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Symptomatic neonatal congenital infections in North Vietnam: a single-centre observational study

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ABSTRACT:

— ***Objective:*** Little is known about the prevalence and characteristics of symptomatic congenital infections in developing countries. To determine them in Vietnam, we conducted a study of neonates managed at the Neonatal Centre, Vietnam National Children's Hospital for congenital infections caused by *Toxoplasma gondii*, *Treponema pallidum*, hepatitis B virus, rubella virus, cytomegalovirus (CMV), or herpes simplex virus (HSV).

— ***Patients and Methods:*** This retrospective observational study was conducted between January 2018 and June 2021. The diagnosis of symptomatic congenital infection in neonates was confirmed by serological testing. CMV polymerase chain reaction (PCR) testing in the blood was performed when the results of CMV serology were inconclusive.

— ***Results:*** Sixty-eight infants were diagnosed with congenital infections (32 preterm). The highest infection rate, either as a single pathogen infection or in association with other organisms, was for CMV (n=38, 58.8%), followed by syphilis (n=29, 42.6%), rubella (n=3, 4.4%) and toxoplasmosis (n= 3, 4.4%). Co-infections were observed in eight infants (11.7%). Clinical manifestations included petechial rash (47.1%), hepatomegaly (45.6%), splenomegaly (44.1%), congenital sensorineural hearing loss (23.5%), and congenital heart disease (22.0%). The mortality rate was 10.3%, attributed mainly to CMV and syphilis, increasing with the number of co-infections. At the 6-month evaluation of the surviving 61 neonates, developmental delay was present in 13 (21.3%), all of whom had congenital CMV infection.

— ***Conclusions:*** Symptomatic congenital infections were common, with a high mortality rate. Implementation of appropriate public health measures is therefore required.

— ***Keywords:*** *Cytomegalovirus, Foetal infection, Newborn,* Herpes simplex*, Infectious diseases, Pregnancy, Rubella, TORCH,* Toxoplasma gondii.

INTRODUCTION

Congenital infections, previously known as TORCH (Toxoplasma, Other, Rubella, Cytomegalovirus, Herpes simplex), are either transmitted transplacentally to the fetus (fetal infection) or to the infant during the birth process. Their manifestations range from asymptomatic infants to severe debilitating disease and stillbirth[1]. The organisms traditionally involved include *Toxoplasma gondii*, *Treponema pallidum*, hepatitis B virus, rubella virus, cytomegalovirus (CMV), and herpes simplex virus (HSV). Human immunodeficiency virus (HIV), varicella virus, and Zika virus have since also been added[2]. Congenital infections result in significant fetal and

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neonatal mortality as well as later neurodevelopmental morbidity[1]. They result, therefore, in a considerable burden on health care and on the educational systems, especially in developing countries[2].

Symptoms are variable and include prematurity, petechial rash, anemia, early and/or prolonged jaundice, hepatosplenomegaly, fetal growth restriction, microcephaly, cataracts, sensorineural hearing loss, impaired vision, cerebral palsy, epilepsy, and mental retardation. In addition to suggestive clinical manifestations, their diagnosis is primarily based on serology to identify the presence of pathogen-specific immunoglobulin M (IgM) antibodies[2].

The incidence of congenital rubella syndrome varies worldwide. This depends on levels of naturally acquired immunity, overcrowding, and immunization policies and practices[3]. In Vietnam, a country with a low standard of living and a developing healthcare system, congenital infections remain a significant problem. The expanded program on immunization (EPI) was implemented in 1981. However, although rubella vaccination was added in 2014, it is not always administered to all women[4,5]. Among the mothers of infants with confirmed congenital rubella in Vietnam, it has been shown[4] that none had received rubella vaccine in the past. Furthermore, unless the woman is symptomatic, there is currently no universal serological screening for congenital infections during pregnancy in Vietnam.

