

Case Report

Congenital neurosyphilis presenting as neonatal sepsis

Wedi Iskandar^{1,2}, Vidi Permatagalih¹, Aris Primadi^{3,4}, Uni Gamayani^{4,5}

¹ Group of Medical Staff for Child Health at Al Islam Hospital Bandung, Indonesia

² Laboratory of Child Health, Faculty of Medicine, Universitas Islam Bandung, Indonesia

³ Department of Child Health, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

⁴ Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

⁵ Department of Neurology, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

Abstract

Introduction: Congenital syphilis involves any organs with various symptoms, including neurological signs. Neurosyphilis is a severe syphilis complication that can develop at any stage of illness.

Case presentation: A 2,520 g male infant was spontaneously born at term from an untreated syphilis mother. Physical examination revealed decreased consciousness, respiratory distress, seizure, but without neurologic abnormality sign. The serum and cerebrospinal fluid Venereal Disease Research Laboratory and Treponemal Pallidum Hemagglutination Assay TPHA tests titers were 1:16 and 1:1,280, respectively. The diagnosis at admission was respiratory failure and neonatal sepsis. The infant was mechanically ventilated and treated with early management of sepsis. Blood culture was sterile later on. Then, the infant was administered intramuscular benzathine penicillin G (50,000 units/kg/dose) for a total of three weeks. The infant's condition was improved during the treatment.

Conclusions: There are many challenges associated with screening and monitoring neurosyphilis in congenital syphilis. Congenital syphilis presenting as sepsis is easily misdiagnosed as bacterial sepsis.

Key words: Neonates; neurosyphilis; sepsis.

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Introduction

For a long time, congenital syphilis (CS), the consequence of prenatal infection with *Treponema pallidum*, has been a public health concern. It will have a severe impact on the fetus's growth, development, and organ formation stages. From 9-10 weeks gestation, fetus can become infected through transplacental transmission from the infected mother, which can cause pathological changes during pregnancy. The skeletal, brain, liver, and lung systems and organs are the most impacted. Multiple organ involvement, such as hepatosplenomegaly, sepsis, and meningitis, might cause asymptomatic or clinical symptoms in these babies [1].

Despite a comprehensive understanding of the disease and preventive strategies, congenital syphilis remains a significant public health problem globally due to its high morbidity and mortality burden. The World Health Organization (WHO) estimates that more than 11 million new cases every year, and more than 90% occur in developing countries. In 2012, an estimated 350,000 adverse pregnancy outcomes

worldwide were attributed to syphilis, including 143,000 early fetal deaths/stillbirths, 62,000 neonatal deaths, 44,000 preterm/low-birth-weight babies, and 102,000 infected infants [1].

Neurosyphilis is a rare but serious complication of syphilis can develop at any stage of illness. Neurosyphilis is challenging to diagnose. Neurosyphilis is diagnosed clinically based on neurologic signs and symptoms as well as the findings of serologic and cerebrospinal fluid (CSF) testing (including CSF cell count, protein, and CSF Venereal Disease Research Laboratory [CSF-VDRL]). Current guidelines from the Centers for Disease Control and Prevention (CDC) for treating sexually transmitted diseases recommend lumbar puncture and cerebrospinal fluid analysis for syphilis patients who symptomatic for neurosyphilis. The prevalence of reported neurosyphilis among early syphilis cases varied from 2009 to 2015, but the overall prevalence remained low. Based on a retrospective health record review in the United States, the 1.8% prevalence estimate is comparable to the previous cohort

prevalence estimate, ranging from 1.2% to 1.7% [2]. Meanwhile, Daey Ouwens *et al.*, reported in the Netherlands, the annual incidence of neurosyphilis varies from 0.16 to 2.10 per 100,000 people [3]. Until now, in Indonesia, the prevalence of congenital syphilis and neurosyphilis does not exist yet.

