CLINICAL AND PRECLINICAL CHARACTERISTICS OF NEONATES WITH CONGENITAL SYPHILIS IN THE NATIONAL CENTER OF VIETNAM NATIONAL CHILDREN'S HOSPITAL

Nguyen Thi Quynh Nga[1,2], Pham Thao Nguyen[1,2,✉]

[1]Hanoi Medical University
[2]Vietnam National Children's Hospital

This prospective observational study was conducted to investigate epidemiological and clinical features of neonates with congenital syphilis at the Neonatal Center of Vietnam National Children's Hospital from January 2018 to June 2021. Twenty-nine patients were diagnosed with congenital syphilis by Treponema Pallidum hemagglutination assay (TPHA) reaction. The most common manifestations of congenital syphilis were desquamation (41.4%), hepatomegaly (31.4%), splenomegaly (37.9%), and early jaundice (24.1%). Thrombocytopenia, anemia, elevated liver enzymes, and conjugated hyperbilirubinemia were common laboratory findings of congenital syphilis. The mortality rate of congenital syphilis was 13.7%. Parental syphilis status of 51.9% of neonates born with congenital syphilis was unknown. Thus, a systematic launch of a screening program for syphilis for all pregnant women is critical.

Keywords: Congenital infection, syphilis, neonate.

I. INTRODUCTION

Congenital syphilis (CS) occurs when a mother infected with the spirochete *Treponema pallidum* transmits the infection to her child through the placenta during pregnancy. Despite the comprehensive understanding of the disease and optimal preventive strategies, CS continues to plague neonates worldwide.[1] Concurrently, CS has increased and now occurs at a rate of 33.1 cases per 100000 live births.[2] This disease can cause different sequelae ranging from asymptomatic infection to severe debilitating disease and stillbirth.[3]

CS is still a significant issue for public health, especially in developing countries. This infection can result in fetal and neonatal mortality and can become an important contributor to early and later childhood morbidity.[1] CS is the second most common cause worldwide of preventable stillbirth. It could also result in premature birth and low birth weight. It may be clinically apparent after birth, or it can remain asymptomatic for months or years.[4,5] CS is divided into early CS (before two years of age) and late CS (after two years). Manifestations of CS are variable, including hepatomegaly, jaundice, rhinitis, generalized lymphadenopathy, rash, and skeletal abnormalities. CS is also a critical cause of nonimmune fetal hydrops, ophthalmologic manifestations, and several central nervous system disorders in children globally, leading to decrease in standard of living and imposing burden on health care and educational systems.[1,3]

Identifying the exact pathogen causing congenital infection solely from clinical manifestations is challenging.The CS diagnosis is established by observing spirochetes in body fluids or tissue and suggested by serologic test results. Serologic testing can confirm a diagnosis of proven/highly probable, at-

Corresponding author: Pham Thao Nguyen
Hanoi Medical University
Email: ocgiang@gmail.com
Received: 09/05/2022
Accepted: 21/06/2022

risk, or unlikely congenital syphilis infection. *Treponema pallidum* hemagglutination assay (TPHA) is a measurement usually used as a confirmatory test to diagnose CS.

Vietnam is a developing country with a low standard of living and health care system, where CS is still a significant issue for mortality and morbidity in neonates with severe future consequences, creating a burden for their families and society. Therefore, it is essential to understand CS thoroughly regarding the epidemiologic and clinical features and laboratory tests to determine the disease as soon as possible and to deliver exact treatment punctually. This research also provided more information about CS in North Vietnam principally as well as all other regions of Vietnam.

II. SUBJECTS AND METHODS

1. Subjects

A descriptive study was conducted in Neonatal Center in Vietnam National Children's Hospital, Hanoi, Vietnam, from January 2019 to June 2021. This prospective work was approved by the Ethics Committee of Vietnam National Children's Hospital (No1841/BVNTW-VNCSKTE). Neonates consecutively admitted to our Neonatal Center were selected based on the following inclusion criteria:

1) Neonate's parents gave consent to participate in our research;

2) All neonates diagnosed with congenital syphilis by antibody serology test. In our study, patients had positive results for serology tests when they positively impacted *Treponema pallidum* hemagglutination assay (TPHA) reaction. Neonates were excluded from our study when specimens could not be obtained.