It is important to ascertain the current burden of symptomatic congenital infections to allow early diagnosis and appropriate management. In the absence of data from Vietnam, this study aims to report our current experience with epidemiological, clinical, and available diagnostic data on symptomatic congenital infections caused by *Toxoplasma gondii*, *Treponema pallidum*, hepatitis B virus, rubella virus, CMV, and HSV.

PATIENTS AND METHODS

This retrospective observational study was conducted in the Neonatal Center, Vietnam National Children's Hospital, Hanoi, Vietnam, from 1 January 2018 to 30 June 2021. This is the main pediatric referral center for all the northern regions of Vietnam. It has a bed capacity of 4,000, with approximately 55,000 annual admissions. The hospital does not have an obstetric department, but the neonatal center (200-bed capacity) admits outborn infants referred from other regional hospitals.

All admitted neonates who were suspected of having a symptomatic congenital infection and had either a positive T*reponema pallidum* haemagglutination assay (TPHA), or at least one specific immunoglobulin M (IgM) antibody for *Toxoplasmas gondii*, rubella, HSV, or CMV (before three weeks of age) or a positive CMV polymerase chain reaction (PCR) test whenever CMV serology was inconclusive were included.

Infants without congenital infections, those whose CMV infection was diagnosed after 21 days of age, or those who had received a prior blood transfusion were excluded.

Data and Variables

We collected demographic, clinical, and laboratory data for all affected infants. Serum samples were tested for IgG and IgM antibodies against CMV, rubella, and *Toxoplasma gondii* using commercially available indirect ELISA kits (Roche, Germany) according to the manufacturer's instructions. Blood was also tested for HSV (1 and 2) IgG and IgM antibodies using commercially available capture ELISA kits (Virion, Serion, Germany), according to the manufacturers' instructions. The *Treponema pallidum* haemagglutination assay (TPHA) was used to diagnose infection with T. *pallidum* according to the manufacturers' instructions (Beckton, Dickinson & Co., and Wellcome Research Laboratories, respectively).

CMV PCR testing of blood samples was carried out when CMV serology results were inconclusive. CMV-DNA in the blood was detected using the real-time PCR method. Nucleic acid extraction was carried out using 100 µL by the MagNAPure LC 2.0 robot (Roche Molecular Systems, Mannheim, Germany). PCR amplification was conducted in a total volume of 25 µL, incorporating TaqMan Universal PCR master mix (2X) (Qiagen, TaqMan MGB Probe, Germany), along with specific primers and TaqMan probes, utilizing the TaqMan PCR procedure that uses the IQ5 real-time PCR system (Bio-Rad, Hercules, CA, USA) with the following parameters: 2 minutes at 46°C initially, then 10 minutes at 95°C, followed by 45 cycles of denaturation at 95°C for 15 seconds before ending at 58°C for 1 minute.

Otoacoustic emission or automated auditory brainstem response testing, echocardiography, cranial ultrasound, and ophthalmological examinations were performed on affected infants. The surviving children were followed up in our institution until six months of age, after which they were followed up in their referring hospitals.

Statistical Analysis

Statistical analysis was conducted using the Stata software version 17 (StataCorp, Texas, USA). The point prevalence of symptomatic congenital infections was calculated with 95% confidence intervals (95% CI). For normally distributed quantitative data, the Student's independent *t*-test was used to compare two groups, and the analysis of variance (ANOVA) for more than two groups. The Kruskal-Wallis' test was used to compare skewed data. Categorical data were compared using the Chi-squared test and Fisher's exact test for small samples. Statistical significance was defined as a two-sided p-value < 0.05.

