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Clinical Problems of Congenital and Perinatal Cytomegalovirus (CMV) Infection

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Abstract: *Congenital CMV (cytomegalovirus) infection occurs in one out of 1,000 births and remains a serious health problem for children both in the developed and developing countries. It has been shown that perinatal CMV infection also has a risk for impaired psychomotor development. Although the strategy for congenital CMV infection is an early detection and treatment, effective prevention or treatment methods remain to be developed so far in spite of remarkable medical progress. It is important to disseminate accurate clinical information widely and promote further investigations.*

Keywords: *congenital CMV infection, sensorineural hearing loss, ganciclovir, hyperimmune globulin, dried blood sample*

CMV (cytomegalovirus) is a virus of the herpes genus existing universally in the world and every human being is infected once during one's life. It may present sometimes with fever and hepatitis when infected, but it is almost self-limiting or asymptomatic and not serious in nature. However, when CMV infects the neonates, and immunocompromised hosts, it will be serious and fatal eventually. CMV can infect various cells such as mesenchymal cells (fibroblasts, vascular endothelial cells, smooth muscle cells), epithelial cells, hematopoietic cells, and neuronal cells.[1] Once, infected primarily, it continues to infect latently in the myeloid progenitor cells as an episomal form, and is reactivated and induces various complications in the patients under immunosuppressive conditions.[2] Molecular mechanism of CMV reactivation is being disclosed and it is considered that TNF-α and cyclic AMP are important triggering factors.[3] CMV infection is also known to induce thrombosis or microangiopathy[4], for which precise mechanisms are not well understood.[5]In the field of transplantation medicine, the control of CMV infection is one of the most important clinical concerns.[6]

Table1. *Definitions of congenital CMV infection and disease*

• Moderate to severe symptomatic congenital CMV disease Multiple manifestation： thrombocytopenia・hepato-splenomegaly・intrauterine growth restriction・hepatitis, or Central nervous system involvement： microcephalus・ventriculopathy・intracerebera calcifications・chorioretinitis, sensorineural hearing loss,CMV in cerebrospinal fluid etc
• Mildly symptomatic congenital CMV disease One or two isolated manifestations of congenital CMV infection
• Asymptomatic congenital CMV infection with isolated SNHL Sensorineural hearing loss(SNHL) (>=21 decibels)
• Asymptomatic congenital CMV infection Others except for the above

Modified from reference 23

Meanwhile, CMV infects the fetuses via the placenta through a viremia in the primarily infected pregnant mothers, and induces congenital CMV infection, resulting in the serious sequels such as intrauterine growth retardation, hydrocephalus, mental retardation, sensorineural hearing loss, thrombocytopenia, and so on (Table-1).[7] Recently, the number of

uninfected pregnant mothers is increasing through the improvement of the hygiene environment, and there is a growing concern for the increased risk of congenital CMV infection. It is estimated that symptomatic congenital CMV infection occurs in one out of 1,000 births. However, it is considered that there are three to four folds asymptomatic congenital CMV patients, who are diagnosed later as a sensorineural hearing loss of unknown etiology.[8] Until now, a majority of a congenital sensorineural hearing loss other than genetic diseases is considered to be caused by asymptomatic congenital CMV infection.[9]

The protective efficacy of the high titer anti-CMV antibody containing immunoglobulin (hyperimmune globulin) administration is still controversial. The effect of hyperimmune globulin to prevent congenital CMV infection has been reported in several non-randomized or retrospective clinical studies.[10-13] However, recent randomized clinical study in USA could not show significant preventive effect.[14]

The fact that effective vaccine for CMV has not been developed so far is another serious problem. Up to date, preliminary data has been published that vaccine of monomeric recombinant CMV envelope glycoprotein B (gB) with MF59 adjuvant may prevent non-infected human mother from primary CMV infection during pregnancy, and reduce congenital CMV infection by 43%.[15] It is known that the natural conformation of human CMV gB within the viral envelope is a trimer, and the development of trimer gB has been investigated. Immunization of mice with trimeric human CMV gB induced up to 11-fold higher serum titers of total gB-specific IgG relative to monomeric human CMV gB.[16] It is also recognized that congenital CMV infection could develop through CMV reactivation of the pregnant mother already infected and immunized, although infectivity is much lower than in case of primary infection.[9] Furthermore, CMV is secreted in breast milk, and infects neonates after birth, especially premature newborns.[17]Recent report indicates that there is still a risk for impaired psychomotor development even in the case of primary infection in the early stage of a newborn period.[18]

At present, the strategy for congenital CMV infection is an early detection and treatment of CMV infection, so far.[19] Effective antiviral drug available right now includes intravenous ganciclovir and foscarnet in Japan. For congenital CMV infection, the long-term anti-viral treatment for 6 months has been reported to reduce the severity or progression of hearing and psychomotor impairment.[20, 21] The possible side effects such as myelosuppression and renal impairment are problems to be discussed. However, it has been reported that most of the neonates are well tolerable to a long-term ganciclovir administration. To monitor during treatment, it is recommended that absolute neutrophil counts should be followed weekly for 6 weeks, then at 8th week, and monthly thereafter.[22] For the former, oral medicine; valganciclovir is developed and is reported as effective as ganciclovir and beneficial for the long-term treatmentofneonates or early infants practically.[21]

This new oral medicine may solve the serious blood access problem frequently experienced in neonates with low birth weight. In the recent consensus recommendation, valganciclovir is only recommended for neonates with moderate to severe symptomatic congenital CMV infection because of its possible adverse effects, cost-benefit and limited clinical effectiveness. Also, preventive use is not recommended for the same reasons above.[22]

Table2. *Frequency of congenital CMV infection and other diseases*

Disease	**Frequency**
Congenital CMV infection(total)	1/300
Congenital CMV infection (symptomatic)	1/1,000
Down syndrome (mother >=35 years old)	1/300
Down syndrome (total)	1/1,000
Congenital hypothyroidism	1/3,000
Congenital adrenal hyperplasia	1/15,000
Galactosemia	1/40,000
Phenylketonuria	1/80,000
Homocystinuria	1/250,000
Maple syrup urine disease	1/400,000

The highly sensitive diagnostic method of CMV infection is a polymerase chain reaction (PCR). It is shown that dried blood sample (DBS) used in mass screening for newborns is available as a specimen to detect CMV by PCR.[23] Recently, DBS is also used for screening of primary immunodeficiency.[24] The frequency of congenital CMV infection is higher than the other diseases which are targeted for present mass screening system as presented in Table-2.

Several clinical studies which evaluated the efficacy of universal CMV infection screening by PCR with DBS have been reported. Most of the reports have concluded that sensitivity of PCR to detect CMV in DBS is not sufficient enough as a screening method for congenital CMV infection clinically.[25-28] Detection of CMV DNA in the saliva or urine by PCR is a most sensitive method at present and it is now considered that DBS should be used for confirmation of congenital CMV infection but not for universal screening.[22, 28] Recently, the result of hearing-targeted congenital CMV infection screening program has been published from Utah in USA.[29] In this program, infants who failed newborn hearing screening test were placed for CMV detection program as early as possible. In spite of remarkable medical progress, congenital CMV infection remains largely unrecognized in the developed and developing world.[30] It is now a major infectious cause of sensorineural hearing loss and psychomotor developmental defects in infants born in developed countries,[31] and second only to cerebral palsy in all causes of serious malformation in many countries. It is important to disseminate accurate clinical information and insidious thread of congenital CMV infection widely and promote further clinical investigation and basic scientific research of CMV to conquer this problem.

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