Case

A male infant with a weight of 2,520 grams was born to a 22-year-old primigravida primipara woman at 38 weeks gestation; spontaneous labor by the midwife, with Apgar scores were 6 and 9 at 1 and 5 minutes, respectively. The baby was referred to hospital, presented with respiratory distress. The mother had a history of reactive serologic tests for syphilis in the third trimester of pregnancy, and Rapid anti-HIV was not reactive. However, she did not receive treatment for syphilis. Physical examination revealed severely ill respiratory distress symptoms (Downe score was 6, such as tachypnea, chest retraction, grunting, cyanotic, and partial air entry). The baby had pallor and jaundice with liver and spleen enlargement, but no skin rash, no nasal discharge, no edema. Several hours after being in the emergency room, the infant had decreased consciousness and was followed with seizure, but no sign of neurologic abnormality.

Laboratory findings revealed hemoglobin; 10.7 g/dL, hematocrit; 31.6%, white blood cells (WBC); 56,000/mL, platelet; 42,000/mL, elevated C-reactive protein (CRP); 37.1mg/dL. The blood gas analysis demonstrated acidosis respiratory and hypoxemia (pH = 7.131, pCO₂ = 61.9 mmHg, pO₂ = 52.9 mmHg, HCO₃ = 20.3 mmol/L, BE = -8.9 mEq/L, SaO₂ = 77.4%), and on chest x-ray showed aspiration pneumonia. The diagnosis at admission was respiratory failure and neonatal sepsis. The infant was immediately mechanically ventilated; furthermore, early management of sepsis was done. Antibiotic treatment, including ampicillin-sulbactam and amikacin, as well as supportive care, was initiated. The baby was given a 35 cc (14 cc/kg) Pack Red Cell transfusion to treat anemia.

The serum Venereal Disease Research Laboratory (VDRL) and Treponema Pallidum Hemagglutination (TPHA) test were reactive with titers 1:16 and 1:1,280, respectively. Initial liver function tests revealed elevated total bilirubin (16.06 mg/dl) with the direct bilirubin (12.57 mg/dL) and raised aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (728 and 325 IU/L, respectively). CSF analysis disclosed a VDRL was reactive, with mononuclear (MN) 46 and polymorphonuclear (PMN) 54, Nonne,

and Pandy were positive, and the glucose level of 14 mg/dL. Thus, the diagnosis of symptomatic congenital neurosyphilis was confirmed. Furthermore, a course of intramuscular benzathine penicillin G (50,000 units/kg/dose), every 12 hours for one week and continue with every 8 hours for a total of 3 weeks, was established. After blood culture examinations came out, it turned out that the results of sterile culture examinations from bacterial growth, so antibiotics (ampicillin-sulbactam and amikacin) were stopped then only given a single penicillin therapy.

The direct hyperbilirubinemia was reduced after starting penicillin treatment until the 5th day of treatment, total bilirubin (14.84 mg/dL) with the direct bilirubin (13.51 mg/dL). Serum bilirubin, ALT, and AST levels were decreased after a complete course of parenteral penicillin (693 and 373 IU/L, respectively). On hepatobiliary ultrasound examination, there was hepatosplenomegaly with minimal ascites.

The baby was admitted to the Neonatal Intensive Care Unit (NICU) for seven days with mechanical ventilation and continued on non-invasive ventilation (NIV), then treated for stabilization at intermediate care. The baby's condition was stable, full-feeding, no respiratory distress, no seizures, or other neurological symptoms. However, the baby still looks jaundice. On the 17th day of care, the baby is discharged and continue to follow up in the outpatient clinic.

After 30 days post-treatment, the baby's condition was stable with no seizures and other neurological signs. However, the patient still looks jaundice, which gradually improved after that. The direct AST and ALT were 262 and 92 IU/L, respectively. The head CT scan showed that there was no hydrocephalus or any brain abnormalities. In addition, there was not diffuse osteochondritis identified on long-bone radiographs.

Patient consent

Patients and families have agreed and given their consent to be reported in an academic journal.

Discussion

Since 2001, the primary and secondary (P and S) syphilis rate in the United States has risen virtually every year. As the incidence of P and S syphilis increases, the incidence of poor health outcomes linked with syphilitic infection, such as neurosyphilis, is expected to rise as well. Several large American cities have reported increases in neurosyphilis in recent years; however, it is unclear if these findings reflect a nationwide trend in neurosyphilis [2].