RESULTS

During the 30-month study period, there were 418,455 live births in North Vietnam, with 12,566 neonates transferred to our unit from other regional hospitals. Sixty-eight infants satisfied the inclusion criteria for the

study. The point prevalence of symptomatic congenital infections was 5.4 per 1,000 admissions (95% confidence intervals 4.2, 6.8) and 1.62 per 10,000 live births (95% CI 1.26, 2.06). For cytomegalovirus (CMV) infection, it was 0.91 per 10,000 live births (95% CI 0.64, 1.24), and for congenital syphilis, 0.55 per 10,000 (95% CI 0.35, 0.82). The prevalence of infection with more than one pathogen was 0.16 per 10,000 births (upper 95% CI 0.34). The highest infection rate, either as a single pathogen infection or in association with other organisms, was for CMV (n=38, 58.8%), followed by syphilis (n=29, n=42.6%), rubella (n=3, 4.4%) and toxoplasmosis (n= 3, 4.4%). Co-infections were observed in 8 infants (11.7%).

As all infants were outborn, no information was available on maternal exposure or symptoms suggestive of congenital infections during pregnancy except for syphilis, where 14 (21.6%) women were known to be antenatally infected.

A high proportion of mothers of affected infants (60.3%) was between 20 and 30 years of age, 61% of neonates were male, 32 (54%) were born preterm (mean gestational age 37.0 ± standard deviation 2.3 weeks), and 31 (45.6%) were small for gestational age. The prevalence of infection was not significantly different between preterm and term infants (Table 1). As all infants were transferred from peripheral hospitals without their mothers, none of them were breastfed during their stay in our hospital.

The clinical manifestations included respiratory distress (39.7%), congenital heart disease (39.7%, of which 87.5% had atrial septal defects), splenomegaly (36.7%), hepatomegaly (38.2%) and petechiae (35.3%; Table 2). The most significant laboratory results included thrombocytopenia (platelet count <150 x 10^9/L) in 66.6% of patients, elevated liver transaminase levels (64%), and conjugated hyperbilirubinemia (>54 µmol/L) in 52.9% (Table 3). Intracranial calcifications were present in three infants (6%), and other abnormal skeletal findings in another three neonates: two with congenital syphilis and one infected with several pathogens. Sensorineural hearing loss was identified in 10 (14.7%) infants.

Penicillin therapy was administered to seven infants (24%) with congenital syphilis, and Ganciclovir to nine neonates (23%) with congenital CMV infection.

While in the hospital, 61 babies (89.7%) fully recovered from their infection, but seven died (10.3%). The identified pathogens, either alone or in combination, and their corresponding mortality rates are shown in Figure 1. The highest mortality rate (100%) was observed with concurrent infection by three pathogens (*Treponema pallidum*, herpes simplex, and CMV), followed by *Treponema pallidum* (12.5%) and CMV (8.3%).

At the 6-month follow-up evaluation of the surviving 61 neonates, the developmental delay was present in 13 (21.3%), all of whom had congenital CMV infection; one also had periventricular leukomalacia, and two had ventricular dilatation on ultrasound scan. No developmental delay was observed in infants infected with other pathogens. As all infants had subsequent follow-ups in their referring hospitals, long-term outcomes were unavailable to us.

DISCUSSION

There is scant information on the incidence of congenital infections in Vietnam[2]. This first study in the country showed that, during the study period, the prevalence of symptomatic congenital infections was 5.4 per 1,000 neonatal admissions to the hospital. The most commonly identified pathogens were CMV and syphilis. The predominance of congenital CMV infections confirms previous reports where 10-15% of the affected infants were symptomatic[5,6], and that infection was more prevalent in developing countries[7,8]. The high prevalence of congenital rubella in Vietnam, when compared to developed countries, is the consequence of the late introduction of the rubella vaccine, compounded by a persistent poor uptake[3]. Another cause, shared among all other congenital infections, is the lack of systematic serology testing during pregnancy in Vietnam. The co-infection rate (10.3%) was found to be lower than in other studies[1,5,6] from Southeast Asia, with rates varying from 24% to 32%. Similarly, the maternal age of affected infants (60.3% of mothers between 20 and 30 years) was lower than that in India, where the mothers were found to be younger (89.4% in that age bracket)[1]. The difference could be due to cultural differences, maternal literacy, sanitation, quality of life, and health care systems[1,5,6].

Table 1. Number (percentage) of infants diagnosed with congenital infections by gestational age.

