic has caused disruption to health services for various diseases in the world, including TB. The decrease in TB notification cases by 25% in various TB endemic countries, such as Indonesia, raises concerns about delays in TB diagnosis so that TB patients suffer to have severe condition when taken to the hospital, as seen in this patient. The importance of strengthening TB health services in the community is currently demonstrated, both in establishing a diagnosis, identifying contacts, as well as managing and monitoring them during the pandemic to post-pandemic.[6,24,25]

TB and COVID-19 co-infection cases are mostly reported in Italy, China, and India, and this co-infection could be found in all age groups.[26,27] TB and COVID-19 co-infection affects the severity of COVID illness. Active TB can increase the severity of COVID-19 due to increased myeloid cells, circulating interferon type I and III levels in severe COVID-19 patients. SARS-CoV-2 infection, as well as the presence of COVID-19 can cause TB disease to become more severe.[28]

This case report shows that delay in TB diagnosis may play a role in increased severity, as in this case, it developed to involve the central nervous system. The severity of TB disease is also increasing due to COVID-19 disease.[21] The pathomechanism of SARS-CoV-2 is to bind to the ACE-2 receptor which is also present in the brain so that the virus can injure the central nervous system by binding to vascular

endothelial cells causing blood vessel injury and platelet aggregation, contributing to the hypercoagulable state in tuberculous meningitis.[22,29]

There is no difference in TB management for children with COVID-19 or not. The management of disseminated TB is the administration of a regimen of four anti-tuberculosis drugs rifampicin, isoniazid, pyrazinamide, ethambutol for 2 months in the intensive phase (2 RHZE) and rifampicin, isoniazid for 10 months in the continuation phase (10 RH).[18,20]

Around 14–52% of children with TB meningitis will have neurological sequelae, while the mortality rate varies between 5–23%. This prognosis also depends on the clinical stage that each patient is undergoing when receiving therapy. The more advanced of the clinical stage when the child receives TB therapy, the prognosis is worser.[21,22,29] In our case, patient clinically showed improvement after receiving TB therapy with clinical improvement of recurrent seizures, fever, and cough. However, long-term monitoring should still be done to determine the possible of neurological sequelae.

CONCLUSION

Co-infection of TB and COVID-19 can occur in children, and the occurrence of both diseases can cause more severe manifestations of TB and COVID-19. The limitation of TB services in the community during the COVID-19 pandemic show the importance of reinforcing TB services in terms of case identification, diagnosis, administration of appropriate anti-tuberculosis drugs and monitoring of treatment. The delay in TB diagnosis due to service disruptions also contributes to the increasing severity of TB manifestations which ultimately affects the prognosis.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFFERENCE

1. World Health Organization. WHO COVID-19 dashboard [Internet]. World Health Organization. 2022 [cited 2022 Mar 16]. Available from: https://data.who.int/dashboards/covid19/cases?n=c
2. World Health Organization. Coronavirus disease (COVID-19) outbreak situation [Internet]. World Health Organization. 2022 [cited 2022 Mar 16]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
3. World Health Organization. WHO COVID-19 dashboard [Internet]. World Health Organization. 2023 [cited 2023 Aug 20]. Available from: https://data.who.int/dashboards/covid19/cases?n=c
4. Satuan Tugas Penanganan COVID-19. Peta Sebaran COVID-19 [Internet]. Satuan Tugas Penanganan COVID-19. 2022 [cited 2022 Apr 12]. Available from: https://covid19.go.id/peta-sebaran
5. Dewi R, Kaswandani N, Karyanti MR, Setyanto DB, Pudjiadi AH, Hendarto A, et al. Mortality in children with positive SARS-CoV-2 polymerase chain reaction test: Lessons learned from a tertiary referral hospital in Indonesia. Int J Infect Dis. 2021;107:78–85.
6. World Health Organization. Global Tuberculosis Report 2022 [Internet]. 2022 [cited 2022 Aug 10]. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022
7. Directorate General of Prevention and Disease. Tuberculosis control in Indonesia 2022. Jakarta: Ministry of Health, Republic of Indonesia; 2022
8. Kementerian Kesehatan Republik Indonesia. Penanggulangan TBC di masa pandemi COVID-19. Jakarta: Kementerian Kesehatan Republik Indonesia; 2020.

