Jpn. J. Obstet. Gynecol. Neonatal Hematol. Vol.34 No.2, 131-136, 2025

先天性サイトメガロウイルス感染症に対する新生児マススクリーニングの重要性：無症候性で、聴覚スクリーニングをパスした胎内感染症の１例

Importance of universal newborn screening for congenital cytomegalovirus infection: A case involving a patient who did not present with clinical manifestations and passed the automated auditory brainstem response test

金子政時[1, 2)]
Masatoki KANEKO

児玉由紀[1)]
Yuki KODAMA

要　旨

日本では、サイトメガロウイルス（CMV）胎内感染を疑う所見を有する新生児に対するtarget screeningが推奨され、症候性感染児に対してバルガンシクロビル（VGCV）による治療が行われる。しかし、適切な時期に診断し、治療を開始することは、時に困難である。母体は、妊娠初期CMV IgG抗体陽性、IgM抗体陰性であった。妊娠32週にCOVID-19、妊娠35週にインフルエンザに罹患した。妊娠35週に帝王切開が施行され、2,363gの児を出産した。新生児に、点状出血斑、肝腫大、肝機能障害、黄疸、血小板減少を認めなかった。聴力スクリーニング検査では、両耳passであった。５生日のろ紙尿中CMV検査で陽性、液体尿PCR検査で、胎内感染を確定した。聴性脳幹反応検査では、両耳ともに聴力障害を認めた。６か月間のVGCVの経口投与の結果、生後９ヶ月の発達は正常で、聴力障害を認めない。本症例は、新生児に対するユニバーサルスクリーニング検査の必要性を示唆する症例であると考える。

Key words; Congenital cytomegalovirus infection, pregnancy, screening

１）宮崎大学医学部産婦人科：Department of Obstetrics and Gynecology, Faculty of Medicine, University of Miyazaki
２）宮崎大学大学院看護学研究科：Graduate School of Nursing Science, Faculty of Medicine, University of Miyazaki
著者連絡先：〒889-1692 宮崎市清武町木原5200　宮崎大学医学部産婦人科　金子政時
TEL: 0985-85-0988　e-mail: mkaneko@med.miyazaki-u.ac.jp

Introduction

Congenital cytomegalovirus (CMV) infection is the most common viral infection causing morbidity and mortality in newborns with congenital infections. This condition results in neurological sequelae including sensorineural hearing loss, visual impairment, and motor and cognitive deficits [1]. The prevalence rates of congenital CMV infection are 0.2%-2.0% in newborns [1,2] and 0.31% in Japanese [3]. Despite the significant impact of CMV infection on the perinatal field, maternal serological screening for CMV is not globally recommended due to the lack of effective preventive measures for vertical transmission and intrauterine treatment of congenitally infected fetuses [1]. However, the use of oral antiviral liquid suspension (valganciclovir [VGCV]) has been recently approved for treating symptomatic congenital CMV infection in Japan. Accordingly, in Japan, targeted screening with polymerase chain reaction (PCR) using neonatal urine samples is recommended for neonates at risk of congenital CMV infection [4]. Nevertheless, not all patients with congenital CMV infection requiring treatment can be identified using conventional risk factors. Herein, we present a patient who did not meet the conventional risk factors for screening. Moreover, the need for universal neonatal screening was discussed.

Case presentation

A 25-year-old pregnant woman (gravida 4 and para 2) was managed at Miyazaki University Hospital for a Jr^a incompatible pregnancy. During her first pregnancy, she tested positive for human cytomegalovirus (HCMV) IgG (24.8 mg/dL) and HCMV IgM (2.73). She delivered a healthy neonate weighing 2,926 g at 38 weeks of gestation via vaginal birth 6 years before the current delivery. In her second pregnancy, she tested positive for HCMV IgG (14.6 mg/dL) and HCMV IgM (2.99) and delivered a neonate weighing 1,664 g (small for gestational age of unknown cause) via cesarean section at 34 weeks of gestation 5 years before the current delivery. The PCR results for HCMV using neonatal urine samples were negative in both cases.

In her current pregnancy, the patient tested positive for HCMV IgG (≥250 AU/mL) and negative for HCMV IgM (0.24) at 12 weeks of gestation. Routine ultrasonography at 21 weeks of gestation did not show fetal abnormalities. She contracted the coronavirus disease 2019 (COVID-19) at 32 weeks of gestation. She also had the influenza A viral infection and was hospitalized due to possible premature labor at 35 weeks of gestation. Cesarean section was performed on the same day of admission due to labor onset and a previous history of cesarean section. She delivered a male newborn weighing 2,363 g (appropriate for gestational age), with 1- and 5-min Apgar scores of 8 and 9, respectively. Umbilical arterial blood gas analysis revealed the following results: pH, 7.167; partial pressure of arterial carbon dioxide, 65.1; partial pressure of oxygen, 32.0; bicarbonate anion, 23.6; and base excess, -6.7. The results of the IgG avidity index at 15 days after delivery was 73.7%.