Pathogens	Term 36 (53%)	Preterm 32 (47%)	Total 68 (100%)	*p*-value*
CMV	18 (50%)	18 (50%)	36 (100%)	0.6
CMV + HSV	1 (100%)	0 (0%)	1 (100%)	1.0
CMV + HSV + Syphilis	1 (100%)	0 (0%)	1 (100%)	1.0
CMV + Toxoplasmosis	2 (100%)	0 (0%)	2 (100%)	0.49
Rubella + Syphilis	2 (67%)	1 (33%)	3 (100%)	1.0
Syphilis	12 (50%)	12 (50%)	24 (100%)	0.72
Total	36 (53%)	32 (47%)	68 (100%)	0.52

Preterm: birth before the completion of 37 weeks of gestation; CMV, cytomegalovirus; *T. pallidum*, *Treponema pallidum*. *Chi-squared test or Fisher exact test if values <5.

Table 2. Epidemiologic and clinical characteristics of 68 neonates diagnosed with symptomatic congenital infections.

Characteristics	CMV n = 38	*T. pallidum* n = 23	> 1 pathogen§ n = 7	*p*-value	All congenital infections n = 68
Clinical manifestations					
Small for gestational age	21 (55.2)	7 (30.4)	3 (42.8)	0.14*	31 (45.6)
Respiratory distress	11 (28.9)	10 (43.5)	6 (85.7)	0.06*	27 (39.7)
Congenital heart defects	16 (42.1)	9 (39.1)	2 (28.6)	0.87*	27 (39.7)
Ventricular septal defect	1 (4.7)	0 (0)	0 (0)	1.0*	1 (3.1)
Atrial septal defect	17 (85)	9 (90)	2 (100)	1.0*	28 (87.5)
Patent ductus arteriosus	6 (30)	3 (33.3)	0 (0)	1.0*	9 (29.0)
Hepatomegaly	13 (34.2)	8 (34.8)	5 (71.4)	0.43*	26 (38.2)
Splenomegaly	13 (34.2)	7 (30.4)	5 (71.4)	0.36*	25 (36.7)
Petechial rash	18 (47.3)	2 (8.7)	4 (57.1)	0.003*	24 (35.3)
Jaundice on day 1	12 (31.6)	5 (21.7)	2 (28.6)	0.82*	19 (27.9)
Anaemia	4 (13.8)	3 (15.8)	1 (16.6)	1.0*	8 (14.8)
Seizures	1 (2.6)	1 (4.3)	0 (0)	0.03*	2 (2.9)
Cataracts	2 (5.2)	1 (4.3)	0 (0)	0.89*	3 (4.4)
Imaging					
Ventriculomegaly	6 (15.8)	1 (4.3)	0 (0)	0.20*	7 (10.3)
Parenchymal hypoechogenicity	2 (7.1)	1 (6.7)	0 (0)	1.0*	3 (6.0)
Brain atrophy	2 (7.1)	1 (6.7)	0 (0)	1.0*	3 (6.0)
Intracranial calcifications	3 (7.9)	0 (0)	0 (0)	0.27*	3 (4.4)
Abnormal skeletal radiology	0 (0)	2 (8.7)	1 (14.3)	<0.001*	3 (4.4)

Results expressed as number of infants (%) or median [interquartile range].
CMV, cytomegalovirus; *T. pallidum*, *Treponema pallidum*; §3 infants with syphilis and rubella, 2 with syphilis and toxoplasmosis, 1 with cytomegalovirus with herpes simplex and 1 with cytomegalovirus with herpes simplex. *Chi-square or Fisher exact test; §Kruskal-Wallis' test.

Table 3. Laboratory findings in 68 neonates with symptomatic congenital infections.

