Clinical Clues / *Klinik İpuçları*

DOI: 10.5578/ced.20229910 • *J Pediatr Inf 2022;16(1):e55-e58*

Asymptomatic Congenital CMV Newborn Who Failed Unilateral Hearing Screening; Shall We Give Treatment?

Tek Taraflı İşitme Taramasında Başarısız Olan Asemptomatik Konjenital CMV'li Yenidoğan; Tedavi Etmeli mi?

Beyhan Bülbül(İD), Mustafa Hacımustafaoğlu(İD)

Division of Pediatric Infectious Diseases, Department of Pediatrics, Uludag University School of Medicine, Bursa, Turkey

Question: *It was learned that the mother had CMV-IgM positivity during pregnancy. Her five-day-old baby who was hospitalized due to neonatal jaundice (total bilirubin 17.28 mg/dl, indirect bilirubin 16.8 mg/dl). The baby, whose percentiles were normal, fed normally and had no other problems, did not pass the screening test in the right ear in the hearing test performed on the second day in the hospital. The baby was positive for CMV IgM and CMV IgG. Should this patient be treated for CMV (ganciclovir)?* **Md. Kaan Salgır**

Cite this article as: Bülbül B, Hacımustafaoğlu M. Asymptomatic congenital CMV newborn who failed unilateral hearing screening; shall we give treatment? J Pediatr Inf 2022;16(1):e55-e58.

Answer (Beyhan Bülbül, MD; Mustafa Hacımustafaoğlu, MD)

Introduction and general information: In order to answer this question, the nature of the maternal infection in the pregnant such as primary or reinfection, and the maternal infection in which trimester of pregnancy will be important. The information whether a congenital infection has developed in the baby and whether this congenital infection is symptomatic or not, will also be important. Therefore, it would be appropriate to review some information on the diagnosis of maternal cytomegalovirus (CMV) infection in pregnant women and the diagnosis and clinical findings of CMV infection/disease in the baby.

CMV infection is the entry of the virus into the body. This is confirmed by virus isolation or in practice, viral molecular test positivity (PCR), and in some cases, newly developed serologic positivity/seroconversion (CMV-IgM positivity or increased CMV-IgG titer in a double serum sample).

CMV disease is defined as symptoms and physical examination findings attributed to CMV infection. Practically; it is diagnosed with PCR positivity (in some cases with positivite serology) together with clinical and laboratory findings compatible with CMV.

Risk of developing fetal/congenital CMV infection after maternal infection during pregnancy: Maternal CMV infection during pregnancy can be transmitted to the fetus, and may lead to congenital infection and sometimes to congenital CMV disease (with clinical and laboratory findings in the fetus and newborn baby). Risk of vertical transmission to fetus after maternal CMV infection, is higher in maternal primary infection (32%) compared to maternal re-infection or maternal recurrent infection (1.4%). In a meta-analysis of 10 studies in which 2942 fetuses related to maternal-fetal CMV transmission were evaluated. In women, who newly seroconverted (primary CMV infection) just before or during pregnancy; the probability of developing congenital CMV infection in primary maternal infection was 21% in the ma-

Correspondence Address / Yazışma Adresi

Mustafa Hacımustafaoğlu

Uludağ Üniversitesi Tıp Fakültesi,
Çocuk Sağlığı ve Hastalıkları Anabilim Dalı,
Çocuk Enfeksiyon Hastalıkları Bilim Dalı,
Bursa-Türkiye

E-mail: mkemal@uludag.edu.tr

Received: 20.01.2022 **Accepted:** 25.02.2022 **Available Online Date:** 09.06.2022

ternal primary infection during the periconceptional period, 36% in the first trimester of pregnancy, 40% in the second trimester of pregnancy, and 66% in the infection in the third trimester. The risk of maternal-fetal viral transmission; is lower maternal infection in early pregnancy (compared to late pregnancy), although, the risk of symptomatic disease at birth and long-term sequelae is higher when infection occurs in early pregnancy. Therefore, it is useful to know the characteristics of maternal infection in the initial evaluation of CMV infection in the newborn baby.

Diagnosis of CMV infection: CMV infections are usually asymptomatic or minimally symptomatic in immunocompetent patients. In normal children and adults (including pregnant women), the diagnosis of primary CMV infection is usually made serologically. Serologically, newly developed anti-CMV-IgM positivity or a four-fold increase in CMV-IgG titers (acute and convalescent serums at 3-4 weeks intervals) suggests a possible diagnosis, in an immunologically normal person with a clinical picture compatible with CMV infection/disease. CMV IgG seroconversion is more valuable in this respect and makes the diagnosis of a new acute infection in this population.