2. Data and variables

The following data was collected - gestational age at birth (preterm < 37 weeks and term ≥ 37 weeks), birth weight (Small for gestational age (SGA)<10th percentile or normal ≥ 10thpercentile), sex, and age of mother at birth. The clinical symptoms observed in neonates with congenital infection are body temperature, skin abnormality (jaundice, petechial rash, vesicular, etc.), hepatosplenomegaly, anemia, and other congenital defects such as hearing loss, congenital heart diseases, cataracts, etc. Laboratory findings were attained upon hospital admission, including complete blood count, liver function test, kidney function test, coagulation test, C-reactive protein (CRP), and total and directed bilirubin. We performed antibody serology tests to detect the presence or level of specific IgG and IgM antibodies to *Toxoplasma gondii*, Rubella virus, cytomegalovirus (CMV), and herpes virus simplex (HSV). For Syphilis,we used the TPHA test to detect serology antibodies to *Treponema pallidum*. Patients also underwent diagnostic radiology exams such as cranial ultrasound, long bone X-ray, and computed tomography (CT) scan to detect other organ lesions.

3. Statistical analysis

Statistical analysis was conducted using SPSS20.0 software. Quantitative data differences between groups were compared by Student t-test for normally distributed data or Mann-Whitney test for non-normal distributed data. Categorical data were compared using the chi-square test when all expected numbers are at least one or otherwise by using Fisher's exact test. P-values less than 0.05 were considered statistically significant.

III. RESULTS

From January 2018 to June 2021 at the Neonatal Center of Vietnam National Children's Hospital, 29 neonates satisfying the inclusion criteria were recruited into the study. The neonatal demographics are shown in **Table**

1. the median mother's age was 25 years old, 48.3% of neonates were born preterm, and 58.6% were male.

The most common clinical manifestations overall were respiratory distress (51.7%), desquamation (41.4%), hepatomegaly (41.4%), splenomegaly (37.9%), small for gestational age (31.0%), congenital heart disease (31%) of which 100% were atrial septal defects and abnormal skeletal radiology (10.3%). The clinical manifestations of 29 neonates diagnosed with congenital syphilis are shown in **Table 1**.

Table 1. Epidemiologic and clinical characteristics of 29 neonates diagnosed with congenital syphilis

Characteristics	Results
Sex (male)	17 (58.6)
Preterm	14 (48.3)
Mother's age	25 (22.5, 30)
Caesarean delivery	12 (41.4)
History of miscarriage	5 (17.2)
Clinical manifestations	
Small for gestational age	9 (31.0)
Respiratory distress	15 (51.7)
Hepatomegaly	12 (41.4)
Splenomegaly	11 (37.9)
Petechial rash	5 (17.2)
Desquamation	12 (41.4)
Jaundice on 1st day of life	7 (24.1)
Anemia	4 (13.8)
Seizure	1 (3.4)
Cataracts	1 (3.4)
Congenital heart defects	9 (31.0)
Ventricular septal defect	0 (0)
Atrial septal defect	9 (31.0)
Patent ductus arteriosus	3 (10.3)
Imaging	
Ventriculomegaly	1 (3.4)

Characteristics	Results
Parenchymal hypoechogenicity	1 (3.4)
Brain atrophy	1 (3.4)
Abnormal skeletal radiology	3 (10.3)

Results express as number of infants (%) or median (25-75%).

Table 2 illustrates laboratory findings in neonates diagnosed with congenital syphilis. The most common abnormal results were thrombocytopenia (PLT <150 G/L), conjugated hyperbilirubinemia (>54 µmol/L), and elevated liver enzymes.