The neonate did not exhibit any symptoms such as abdominal petechial rash and hepatomegaly. The neonatal laboratory findings did not indicate liver dysfunction, icterus, or low platelet counts. The neonate tested negative for Jr^a antibody, and he had a positive indirect Coombs test result and had a negative direct Coombs test result. On day 5 of life, the neonate passed the hearing screening test using automated auditory brainstem responses in both ears. The PCR conducted on day 5 of life using a neonatal urine sample collected on a filter paper (Shino-test Science Laboratories Inc.) had positive results, and the findings were confirmed via PCR using a liquid urine sample on day 11 of life. The auditory brainstem response testing conducted on day 20 of life revealed bilateral sensorineural hearing loss (right: 40 dB, left: 50 dB). Cranial magnetic resonance imaging did not show any abnormal findings, except for a punctate white

matter lesion. The newborn received oral VGCV at a dose of 16 mg/kg for 6 months. He had a normal development without hearing loss at 9 months after birth.

Discussion

Herein, we present a patient who did not exhibit clinical manifestations indicating neonatal CMV screening. In addition, he passed the universal hearing test. Neonatal CMV screening is recommended if the patient has factors such as maternal CMV IgM positivity, abnormal fetal ultrasound findings (e.g., fetal growth restriction, ventricular dilation, ascites, and hyperechogenic bowel), and neonatal abnormalities (e.g., small for gestational age, ventriculomegaly, ascites, petechiae, hearing impairment, liver dysfunction, and thrombocytopenia) [4]. These findings are not specific to congenital CMV infection. However, targeted screening based on these clinical findings may effectively detect patients at high risk of congenital CMV infection [5]. In addition, there are reports on the feasibility of targeted screening in newborns who did not successfully undergo universal hearing screening [6, 7]. However, over half of patients did not present with prenatal or neonatal signs of congenital CMV infection or a maternal history of CMV infection during pregnancy. Therefore, some patients may not be diagnosed via targeted screening [8]. Canon et al. reported good evidence on the potential benefit of antiviral therapy in children with delayed hearing loss at 9 months of age and fair evidence on potential benefits in children with delayed hearing loss between 9 and 24 months of age and those with CMV-related cognitive deficits [9].

In this case, an infant with congenital infection was born to a mother with preconceptional CMV immunity. Maternal preconceptional CMV immunity does not protect the fetus from acquiring congenital CMV infection. Nonprimary infection due to recurrent latent infections or reinfection with novel virus strains during pregnancy can result in fetal infection [1]. In clinical practice, it is difficult to distinguish these two mechanisms. Moreover, the timing of intrauterine transmission with such reactivation or reinfections during pregnancy is nearly impossible to identify due to the absence of virological or serologic markers [1]. Thus, the timing of transmission in this case could also not be identified. However, the mother in this case contracted COVID-19 at 32 weeks of gestation and influenza A infection at 35 weeks of gestation. We believe that the association between these infections and the transmission of CMV should be considered. The influenza A infection was not relevant because the patient had delivered her baby immediately after the infection. However, the impact of COVID-19 on maternal immunity should be considered. Some women who had a history of therapeutic immune suppression and lupus or AIDS developed symptomatic congenital infection due to altered maternal immunity either from immunosuppression or an inability to recognize a recurrent maternal infection [10-12]. In this case, the mother did not receive immunosuppression treatment. Interestingly, CMV transmission in utero is more frequent with increasing gestational age. In contrast, maternal infection at an earlier gestational age is associated with more severe congenital infection and worse outcome in infants [13]. In view of the severity of the congenital infection, the time of vertical transmission might have been late in the pregnancy in this case. As a critical balance between fetal immunity, maternal immunity, and viral inoculum will determine the extent and severity of fetal infection, nonprimary infection was challenging to prevent or suspect during pregnancy. Accordingly, universal neonatal screening is essential as in our case.

