Research Progresses of Congenital Cytomegalovirus Infection

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Abstract: Congenital cytomegalovirus infection (cCMVi) in the newborn is one of the most common congenital infections. The children who are infected will present different clinical manifestations. The mild symptoms may be asymptomatic. However, severe cases may have permanent sequelae and even endanger their life. This paper would review the research progresses in the following fields including the epidemiology, the route of transmission, clinical manifestation, screening methods , narrative perspective of prevention and control means. Then the prevention strategies would be summarized.
***Keywords*:** cytomegalovirus, congenital cytomegalovirus infection, clinical manifestation, screening methods, prevention strategies

Congenital cytomegalovirus infection (cCMVi) is the most common congenital virus infection. Cytomegalovirus is the most common intrauterine infection pathogen in fetal congenital defects. The proportion of infected newborns with CMV-specific symptoms at birth is 12.7%. About 40-58% infants are symptomatic. The percentage of infants, who are asymptomatic at birth but present permanent sequelae in the later life, is about 13.5%. Approximately 25 percent children have sequelae in the first two years of life[1]. In recent years, with the improvement of the testing methods and the further understanding of cCMVi, early prevention, early identification and early treatment are particularly important. The epidemiology of cytomegalovirus, the transmission route of cCMVi, clinical manifestations, screening methods, prevention and treatment methods are reviewed.

1. Epidemiology of cytomegalovirus

Cytomegalovirus (CMV), also known as human herpesvirus type 5, is widely prevalent both in developed and developing countries, with a high global seroprevalance (60%~100%) [2]. In our country, the serological positive rate of CMV-IgG in pregnant women is 94%~98%, and the prevalence rate of neonatal infection is about 0.7% [3,4]. The transmission patterns of mother-to-child cytomegalovirus infection is including cCMVi (intrauterine infection) and acquired CMV infection (contacting with infected person's body fluids such as urine, saliva, blood, breast milk and genital secretions, organ transplantation and blood transfusion) .

2. Transmission mode of cCMVi

20% of cCMVi occurs in the first 3 months of pregnancy, and the proportion gradually increases with the process of pregnancy, reaching 75% in the last three months of pregnancy [5]. The patterns of CMV active infection in pregnant mothers are including primary infection and non-primary infection. The former refers to that CMV infects mother first time shortly before or during pregnancy, in the other words, the CMV-IgG antibody in the pregnant woman is negative before the infection. The latter includes the reactivation of the CMV in vivo and reinfection viruses with different genotypes. The virus in the pregnancy mothers is vertically transmitted to the child through the placenta. The risk of teratogenicity is greater in the first three months of pregnancy than in the middle and late stages of pregnancy. For intrauterine infection, the primary infection of CMV (30-35%) is more common than non-primary infection (1.1-1.7 %) [4].

3. Clinical manifestations of congenital cytomegalovirus infection

The clinical manifestations of the disease are diverse and could involve multiple organs and systems. For fetal ,cCMVi could lead to central nervous system abnormalities including severe malformations, such as microcephaly, encephalocoele calcification, cerebellar hypoplasia, small eye disease and optic atrophy [6].A number of newborns have subclinical manifestations at birth, followed by gradual mental retardation, such as sensorineural hearing loss (SNHL), visual impairment, epilepsy, etc, which all affect children's follow-up life. Mouse models have shown that fetal brain stem progenitor cells (NSPC) were more susceptible to mouse CMV (MCMV) than embryonic stem cells. In the second trimester, virus affects the organogenesis of the brain, eyes, mouth and face. It also inhibits neuronal migration and

synaptic formation, which indirectly leads to placental dysfunction [7,8] . A cohort study showed that cCMVi increased the prevalence of microcephaly by more than 7 times in the United States [9]. Other common clinical manifestations include pathological jaundice (early appearance and delay subsided), elevated liver enzymes, thrombocytopenia in the first week after birth (spontaneously rising to normal in the second week), neutropenia, etc.[10].