Table 2. Laboratory findings in 29 neonates with congenital syphilis

Characteristics	Results
Hemoglobin (g/l)	116.9 ± 37.8
White blood cell (x 10^9/L)	20.8 (16.4, 32.6)
PLT	
<50 G/L	10 (34.5)
50 - <100 G/L	4 (13.8)
100 - <150 G/L	3 (10.3)
Conjugated hyperbilirubinemia (>54 µmol/L)	23 (79.3)
Elevated liver enzyme	
ALT > 80 U/L	13 (44.8)
AST > 80 U/L	23 (79.3)
Serum C-reactive protein (mg/L)	41.0 (0.56, 89.0)
Treponema pallidum hemagglutination test (TPHA)	1:10240 (1:960 – 1:20480)

Results express as n (%), mean ± standard deviation, or median (25-75%).
AST, Aspartate aminotransferase; ALT, Alanine Aminotransferase; PLT, platelet

The identified pathogens, alone or in combination, are reported in **Figure 1**. Among 29 Syphilis neonates, there were four deaths, including two patients infected with only *Treponema pallidum,* one patient infected with both *Treponema pallidum* and *Toxoplasma gondii,* and onepatient infected with *Treponema pallidum,* CMV, HSV.

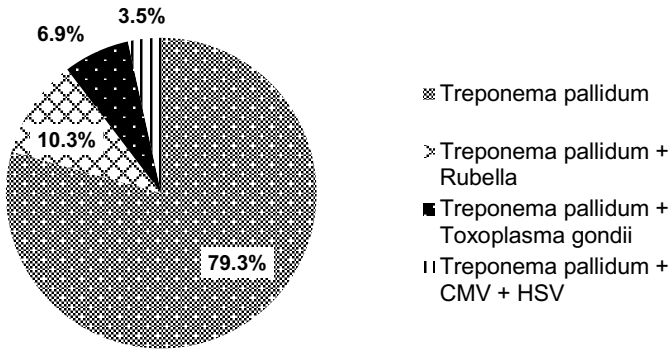

Figure 1.Indentified pathogens and coinfection in 29 neonates diagnosed with congenital Syphilis (n=29)

The history of exposure or diagnosis of congenital infection during pregnancy was shown in **Table 3.**

Table 3. Parental syphilis status in 29 infants with congenital syphilis

Parental syphilis status	n, %
Positive status	
Mother TPHA positive in pregnancy	10 (34.5)
Syphilis in mother	2 (6.8)
Syphilis in both parents	2 (6.8)
No information	15 (51.9)

IV. DISCUSSION

Despite the expansion of antenatal syphilis screen programs over the past few decades, syphilis continues to be a major public health concern worldwide. However, there are minimal studies about CS worldwide generally and in Vietnam particularly. This study is one of the first studies on the clinical and preclinical manifestations of CS in Vietnam.

Our study showed that 48.3% of patients with CS were preterm (< 37 weeks), and the male to female ratio was 1.4:1. The median mothers' age was 25 years old, and 17.2 % reported a history of miscarriage. 41.4 % of neonates were born by cesarean section. Our results were similar to previous studies.[6,7] Sam et al. reported the prevalence of CS in Mbarara Regional Referral Hospital was 3.8%.[6] Generally, many studies demonstrated that the majority of CS had been higher in the developing countries than industrialized countries. Sam et al. also showed newborns were more likely to acquire CS when born to mothers < 25 years of age, and maternal age < 25 years old was associated with an increased risk of CS.[6] In contrast, studies in Nigeria and Tanzania found no significant association with maternal age.[8] However, it is commonly known that younger women are more sexually active, which may imply early and unprotected sex with multiple sexual partners and are more likely exposed to a high number of sexually transmitted diseases while older women, may have had a chance of

previous counseling and treatment. Moreover, in a case series of 130 chinese neonates with CS by Zhow et al., 44.6% of neonates were preterm, and preterm neonates with CS had more severe clinical evidence than term ones. Interestingly, Zhow et al. also reported a higher rate of mothers with previous miscarriages which arose to 46.1%.[7]