Parameter	Cytomegalovirus n=38	*Treponema pallidum* n=23	> 1 pathogen§ n=7	*p*-value	All congenital infections n=68
Hemoglobin (g/L)	142.6 ± 39.4	121.4 ± 37.2	121.8 ± 62.1	0.17*	133.0 ± 42.4
White blood cell (x 10^9/L)	11.6 [8.5, 18.0]	19.2 [15.0, 27.4]	27.3 [19.7, 68.3]	<0.001§	17.4 [11.3, 23.0]
Platelet count (x 10^9/L)	69 [29, 145]	183 [97, 318]	34 [16, 46]	<0.001§	34 [16, 215]
Total bilirubin (µmol/L)	168 [111, 278]	194 [149, 422]	217 [149, 422]	0.83§	194 [119, 278]
Direct bilirubin (µmol/L)	25.9 [17.3, 99.9]	42.7 [22.3, 144.8]	11.8 [70.8, 240.5]	0.39§	48.4 [18.0, 144.8]
AST (U/L)	140.7 [55.0, 289.0]	114.8 [53.6, 232.9]	63.3 [103.8, 828.2]	0.39§	116.4 [60.3, 311.9]
ALT (U/L)	28.6 [11.0, 87.5]	20.3 [13.7, 91.4]	59.3 [21.6, 93.3]	0.52§	28.6 [14.6, 87.5]
Serum albumin (g/L)	32.8 ± 4.4	32.1 ± 7.3	21.4 ± 2.2	<0.001*	31.1 ± 6.4
Prothrombin time (%)	73.1 ± 7.8	70.2 ± 28.5	62.0 ± 13.8	0.46*	70.8 ± 21.0
Serum C-reactive protein (mg/L)	11.7 [0.5, 64.8]	6.0 [1.8, 19.4]	94.8 [25.5, 110.9]	0.02§	8.9 [1.4, 64.5]

Results expressed as number of infants (%) or median [interquartile range].
CMV, cytomegalovirus; *T. pallidum*, *Treponema pallidum*; §3 infants with syphilis and rubella, 2 with syphilis and toxoplasmosis, 1 with cytomegalovirus with herpes simplex and 1 with cytomegalovirus with herpes simplex. *Chi-square or Fisher exact test; §Kruskal-Wallis' test.