9. Duarte R, Aguiar A, Pinto M, Furtado I, Tiberi S, Lönnroth K, et al. Different disease, same challenges: Social determinants of tuberculosis and COVID-19. Pulmonology. 2021;27(4):338–44.
10. Aznar ML, Espinosa-Pereiro J, Saborit N, Jové N, Sánchez Martinez F, Pérez-Recio S, et al. Impact of the COVID-19 pandemic on tuberculosis management in Spain. Int J Infect Dis. 2021;108:300–5.
11. Hashem MK, Hussein AARM, Amin MT, Mahmoud A, Shaddad AM. The burden of COVID-19 pandemic on tuberculosis detection: A single-center study. The Egyptian Journal of Bronchology. 2022;16(1):14.
12. Mishra AK, George AA, Sahu KK, Lal A, Abraham G. Review of clinical profile, risk factors, and outcomein patients with Tuberculosis and COVID -19. Acta Bio Medica : Atenei Parmensis. 2021;92(1):e2021025.
13. Freij BJ, Gebara BM, Tariq R, Wang AM, Gibson J, El-Wiher N, et al. Fatal central nervous system co-infection with SARS-CoV-2 and tuberculosis in a healthy child. BMC Pediatr. 2020;20(1):1–7.
14. Visca D, Ong CWM, Tiberi S, Centis R, D'Ambrosio L, Chen B, et al. Tuberculosis and COVID-19 interaction: A review of biological, clinical and public health effects. Pulmonology. 2021;27(2):151–65.
15. World Health Organization. Roadmap towards ending TB in children and adolescents. 2nd ed. Geneva: World Health Organization; 2018.
16. U.S. Agency for International Development. COVID-19 mitigation and humanitarian and social protection in Indonesia [Internet]. U.S. Agency for International Development. [cited 2024 Feb 18]. Available from: https://www.usaid.gov/indonesia/fact-sheets/covid-19-mitigation-and-humanitarian-and-social-protection-indonesia
17. Lamb GS, Starke JR. Tuberculosis in infants and children. Microbiol Spectr. 2017;5(2):553–7.
18. Kementerian Kesehatan RI. Petunjuk teknis manajemen dan tatalaksana TB anak. Jakarta: Kementerian Kesehatan RI; 2016.
19. Caren GJ, Iskandar D, Pitaloka DAE, Abdulah R, Suwantika AA. COVID-19 pandemic disruption on the management of tuberculosis treatment in Indonesia. J Multidiscip Healthc. 2022;15:175–83.
20. Rahajoe NN, Supriyatno B, Setyanto DB. Pedoman nasional tuberkulosis anak. Jakarta: UKK Respirologi PP IDAI; 2008.
21. Maaroufi A, Diai A, Jebbar N, Bibiche L, Jaber K, Jbili N, et al. Tuberculous meningitis and COVID-19 co-Infection: About a case. Open J Clin Diagn. 2021;11(2):52–8.
22. Daniel B, Grace G, Natrajan M. Tuberculous meningitis in children: Clinical management & outcome. Indian J Med Res. 2019;150(2):117–30.
23. Bates M, O'Grady J, Maeurer M, Tembo J, Chilukutu L, Chabala C, et al. Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: A prospective descriptive study. Lancet Infect Dis. 2013;13(1):36–42.
24. World Health Organization. Pulse survey on continuity of essential health services during the COVID-19 pandemic: Interim report, 27 August 2020 [Internet]. Geneva: World Health Organization; 2020. Available from: https://iris.who.int/handle/10665/334048
25. Migliori GB, Thong PM, Akkerman O, Alffenaar JW, Álvarez-Navascués F, Assao-Neino MM, et al. Worldwide effects of coronavirus disease pandemic on tuberculosis services, January-April 2020. Emerg Infect Dis. 2020;26(11):2709–12.
26. Tadolini M, Codecasa LR, García-García JM, Blanc FX, Borisov S, Alffenaar JW, et al. Active tuberculosis, sequelae and COVID-19 co-infection: First cohort of 49 cases. European Respiratory Journal. 2020;56:2001398.
27. Yasri S, Wiwanitkit V. Tuberculosis and novel Wuhan coronavirus infection: Pathological interrelationship. Indian J Tuberc. 2020;67(2):264.
28. Sheerin D, Abimanyu, Wang X, Johnson WE, Coussens A. Systematic evaluation of transcriptomic disease risk and diagnostic biomarker overlap between COVID-19 and

tuberculosis: A patient-level meta-analysis. medRxiv. 2020;

29. Essajee F, Solomons R, Goussard P, Van Toorn R. Child with tuberculous meningitis and COVID-19 coinfection complicated by extensive cerebral sinus venous thrombosis. BMJ Case Rep. 2020;13(9):e238597.