Approximately 60 to 90 percent of live-born neonates with CS are asymptomatic at birth. The presence of signs at birth depends on the timing of intrauterine infection and treatment.[1] The patients in our study had multiple symptoms and comorbidities that were non-specific for symptomatic CS, such as respiratory distress, fever, hypothermia, and neurological symptoms. some typical characteristics for CS, including hepatosplenomegaly, early jaundice, petechial rash, desquamation of skin, etc. Moreover, neonates with CS had congenital defects such as congenital heart diseases. Our results were not significantly different from the results of previous reports.[6,7,9] In a study CS in Brazil from 1997 to 2004, among neonates with congenital Syphilis, the rates of hepatomegaly, splenomegaly, early jaundice, and palmoplantar pemphigus were 77.1%, 60.5%, 28.9%, and 21.1% respectively.[9] **Table 1** also showed that 10.3% of neonates had abnormal skeletal radiology. Abnormal long-bone radiographs are a common manifestation of early CS (occurring in 60-80%) and may be the sole manifestation in infants born to mothers with untreated syphilis. The changes usually are present at birth but may appear in the first few weeks of life.[1]

According to the literature, CS causes alteration in laboratory findings. The most common findings are anemia, thrombocytopenia, conjugated hyperbilirubinemia, and elevated liver enzymes. Zhou et al. reported that the incidence of thrombocytopenia (PLT <150 G/L) in neonates with CS was 32.3% which was significantly higher than in full term infants (41.1% vs. 23.6%, p=0.018).[7] Nese et al. also showed that anemia and thrombocytopenia were common hematological findings in CS. They suggested that hemophagocytosis might play a role in the pathogenesis of cytopenia, particularly thrombocytopenia in patients with CS.[10] In our study, 58.6% of neonates had thrombocytopenia, in which the percentage of patients who had the number of platelets under 50 G/L was the highest with 34.5%. In addition, 79.3% of infants in our study had conjugated hyperbilirubinemia (>54 μmol/L). The elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST)was 44.8% and 79.3%, respectively. Previous literature reported that CS is an infectious cause of infantile hepatitis, accounting for about 1.2%.[11] Syphilis hepatitis caused an increase of AST, ALT, and bilirubin and a decrease of protein, mainly albumin.[12] Yang et al. suggested that newborns with abnormal liver function, especially those with anemia, skin rash, peeling, abdominal distension, and hepatosplenomegaly, are highly suspicious of having a syphilis infection.[12]

We used the TPHA test, which detects antibodies against *Treponema Pallidum*, to diagnose syphilis infection. The median of TPHA titer was 1:10240. Gupta et al. recommended that the TPHA test should be used for routine confirmation of a reactive venereal disease research laboratory test (VDRL) irrespective of its titer for accurate diagnosis of syphilis, especially in cases having titer ≤1:8.[13]

Co-infection occurred in 21.7% of the newborns with CS, and the pathogens of co-infection were rubella, CMV, *Toxoplasma gondii*, and HSV. All of these pathogens caused TORCH infection in neonates. The prognosis of CS varies depending on the severity of the initial presentation and co-infection. Complications of CS might be mortality, failure to thrive,

developmental delay, congenital defects, and other disorders. There were four deaths in our study, representing 13.7%.

Parental syphilis status in neonates with congenital syphilis is essential for diagnosing and treating CS. In our study, 51.9% of neonates did not have information about parental syphilis status, and 34.5% had mothers tested positive for TPHA during pregnancy. Although the program of screening and treatment of syphilis in pregnancy was launched quite some time ago, current screening practices have limitations. Lack of prenatal care is the most important. There are many regions where the infrastructure is not available to scale up syphilis screening programs, especially in developing countries. To meet these challenges, increased awareness of the risk, evaluation, and treatment of syphilis punctually in mothers and neonates is very crucial.[1,4]

V. CONCLUSIONS

In conclusion, our study demonstrated that the symptoms of congenital syphilis were diverse, including several typical symptoms such as early jaundice, hepatosplenomegaly, skin rash, peeling, thrombocytopenia, anemia, and some congenital defects. Furthermore, the mortality rate in our study was 13.7%, and alldeaths were co-infection.

