

Cohort study on congenital cytomegalovirus seroprevalence and its association with neonatal cholestasis

Abstract

Cytomegalovirus (CMV) is a frequent causative agent of congenital infection in newborns and results in serious morbidity and mortality. CMV viral infection also have an important role in the pathogenesis of neonatal cholestasis (NC) and related clinical outcomes. To determine the incidence of congenital CMV infection and its association with NC cases, this study included a total of 234 infants who were presented with clinical symptoms suggestive of congenital CMV infection. Serum samples were collected and screened for the presence of serological markers to CMV. Of the 234 samples tested, 15% showed the presence of CMV IgM, among whom 54 had neonatal cholestasis. CMV infection in patients with neonatal cholestasis was found to be 21%. The presence of serological markers to CMV in the congenital infection and in neonatal cholestasis cases strongly suggests their association with this disorder.

Keywords: cytomegalovirus, congenital viral infection, infants, neonatal cholestasis

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Introduction

Cytomegalovirus (CMV) is the most common congenital viral infection and causes birth defects and developmental disabilities. Cytomegalovirus infection may be acquired prenatally or perinatally and may result in symptomatic or asymptomatic infection in neonates. Infants born with symptomatic infection are at high risk for developing adverse outcomes.¹⁻³ CMV is also a possible cause of chronic liver disease in infants and play a role in the pathogenesis of neonatal cholestasis (NC). NC is characterized by conjugated hyperbilirubinemia and results from diminished bile flow by either an extra-hepatic (biliary atresia) or intra-hepatic (non-biliary atresia) disorders.⁴⁻⁶

Diagnosis of congenital CMV infection in neonates is very important for proper clinical management. Detection of CMV specific IgM class antibodies by enzyme-linked immunosorbent (ELISA) assay is used to establish the current or congenital CMV infection.^{1,2} Despite the clinical significance, congenital CMV infection in neonates often goes undetected as screening programs have not been implemented substantially and the related outcomes have not been adequately investigated in our country. A few studies have shown the prevalence and the association of cytomegalovirus in symptomatic congenital infections.⁷⁻¹⁰ However, the etiologic association of CMV and its coexistence in NC cases have not been documented from Central India. Hence, the present study was aimed to estimate the seroprevalence of congenital CMV and to investigate the association with neonatal cholestasis patients at a tertiary care hospital, Central India.

Materials and method

Screening for congenital CMV infection in newborns was conducted over a period of one year (January to December 2019) at the tertiary care hospital in Central India followed by the institutional ethical committee approval. Serum samples collected from a cohort

of neonates exhibiting clinical symptoms suggestive of congenital infection and the samples were referred to the State Virology Laboratory, Bhopal for routine investigations. The presenting clinical features and the liver function test parameters were noted. Neonatal cholestasis (NC) or the conjugated hyperbilirubinemia was determined by using the biochemical parameters (1).

The serum samples of neonates were tested for CMV-IgM antibodies using commercially available enzyme-linked immunosorbent assay method (Anti CMV immunoglobulin M (IgM), Ratio Diagnostics, Germany) for qualitative detection as per the manufacturer's instructions. All assays were performed and the intensity of the color was measured using Infinite® F50 Tecan ELISA reader. Chi-square test with 95% confidence interval (CI) was computed to assess the clinical comparison between neonatal cholestasis cases with CMV-IgM (+) and CMV-IgM (-) and a $p < 0.05$ was considered to be statistically significant.

Results

During the period of the present study, a total of 234 samples were collected from infants exhibiting clinical symptoms for congenital CMV infection. Out of the 234 infants, 148 (63.2%) were male and 86 (36.7%) were female. Out of 234 infants included in the study, 54 (23%) infants were presented with conjugated hyperbilirubinemia and diagnosed as neonatal cholestasis cases among whom 4 (1.7%) had biliary atresia and 49 (20.9%) had cholestasis due to causes intra-hepatic (non-biliary atresia) disorders. Among clinical manifestations reported in the infants, jaundice, and hepatomegaly were the most common feature.

A total of thirty-five serum samples, out of 234 (14.9%) were tested positive for CMV IgM antibodies. Among the 54 patients with neonatal cholestasis, 11 (20.3%) infants were found positive for CMV IgM and 43 (79.6%) infants were found negative for CMV IgM. The clinical comparison between neonatal cholestasis cases with CMV-IgM (+) and CMV-IgM (-) given in Table 1.

Table 1 Clinical comparison of neonatal cholestasis cases

Clinical features	NC cases with CMV-IgM (+) n=11	NC cases with CMV-IgM (-) n=43	p value*
Abdominal pain	05 (45.4%)	17 (39.5%)	0.721#
Dark urine	04 (36.3%)	11 (25.5%)	0.476#
Fever	07 (63.3%)	19 (44.1%)	0.249#
Hepatomegaly	04 (36.3%)	23 (53.4%)	0.310#
Jaundice	08 (72.7%)	32 (74.4%)	0.909#
Vomiting	02 (18.1%)	08 (18.6%)	0.974#

*Chi-square test; #P value not significant

Discussion

Congenital CMV is a leading cause of public health problem throughout the world including India. The prevalence of congenital CMV infection may vary on the basis variety of epidemiological factors (geographical region, racial, ethnic and socioeconomic background).^{2,3} Neonatal cholestasis is caused by a number of factors including some viral aetiologies. CMV infection has been proposed as a possible etiologic agent of neonatal cholestasis.⁶ Very limited information is available in our country about the seroprevalence of CMV^{8,9} and no regarding the incidence of CMV in association with conjugated hyperbilirubinemia or neonatal cholestasis cases among the infant population. Therefore, in this retrospective study, samples from infants reported with symptomatic congenital infections at the tertiary care hospital in Central India, were referred to the laboratory. The presence of CMV specific IgM antibodies and its association with neonatal cholestasis and the clinical manifestations were studied.

Majority of the studies conducted in India and globally have documented the high incidence of congenital CMV infection among infants born with various birth defects.⁶⁻⁹ The present study showed a seroprevalence of 15% for CMV IgM which is almost similar to other studies. In the literature, the seroprevalence of CMV in NC cases varies between 11% and 32% in countries like Brazil, China, Egypt and Sweden.^{6,10-14} In our study, we found a high prevalence of CMV infection (20.3%) in neonatal cholestasis cases. Significant associations of clinical features were not found between neonatal cholestasis cases with CMV-IgM (+) and CMV-IgM (-). There are limitations to this study that must be considered during the interpretation of the findings. As this is a seroprevalence study, the molecular detection of CMV DNA was not done which is considered as a standard method for diagnosing CMV infection. To conclude, the presence of serological markers to CMV in the congenital infection and in neonatal cholestasis cases strongly suggests their association with this disorder. Newborns with neonatal cholestasis should be tested for CMV for their timely and proper therapy and also prevent the spread of infection to other children.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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