4. Screening methods for congenital cytomegalovirus infection

4.1 Prenatal screening during fetal period

Ultrasound is one of the most common non-invasive prenatal diagnosis methods. The common malformations of prenatal ultrasound in children infected by CMV are microcephaly (14.5%), intracranial calcification (0.6%-17.4%), and subependymal cyst (11.6%), encephalocoele dilatation (4.5%-11.6%), fetal growth restriction (1.9%-13%), enhanced intestinal echo (4.5%-13%), ascites (8.7%)[11]. Pregnant women can exam CMV antibodies (IgG, IgM) and IgG antibody avidity index (AI) to assess whether pregnant women are infected by CMV and the type of infection(primary infection or non-primary infection). If it shows that CMV antibody IgG negative turns to positive (seroconversion) , antibody IgM positive or AI is lower than the lowest limit of the threshold can diagnose primary CMV infection. And low AI can predict cCMVi in pregnant women less than 14 weeks of gestation. The sensitivity and specificity are 83.3% and 83.8%, respectively [12].

After the fetus is infected by CMV, the virus enters the amniotic fluid through the urine. Amniocentesis is the direct method for the detection of fetal cCMVi. Generally, the polymerase chain reaction (PCR) test is performed to exam CMV-DNA in amniotic fluid at 6 weeks after mother infected virus or 21 weeks of pregnancy. The specificity reaches 97-100%, and the sensitivity is between 45-80% [13]. But as an invasive procedure, it is restricted in clinical use. Using this test results to predict the severity of fetal perinatal period outcomes still needs more evidence-based basis

Studies have found that the CMV-DNA titer in maternal cervical secretions is an reliable predictor for fetal cCMVi in CMV-IgM-positive pregnant women. Its sensitivity and specificity are 50.0% and 94.2%. On the contrary, in CMV-IgM-negative pregnant women, this index is low efficiency [14].

In China, due to the high seropositive rate of child-bearing period women, the lacking of comprehensive benefit analysis in health economics, the dissimilar testing methods in different regions, the reliability of the dubious results (if the IgG antibody AI results are between high and low limit, it is difficult to distinguish the type of infection), and the existence of CMV-antibody IgM false positive and long-term low-level positive after infection [15],routinely screening CMV-related antibodies for pregnant women is not popularization. However, due to the huge economic and social burdens caused by the subsequent occurrence of cCMVi in children, the implementation of prenatal screening is effective for newborns. Early detection of children with cCMVi and the potential benefits of intervention still need further evidence-based analysis.

4.2 Neonatal screening

The 2017 International Expert Consensus [16] recommended that newborns should be screened for cytomegalovirus infection. The result of a study based on the Chinese medical system using the Markov model also suggests that universal screening of cCMVi can improve cost-effectiveness and produce optimal health results [17]. A multi-center study based on nearly 100,000 babies found that at least 57% patients of cCMVi-related SNHL can be identified by cytomegalovirus-related examinations for children who are failed to pass hearing screening, and more than 43% of cases are difficult to be identified. Most of these cases are mild degree of hearing loss, progressive and late-onset hearing loss[18]. Cytomegalovirus screening can identify symptoms such as early intervention in SNHL and growth retardation. In the early birth (within 3 weeks) period, urine and saliva samples have been proven to be reliable CMV screening specimens. Compared with urine which is difficult to collect, saliva samples relatively easier to obtain and store. It is more dominant in the selection of screening specimens. Due to breastfeeding, CMV in the milk may cause a false positive CMV DNA test in saliva. The specimen should be acquired for at least 1 hour after breastfeeding. Dried blood spot (DBS) is a common metabolic detection method. It is used for cCMVi screening with low sensitivity and unstable results (40-85.7%). This may be related to otherness in different DNA extraction methods and PCR detection schemes [19].