The practice of screening and treating syphilis for mothers during pregnancy was limited. Thus, systematically launching a program for screening syphilis for all women during pregnancy is critically important.

RECOMMENDATION

The practice of screening and treating syphilis during pregnancy in Vietnam has limitations, therefore the government needs to raise awareness of the risks and consequences of congenital syphilis and continues reinforcing a mandate screening program for all pregnant women.

REFERENCES

1. Cooper JM, Sánchez PJ. Congenital syphilis. *Semin Perinatol*. 2018; 42(3): 176-184. doi:10.1053/j.semperi.2018.02.005.

2. Kimball A, Torrone E, Miele K, et al. Missed Opportunities for Prevention of Congenital Syphilis - United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2020; 69(22): 661-665. doi:10.15585/mmwr.mm6922a1.

3. Hussain SA, Vaidya R. Congenital Syphilis. In: *StatPearls*. StatPearls Publishing; 2022. Accessed March 26, 2022. http://www.ncbi.nlm.nih.gov/books/NBK537087/.

4. Galvis AE, Arrieta A. Congenital Syphilis: A U.S. Perspective. *Children*. 2020; 7(11): 203. doi:10.3390/children7110203.

5. Lawn JE, Blencowe H, Waiswa P, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet Lond Engl*. 2016; 387(10018): 587-603. doi:10.1016/S0140-6736(15)00837-5.

6. Oloya S, Lyczkowski D, Orikiriza P, et al. Prevalence, associated factors and clinical features of congenital syphilis among newborns in Mbarara hospital, Uganda. *BMC Pregnancy Childbirth*. 2020; 20: 385. doi:10.1186/s12884-020-03047-y.

7. Zhou Q, Wang L, Chen C, Cao Y, Yan W, Zhou W. A Case Series of 130 Neonates with Congenital Syphilis: Preterm Neonates Had More Clinical Evidences of Infection than Term Neonates. *Neonatology*. 2012; 102(2): 152-156. doi:10.1159/000339291.

8. Lawi JD, Mirambo MM, Magoma M, et al. Sero-conversion rate of Syphilis and HIV among pregnant women attending antenatal clinic in Tanzania: a need for re-screening at delivery. *BMC Pregnancy Childbirth*. 2015;15:3. doi:10.1186/s12884-015-0434-2.

9. Lago EG, Vaccari A, Fiori RM. Clinical features and follow-up of congenital syphilis. *Sex Transm Dis*. 2013; 40(2): 85-94. doi:10.1097/OLQ.0b013e31827bd688.

10. Yarali N, Balaban I, Akyurek N, Ucar S, Zorlu P. Hemophagocytosis: the cause of anemia and thrombocytopenia in congenital syphilis. *Pediatr Hematol Oncol*. 2009; 26(6): 461-466. doi:10.3109/08880010903091897.

11. Cifuentes C Y, Vallejo R C. Anicteric Hepatitis as Congenital Syphilis Manifestation. *Infectio*. 2013; 17(3): 163-166.

12. Yang H, Zhang H, Wang C, Pang L. An analysis of the clinical features of children with early congenital Syphilis and Syphilitic Hepatitis. *BMC Pediatr*. 2021; 21(1): 498. doi:10.1186/s12887-021-02932-5.

13. Gupta K, Bhardwaj A, Dash S, Kaur IR. Role of Treponema pallidum hemagglutination assay for diagnosis of syphilis in low titers of VDRL-reactive sera: A prospective study from a large tertiary care center of East Delhi. *J Fam Med Prim Care*. 2018;7(6):1594. doi:10.4103/jfmpc.jfmpc_258_18.