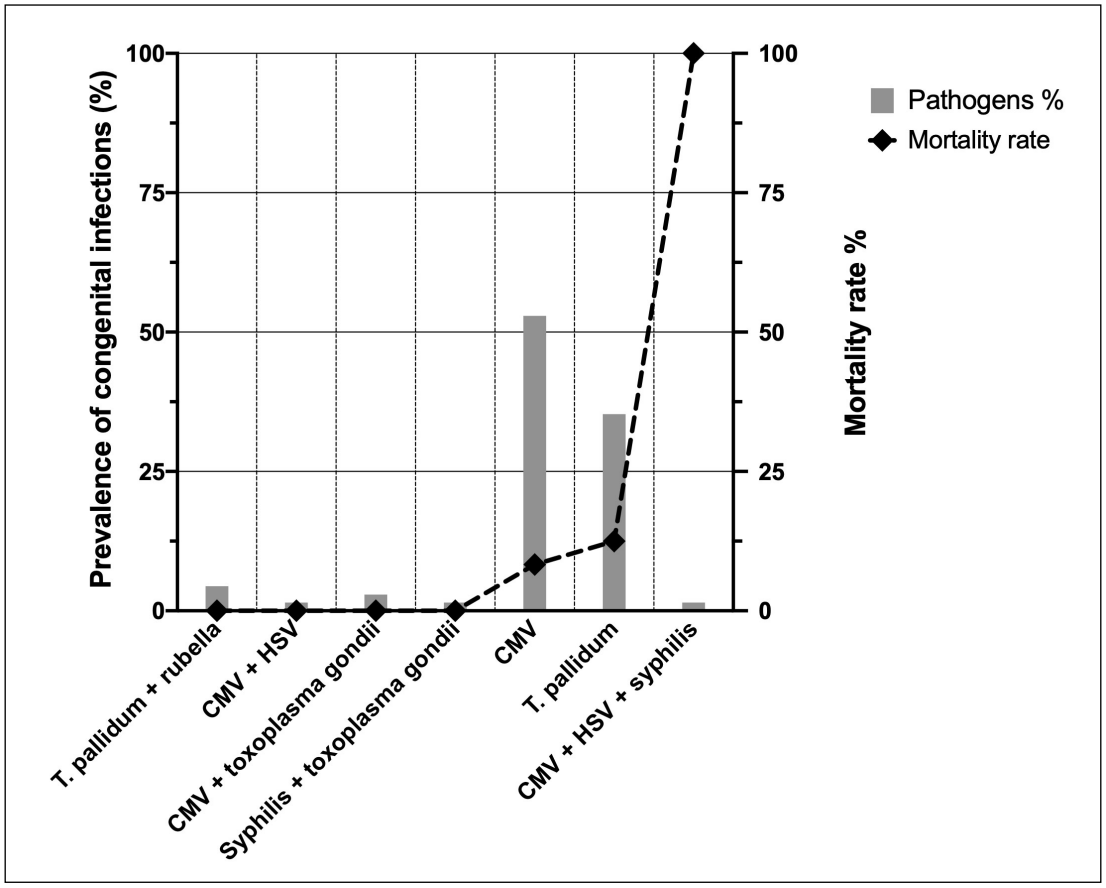

Figure 1. Prevalence and mortality rate of symptomatic congenital infections in 68 affected neonates.

The clinical manifestations and laboratory findings were similar to those of previous reports[1,9-16], as well as the mortality rate[1], although it varied amongst pathogens and rose significantly with the number of co-infections. Unfortunately, as all affected neonates were discharged to the care of their referring hospital, we had little information on their long-term outcomes.

Limitations

This study has some limitations. There was a lack of prenatal maternal information, such as history of contact with infected persons, or of symptoms suggestive of these infections. Furthermore, we believe that the prevalence we found was underreported, as only infants clinically suspected to have a congenital infection were included, without any information on asymptomatic neonates. Similarly, it is also likely that the true burden of these infections was underestimated since their diagnosis relied exclusively on serological results, without pathogen isolation or polymerase chain reaction (PCR) testing. For example, it has been shown[17-19] that, when compared to PCR, CMV IgM serology has low specificity and specificity, with a 100% positive predictive value and a negative predictive value of 52.5%.

Performing blood CMV PCR testing exclusively in infants with inconclusive CMV serology and the absence of urine testing for CMV are additional limitations of our study. Moreover, as this was a single-center study, the results cannot be generalized to the entire country. Another shortcoming is the lack of long-term follow-up of affected neonates.

CONCLUSIONS

Cytomegalovirus and syphilis were the most common causes of symptomatic congenital infections in our setting, with the highest mortality rates, The urgent implementation of appropriate public health measures is therefore required. They include sharing these results with the Ministry of Health, and lobbying for the establishment of a national surveillance program, as well as a registry of congenital infections. Reinforcement of the rubella vaccination program is urgently required, and also the development of a policy of systematic antenatal serology screening for congenital infections. Increasing public awareness of these measures is imperative alongside the encouragement and training of healthcare workers to implement them. A more comprehensive systematic long-term follow-up of the affected infants is essential and must be added to the current child health program. Similar projects, addressing the weaknesses of this study, should also be conducted in other parts of the country.

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Authors' Contributions:
TQNN developed the study concept and contributed with TNP and TMLC to collect the data. TQNN and HN analysed the data, drafted, and edited the manuscript with AS. All authors have read and approved the final manuscript.

Conflict of Interest:
The authors have no conflict of interest to declare.

Data Availability:
The data analyzed during the study are available from the corresponding author upon reasonable request.

Ethics Approval:
The study was approved by the Ethics Committee of Vietnam National Children's Hospital (No. 1841/BVNTW-VNCSKTE).

Informed Consent:
The informed consent requirement was waived as this study is a descriptive observational retrospective medical record review with anonymization of all participants.

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