In this case, neurosyphilis was confirmed based on the presence of neurological symptoms, including seizures and decreased consciousness in infants who were known to confirm the diagnosis of congenital syphilis. On examination of lumbar puncture, cerebrospinal fluid analysis disclosed VDRL test was reactive, with MN 46, PMN 54, Nonne and Pandy Positive, and the glucose level of 14 mg/dl. According to Workowski *et al.*, a reactive CSF VDRL was considered diagnostic of neurosyphilis in a person with neurologic signs or symptoms [4]. A CSF WBC count of 20 cells/L or more, a reactive CSF VDRL, and a positive CSF intrathecal T pallidum antibody index are all required for the diagnosis of neurosyphilis [5]. CSF abnormalities also include elevated protein levels and pleocytosis, found in up to 70% of patients. All patients who have had untreated syphilis for an undetermined period or more than one year should have their CSF examined. Because conventional benzathine penicillin G therapy for early syphilis does not attain treponemicidal levels in the CSF, some experts recommend lumbar puncture in patients who have secondary or early latent syphilis. Because asymptomatic neurosyphilis can coexist with other late sequelae symptoms, lumbar puncture should be used to evaluate latent syphilis that has been present for more than a year, suspected neurosyphilis, and late sequelae other than symptomatic neurosyphilis. The optimum cut-off point for determining whether or not to do a lumbar puncture is a serum rapid plasma reagent (RPR) titer of 1:32. The serial monitoring of abnormal CSF results can subsequently be used as a guide to therapy. Pleocytosis in the CSF continues to be a marker of disease activity. Documentation of resolution of CSF findings the following treatment is required to confirm curative treatment [5].

Adopting a uniform surveillance case definition for neurosyphilis, strengthens Alex de Voux *et al.*, national case report data was used to evaluate the prevalence of neurosyphilis. However, several difficulties related to neurosyphilis monitoring might lead to case reports underestimating the disease's actual prevalence. First, changes in clinical practice, such as screening for neurologic signs and symptoms and using lumbar punctures to assess patients with neurologic signs and symptoms, are likely to result in under-ascertainment of syphilis cases that fit the surveillance case definition of neurosyphilis. Because the surveillance case definition for both probable and confirmed neurosyphilis require abnormal CSF results, clinical settings without performing a lumbar puncture will be less likely to meet the surveillance case definition of neurosyphilis.

Second, variability of early syphilis cases which are followed up by provider or patient interviews to identify cases that might meet the neurosyphilis surveillance case definition, might lead to under ascertainment and underreporting of neurosyphilis cases [2].

Based on the major clinical symptoms, The US CDC criteria for neurosyphilis are divided into three patient groups according to the main clinical manifestations, namely neuropsychiatric, meningeal vascular, and myelopathy. Acute syphilitic meningitis has manifestations such as signs of meningeal irritation, stiff neck, headache, nausea, and vomiting. Fever is unusual. Cranial neuropathies are common. The cranial nerves affected are descending order of frequency, cranial nerves VII, VIII, VI, and II. However, in this case, the neurological symptoms were only signs of decreased consciousness and seizures; no other neurological signs or neurological deficits were found. Active untreated infections may persist and later manifest as more severe forms of neurosyphilis [5].

Meningeal neurosyphilis generally presents with acute meningitis-like symptoms, such as hydrocephalus, cranial neuropathies, and leptomeningeal granulomas, also known as gummas. A gumma is a granulation tissue mass that is well-circumscribed (avascular). A cell-mediated immunological response to T pallidum causes it. Gummas are generally extra-axial and dura-based lesions. As a result of the invasion and direct extension, the cortex is frequently implicated. Seizures may occur as a result of the irritative concentration. There has also been evidence of early parenchymatous involvement [5]. In this case, the neurosyphilis that occurred included the criteria for acute meningitis, even with minimal neurological symptoms. On the head CT scan, hydrocephalus and other brain abnormalities were not found.