4.3 Predicting prognostic indicators of CMV infection

A number of studies have shown that urine CMV viral load is related to clinical symptoms [12,20,21]. When the urine CMV-DNA load reaches 1.415×106/mL, the prediction is more prone to SNHL, and its prediction sensitivity and specificity are 46.3% and 93.2%,respectively. The degree of damage is positively correlated with viral load. The platelet count of children is negatively correlated with the viral load of urine CMV DNA. The viral load of CMV-DNA was

positively correlated with the incidence of cerebral palsy. The viral load of CMV-DNA in liquid was significantly higher than that of CMV-infected patients without central nervous system damage.

The envelope glycoprotein of human cytomegalovirus is the main component of the outermost lipid bilayer envelope of the virus[22]. Taking the envelope glycoprotein gH as an example, the study found that children with the gH1 genotype compared with children carrying the gH2 genotype, the incidence of hearing impairment is higher ,the gestational age at birth is smaller and the probability of thrombocytopenia is greater. On the contrary, children carrying the gH2 genotype have greater possibility to suffer neurological damage and the greater probability of persistent thrombocytopenia[23-27]. The genotyping of envelope glycoprotein can predict the clinical symptoms and prognosis of infected children, but there are regional differences in the distribution of CMV gH genotypes [28,29]. CMV gH2 (60%) in the United States is more common than gH1 (48%). According to statistics in Wuhan, China, gH1 genotype is more dominant. Recently there have been many studies by sequencing the CMV genome, and the genetic diversity of the virus has been confirmed [30], but the relationship between its genetic polymorphism and clinical diseases is not systematic, and further evidence-based analysis is needed to guide the clinical practice.

5. Prevention and treatment of congenital cytomegalovirus

In order to reduce the primary and non-primary infections in pregnant women, some researchers have conducted epidemiological data analysis based on the seropositive rate of CMV and the congenital cytomegalovirus infection rate of pregnant women in different ethnic groups and concluded that pregnancy The CMV seropositivity rate of parturients increases, and the congenital cytomegalovirus infection rate also increases. At the same time, exposure to young children is a risk factor for CMV infection during pregnancy [31-33]. Based on a randomized controlled study of 166 CMV seronegative mothers, it was found that washing hands, paying attention to hand hygiene, using gloves and avoiding close contact with children can effectively prevent CMV infection [34].

The development of CMV vaccines began in the 1970s and has a variety of types.Among them, glycoprotein B (gB) vaccines and gH/gL/UL128/UL130/UL131A pentamer vaccines are designed to prevent fetal CMV infection and are still in clinical trials [35]. There are a number of studies that propose the use of high immunoglobulin (HIG) to prevent mother-to-child transmission during pregnancy, but its effectiveness is controversial[36-38], the sample size of the study is small, and further multi-center randomized controlled trials or meta-analysis are required To evaluate the effectiveness of HIG, and the safety needs further evaluation. Although the observational study based on 149 pregnant women found that although the use of HIG for pregnant women who have recently been infected with cytomegalovirus in the first three months of pregnancy is effective to treat the recent CMV virus infection of pregnant women and reduce mother-to-child transmission [39], routine use is still not supported in clinical practice. HIG to prevent or treat infected mothers.

Intravenous application of ganciclovir and oral treatment of valganciclovir have been used in antiviral treatment of neonates with congenital cytomegalovirus infection, but the side effects of drugs should be vigilant during the treatment process, such as causing thrombocytopenia and neutropenia, which may It has gonadal toxicity and carcinogenicity. It is necessary to measure the risk of medication and choose drugs reasonably. The consensus of experts in my country recommends that the target of antiviral therapy is moderate to severe cCMV neonates (1. neonates with congenital CMV infection have multiple manifestations 2.central nervous system symptoms)[40]. At present, the European Expert Consensus [41]recommends that the course of antiviral therapy for children with central nervous system injury at least for 6 months. There is no consensus on the treatment of children with life-threatening diseases or severe single organ involvement or multiple organ diseases.

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