In primary CMV infection, CMV-IgM antibodies can typically be detected within the first two weeks after the development of symptoms and may persist for months. However, CMV-IgM has some limitations in the diagnosis of acute infection: 1) Only 75 to 90% of women with acute infection have CMV IgM positivity. 2) CMV-IgM may remain positive for a period of four to six months after the onset of symptoms and sometimes it can remain positive for more than a year after an acute infection. 3) CMV IgM can change from negative to positive in women with CMV reactivation or re-infection. 4) CMV IgM may become positive in response to other viral infections such as Epstein-Barr virus. Therefore, the presence of a positive (or negative) CMV-IgM antibody alone can provide misleading information. CMV-specific IgG antibodies are usually undetectable until 2-3 weeks after the onset of symptoms and continue throughout life. In pregnancy, in the absence of documented recent seroconversion, it can sometimes be difficult to distinguish between primary infection, reactivation, and reinfection. Determination of IgG avidity helps to evaluate in this respect. High CMV-IgG avidity suggests that primary infection occurred more than six months ago. Low avidity CMV-IgG suggests a new primary infection usually within 2-4 months.

Although serology is occasionally used in the diagnosis of congenital CMV infection, it is not recommended for the routine diagnosis of congenital CMV. If the newborn is positive for CMV-IgM and CMV IgG, and if there is an increasing (four times) titer in CMV-IgG in paired sera four weeks apart, and if the avidity of CMV-IgG is low, congenital infection is strongly suspected. However, the diagnosis of congenital CMV infection is not based on serology. CMV-IgM antibody in the newborn is insensitive and may be false-negative in more than half of infected newborns. The presence of CMV-IgG antibody in the neonate may mainly reflect passive transplacental transfer of maternal antibody. However, if the newborn baby is CMV IgG negative, congenital CMV infection is unlikely. In practice, the diagnosis of congenital CMV infection is made on the basis of positive CMV PCR positivity in the urine of the newborn baby.

Prevalence of congenital CMV infection: In developed countries, congenital CMV infection, is the most common congenital viral infection with prevalence of 0.48-1.30% in all newborns. CMV seroprevalence in Turkey has been investigated in different studies. In adults, especially in pregnant women, and CMV seropositivity has been reported as of 85-100%. The prevalence of congenital CMV infections has been reported to be between 0.2-1.19% in newborns.

Clinical aspecs of congenital CMV infection: Most infants with congenital CMV infection are asymptomatic. However, 15-25% of these initially asymptomatic newborns may continue to develop neurodevelopmental abnormalities (most commonly sensorineural hearing loss) later in life. Some of the babies who appear asymptomatic at birth, may have sensorineural hearing loss in the neonatal period when tested, and these babies may not pass the newborn hearing screening tests on one or both sides. Therefore, some authors classify this group of infants as asymptomatic infections with isolated hearing loss. In addition, even if the baby is asymptomatic at birth, hearing loss may develop over the years, or the existing hearing loss may progress.

Approximately 10-15% of all infants with congenital CMV infection present as symptomatic infection at birth. In newborns with symptomatic congenital CMV infection, clinical findings (such as septic appearance, petechiae, jaundice at birth, hepatosplenomegaly, SGA, hearing loss, lethargy, hypotonia, decreased suction, convulsion, hemolytic anemia, pneumonia) and laboratory abnormalities (such as increased liver transaminases, increased direct and indirect bilirubin, thrombocytopenia), and nervous system imaging abnormalities (such as periventricular calcifications, cerebral ventriculomegaly, polymicrogyria, pachygriy, lissencephaly) may be seen. In approximately 80% of babies with symptomatic infection, complications (such as hearing loss, low IQ, microcephaly, strabismus, convulsions, dental disorders, chorioretinitis, blindness, cerebral palsy) may develop in the future.

Treatment indications in congenital CMV infection: Antiviral treatment is recommended in moderate and severe symptomatic congenital CMV infection with virological evidence. In severe cases, the treatment is started with ganciclo-

vir intravenously (2x6 mg/kg/dose, iv, for 2-3 weeks) and the treatment is completed for an average of 6 months with oral valganciclovir (2x16 mg/kg/dose, po). Oral valganciclovir is given at the same dose for an average of six months in patients without symptomatic and life-threatening infections, who can take it orally.

Treatment is not routinely recommended for mildly symptomatic congenital CMV infection, or for asymptomatic infants with isolated hearing loss, but individual evaluation according to the patient's condition is appropriate. There are not enough evidence-based studies on this subject yet. There is no consensus among experts on the treatment approach to these infants on the benefit/risks of treatment. Because of the toxicities of antiviral therapy, their use in congenital CMV infection should be evaluated for potential benefit, with known risks (such as neutropenia) and possible risks (gonadal dysgenesis, carcinogenicity). Therefore, it is suggested that in these cases it would be appropriate to act individually according to the patient.

Treatment is not recommended for newborns who are asymptomatic and have normal hearing.

Within the framework of these general approaches, the answer to the question is;

1) In our country, the seroprevalence of CMV infection in pregnant women and the prevalence of congenital CMV infection in newborn babies seem to be higher than in developed western countries. In this context, the awareness of Pediatrics and Pediatric Infectious Diseases specialists should be high in terms of congenital CMV infection.