Recently, the use of oral liquid VGCV suspension has been approved for the treatment of symptomatic congenital CMV infection in Japan. Morioka et al. have revealed the efficacy of this treatment

for symptomatic congenital CMV infection[14, 15]. In a randomized, placebo-controlled trial of VGCV therapy in neonates with symptomatic congenital CMV disease, treatment with VGCV for 6 months, compared with treatment with VGVC for 6 weeks, was associated with modest long-term improvement in hearing and developmental outcomes, but not with short-term improvements in hearing [16]. However, this treatment should be initiated within 3 weeks after birth and continued for 6 months. Therefore, the early and accurate diagnosis of congenital CMV infections in newborns is essential.

Various tests using neonatal specimens, such as dried blood spots, saliva, and urine, are available for universal screening. In our case, congenital infection was detected via PCR using a neonatal urine sample collected on a filter paper. Koyano et al. have revealed that this screening method is feasible [3]. Nagano et al. clinically evaluated these urine collection kits using a filter paper and confirmed their safety and high success rates in collecting samples [17]. The application of PCR evaluation of dried blood spots to screen newborns for congenital CMV infection has demonstrated center-to-center variability in terms of sensitivity [18-21]. High viral loads are shed in both the urine and saliva of infants with congenital CMV infection. Thus, both sites are reliable for diagnosis [1]. In addition, as saliva specimens are readily obtained, saliva CMV PCR may be the preferred diagnostic test for newborn screening. However, notably, CMV is present in the breast milk. It could lead to false-positive results. However, a large-scale study revealed an acceptably low false-positive rate [1]. If the testing was performed over 3 weeks of life, it is challenging to differentiate intrauterine from perinatal acquisition of CMV infection. When infants leave the maternity hospital or clinic, a sample is more difficult to obtain. In addition, as PCR using neonatal urine samples is widely used in Japan, neonatal universal screening should be performed using neonatal urine within 5 days of life.

The frequency of disease, the existence of an established definitive diagnostic method, the existence of neonatal therapies, and the prevention of the development of disability meet the criteria for screening as indicated by the Wilson and Junger criteria [22]. Therefore, universal neonatal screening for congenital CMV infection should be introduced in healthcare practice.

In conclusion, cases of congenital infection may be missed with the current neonatal screening method. Thus, universal neonatal screening should be implemented to ensure appropriate treatment for all infants with CMV infection.

Funding

This work was supported by JSPS KAKENHI (grant number: JP21K09452).

References

1) Rawlinson WD, Boppana SB, Fowler KB, Kimberlin DW, Lazzarotto T, Alain S, Daly K, Doutré S, Gibson L, Giles ML, Greenlee J, Hamilton ST, Harrison GJ, Hui L, Jones CA, Palasanthiran P, Schleiss MR, Shand AW, van Zuylen WJ. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis 2017; 17: e177-88. https://doi.org/10.1016/S1473-3099(17)30143-3.

2) Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev 2013; 26: 86-102. https://doi.org/10.1128/CMR.00062-12.

3) Koyano S, Inoue N, Oka A, Moriuchi H, Asano K, Ito Y, Yamada H, Yoshikawa T, Suzutani T, Japanese Congenital Cytomegalovirus Study Group. Screening for congenital cytomegalovirus infection using newborn urine

samples collected on filter paper: feasibility and outcomes from a multicentre study. BMJ Open 2011; 1: e000118. https://doi.org/10.1136/bmjopen-2011-000118.

4) Itakura A, Satoh S, Aoki S, Fukushima K, Hasagawa J, Hyodo H, et al. Guidelines for obstetrical practice in Japan: Japan society of obstetrics and gynecology and Japan association of obstetricians and gynecologists 2020 edition. J Obstet Gynaecol Res 2023; 49: 5-53. https://doi.org/10.1111/jog.15438.

5) Kaneko M, Sameshima H, Ikenoue T, Minematsu T. A two-step strategy for detecting intrauterine cytomegalovirus infection with clinical manifestations in the mother, fetus, and newborn. Jpn J Infect Dis 2006; 59: 363-6. https://doi.org/10.7883/yoken.JJID.2006.363.

6) Ronner EA, Glovsky CK, Herrmann BS, Woythaler MA, Pasternack MS, Cohen MS. Congenital cytomegalovirus targeted screening implementation and outcomes: a retrospective chart review. Otolaryngol Head Neck Surg 2022; 167: 178-82. https://doi.org/10.1177/01945998211044125.

7) Fourgeaud J, Boithias C, Walter-Nicolet E, Kermorvant E, Couderc S, Parat S, Pol C, Mousset C, Bussières L, Guilleminot T, Ville Y, Nkam L, Grimaldi L, Parodi M, Leruez-Ville M. Performance of targeted congenital cytomegalovirus screening in newborns failing universal hearing screening: a multicenter study. Pediatr Infect Dis J 2022; 41: 478-81. https://doi.org/10.1097/INF.0000000000003474.