However, because more than half of newborns are asymptomatic, symptomatic newborns can have mild and vague symptoms, and serology misinformation may exist. Thus, identifying and controlling congenital syphilis can be difficult. The symptoms of congenital syphilis are similar to those of other congenital diseases. Congenital syphilis that manifests as sepsis, for example, is readily mistaken as bacterial sepsis [1]. Congenital syphilis, despite this, should not be blamed for the disastrous results. Infants with CS presenting sepsis have suffered severe organ failure as a result of CS infection. Most patients, according to Liu *et al.*, have increased inflammatory markers and multiple organ failure. Inflammatory markers include leukocytosis (82.7%), elevated CRP (68.9%), and

elevated procalcitonin (71.4%). In addition, patients had abdominal distension (55.2%), splenomegaly (55.2%), hepatomegaly (72.4%) and skin rash (55.2%) [1]. Due to the anonymous and the high mortality rate of congenital syphilis presenting sepsis, we look forward to distinguishing it from other common sepsis in the early stage. Based on study conducted by Liu *et al.*, to evaluate newborn sepsis distinct from congenital sepsis, general condition, clinical features, and laboratory tests were required [1]. There was a statistically significant difference ($p < 0.05$) between these groups. These newborn sepsis patients showed a positive bacteria or fungal blood culture [1]. The patient responded to clinical improvement, being treated only with the antibiotic single benzathine penicillin, which is the first-line treatment for syphilis.

The current suggested treatment regimen for neurosyphilis is 18–24 million units (MU) of intravenous aqueous penicillin G per day, either as a continuous infusion or split every four days, for 10–14 days. The 2.4 million units (MU) of injectable procaine penicillin with 500 mg oral probenecid four times a day for 14 days is another option. Limited data on ceftriaxone suggested that 1–2 g intravenously or intramuscularly for 10–14 days yields acceptable results. Meanwhile, in this case report, the baby's condition was improved by giving intramuscular benzathine penicillin G (50,000 units/kg/dose) injection every 12 hours for one week and continuing with intramuscular injection every 8 hours a total of 3 weeks. The goal of therapy is to inhibit the progression of the infection and to try and reverse symptoms. Response to treatment depends on the stage of the disease. In patients with early meningeal neurosyphilis, quick resolution of symptoms is the rule [6]. Even though penicillin is the drug of choice in treating syphilis, especially in neurosyphilis, it is still imperfect. Van der Valk *et al.*, found that intramuscular treatment regimen did not consistently yield treponemical penicillin concentrations in the CSF [7]. Meanwhile, Polnikorn *et al.*, patients who received benzathine penicillin G intramuscularly (IM) for the treatment of neurosyphilis had no detectable penicillin in the CSF [8]. They suggested that the drug might have to be given intravenously (IV) to produce a sufficient CSF concentration. Crowe *et al.*, concluded procaine penicillin alone or with probenecid are therefore not recommended for treating neurosyphilis [9]. However, Speer *et al.*, collected simultaneous serum and CSF samples after administering 50,000 units/kg of aqueous procaine penicillin G intramuscularly to 25 newborns; penicillin activity was observed in the CSF of all

patients [10]. Following intramuscular injection of aqueous procaine penicillin G in newborns, spirocheticidal levels (greater than or equal to 0.03 microgram/mL) are obtained in the CSF for at least 24 hours. Nevertheless, Azimi *et al.*, suggested that administration of aqueous penicillin G 100,000 U/kg per day may be the preferred therapy if CSF level is more than 0.018 micrograms/mL, especially for infants with severe disease or congenital neurosyphilis [11]. Neurosyphilis should be treated with high intravenous doses of penicillin to ensure treponemical concentrations in the central nervous system [12].

Conclusions

There are many challenges associated with monitoring neurosyphilis in congenital syphilis, namely by screening for neurological signs and symptoms and variability in the use of lumbar puncture. Congenital syphilis manifests as sepsis, which is easily misdiagnosed as bacterial sepsis. Neurosyphilis should be treated with high intravenous doses of penicillin to attain treponemical concentrations in the central nervous system. In mild cases of neurosyphilis, intramuscular administration of benzathine penicillin G may be an alternative therapy.

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Authors' Contributions

All authors have contributed equally in conducting the study, drafting and revising the manuscript, giving final approval for publication, and have agreeing to be accountable.

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Corresponding author

Uni Gamayani, MD, PhD
Department of Neurology, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital
Raya Bandung Sumedang KM 21 Street, Jatinangor 45363, Indonesia/
Prof. Eyckman Street No.38, Pasteur, Bandung 40161, Indonesia
Phone : (+6222) 7795595 / (+6222) 2034953
Fax: : (+6222) 7795595 / (+6222) 2032216
Email: gamayani@yahoo.com

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