8) Letamendia-Richard E, Périllaud-Dubois C, de La Guillonnière LD, Thouard I, Cordier AG, Roque-Afonso AM, de Luca D, Benachi A, Vauloup-Fellous C. Universal newborn screening for congenital cytomegalovirus infection: feasibility and relevance in a French type-III maternity cohort. BJOG 2022; 129: 291-9. https://doi.org/10.1111/1471-0528.16992.

9) Cannon MJ, Griffiths PD, Aston V, Rawlinson WD. Universal newborn screening for congenital CMV infection: what is the evidence of potential benefit? Rev Med Virol 2014; 24: 291-307. https://doi.org/10.1002/rmv.1790.

10) Laifer SA, Ehrlich GD, Huff DS, Balsan MJ, Scantlebury VP. Congenital cytomegalovirus infection in offspring of liver transplant recipients. Clin Infect Dis 1995; 20: 52-5. https://doi.org/10.1093/clinids/20.1.52.

11) Doyle M, Atkins JT, Rivera-Matos IR. Congenital cytomegalovirus infection in infants infected with human immunodeficiency virus type 1. Pediatr Infect Dis J 1996; 15: 1102-6. https://doi.org/10.1097/00006454-199612000-00010.

12) Jones MM, Lidsky MD, Brewer EJ, Yow MD, Williamson WD. Congenital cytomegalovirus infection and maternal systemic lupus erythematosus: a case report. Arthritis Rheum 1986; 29: 1402-4. https://doi.org/10.1002/art.1780291114.

13) Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol 2007; 17: 253-76. https://doi.org/10.1002/rmv.535.

14) Morioka I, Kakei Y, Omori T, Nozu K, Fujioka K, Yoshikawa T, Moriuchi H, Ito Y, Oka A. Efficacy and safety of valganciclovir in patients with symptomatic congenital cytomegalovirus disease: study protocol clinical trial (SPIRIT compliant). Medicine 2020; 99: e19765. https://doi.org/10.1097/MD.0000000000019765.

15) Morioka I, Kakei Y, Omori T, Nozu K, Fujioka K, Takahashi N, Yoshikawa T, Moriuchi H, Ito Y, Oka A, Japanese Congenital Cytomegalovirus Study Group. Oral valganciclovir therapy in infants aged ≤2 months with congenital cytomegalovirus disease: a multicenter, single-arm, open-label clinical trial in Japan. J Clin

Med 2022; 11: 3582. https://doi.org/10.3390/jcm11133582.
16) Kimberlin DW, Jester PM, Sánchez PJ, Ahmed A, Arav-Boger R, Michaels MG, et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. N Engl J Med 2015; 372: 933–43. https://doi.org/10.1056/NEJMoa1404599.
17) Nagano N, Imaizumi T, Akimoto T, Hijikata M, Aoki R, Seimiya A, Okahashi A, Kawakami K, Komatsu A, Kawana K, Morioka I. Clinical evaluation of a novel urine collection kit using filter paper in neonates: an observational study. Children (Basel) 2021; 8: 561. https://doi.org/10.3390/children8070561.
18) Barbi M, Binda S, Primache V, Caroppo S, Didò P, Guidotti P, et al. Cytomegalovirus DNA detection in Guthrie cards: a powerful tool for diagnosing congenital infection. J Clin Virol 2000; 17: 159-65. https://doi.org/10.1016/s1386-6532(00)00089-5.
19) de Vries JJ, Claas EC, Kroes AC, Vossen AC. Evaluation of DNA extraction methods for dried blood spots in the diagnosis of congenital cytomegalovirus infection. J Clin Virol 2009; 46 Supplement 4: S37-42. https://doi.org/10.1016/j.jcv.2009.09.001.
20) Leruez-Ville M, Vauloup-Fellous C, Couderc S, Parat S, Castel C, Avettand-Fenoel V, et al. Prospective identification of congenital cytomegalovirus infection in newborns using real-time polymerase chain reaction assays in dried blood spots. Clin Infect Dis 2011; 52: 575-81. https://doi.org/10.1093/cid/ciq241.
21) Boppana SB, Ross SA, Novak Z, Shimamura M, Tolan RW, Palmer AL, et al. Dried blood spot real-time polymerase chain reaction assays to screen newborns for congenital cytomegalovirus infection. JAMA 2010; 303: 1375-82. https://doi.org/10.1001/jama.2010.423.
22) Wilson JM, Jungner G. Principles and practice of screening for disease; Public Health Paper No. 34; World Health Organization: Geneva, Switzerland, 1968.