2) In the case in question, maternal CMV-IgM positivity during pregnancy supports maternal CMV primary infection. However, the presence of increased CMV-IgG titer in the paired sera samples during pregnancy is more valuable in this respect. In addition, maternal IgG avidity can give an idea about when the maternal primary infection was experienced. In avidity tests, although it may vary according to the nature of the test being studied; high avidity; indicates infection before 3-6 months on average, low avidity; supports newer infection, i.e. infection before 3-6 months. In this respect, estimating the time of maternal primary infection can provide a general knowledge about the possibility of infection in the baby.

3) There are some the key points here;

3a) whether the newborn has a congenital CMV infection, and

3b) whether the congenital CMV infection is asymptomatic (totally asymptomatic, or asymptomatic with isolated hearing loss) or symptomatic (mild, moderate, severe).

In this context, clinical and laboratory evaluation in the baby; should be done as soon as possible (<3 weeks). And the relationship of current clinical findings with congenital CMV infection should be questioned. In the evaluations made after three weeks, it is not possible to distinguish between congenital CMV infection and perinatal/postneonatal CMV infection.

4a) **Does the baby have a congenital CMV infection?** Presence of CMV-IgG in newborn baby; It can mainly reflect the transplacental maternal level and is not useful in clinical evaluation. Since CMV-IgM is not transmitted transplacentally, it indicates that the fetus/infant is affected, but it is not reliable enough. Congenital CMV infection is diagnosed virologically. In practice, urine CMV PCR positivity is considered the gold standard of congenital CMV infection. Therefore, in our case, CMV PCR should be evaluated in the urine to diagnose congenital CMV infection. If the urine is positive for CMV PCR, there is congenital CMV infection, if it is negative, the diagnosis of congenital CMV infection is excluded.

4b) **Is the baby with congenital CMV infection asymptomatic/symptomatic?** If there is congenital CMV infection (positive CMV PCR); it is checked whether the baby is symptomatic (CMV disease). However, in many other diseases of the newborn (neonatal jaundice, sepsis, feeding problems, etc.), symptoms may be confused with symptomatic congenital CMV infection. Therefore, it is important whether the symptoms in the infant are related with CMV disease. In addition, CMV related laboratory and imaging (such as periventricular hyperechogenicities-calcifications on cranial US, ventriculomegaly, microcephaly) is important as a whole evaluation of the patient. These assessments should be made without delay. In symptomatic CMV infection, if a treatment decision is to be made, treatment should be initiated as soon as possible, within one month at the latest.

In this case, jaundice (indirect hyperbilirubinemia) does not seem to be related to CMV. However, unilateral failure of the hearing test may be associated with CMV (asymptomatic congenital CMV infection with isolated hearing loss). Therefore, it is appropriate to repeat the hearing test a few days later (<1 week). If he still does not pass the screening test, it would be appropriate to request an ENT consultation from the baby and perform a hearing evaluation (BERA; brainstem evoked response audiometry, ABR; Auditory Brain Response).

4b.1) **If the test passes on re-evaluation (no hearing loss);** congenital asymptomatic CMV infection is diagnosed. Then, the family is informed and treatment is not recommended. The baby is followed up in routine outpatient follow-up.

4b.2) **If the hearing test is still not passed in the re-evaluation;** ENT consultation and if possible, BERA are done. If there is loss of hearing assessment (BERA) and there is no other explainable cause, the infant is accepted as asymptomatic congenital CMV infection with isolated hearing loss. Routine antiviral treatment is not recommended in these cases,

or it can be decided individually by discussing the treatment related side effects/possible benefit balance. In such a case, our recommendation is; it would be appropriate to inform the family, take a decision together with the family, considering the balance between the short and possible long-term side effects of the antiviral drug and the possible benefit from the treatment (progression of hearing loss, the possibility of improvement). We also recommend to asses this consideration in writing. In both situation, it would be appropriate to regularly follow up the patient as outpatient visits (including ENT consultation and hearing tests).

References

1. *Demmler-Harrison GJ. Congenital cytomegalovirus infection: Clinical features and diagnosis. Edwards MS, Weisman LE (eds). Available from: www-uptodate-com (Accessed date: 12 December 2021).*
2. *Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol 2007;17(4):253. [CrossRef]*
3. *Chatzakis C, Ville Y, Makrydimas G, Dinas K, Zavlanos A, Sotiriadis A. Timing of primary maternal cytomegalovirus infection and rates of vertical transmission and fetal consequences. Am J Obstet Gynecol 2020;223(6):870. [CrossRef]*
4. *Sheffield JS, Boppana SB. Cytomegalovirus infection in pregnancy. Wilkins-Haug L, Hirsch MS (eds). Available from: www-uptodate-com (Accessed date: 12 December 2021). [CrossRef]*
5. *Demmler-Harrison GJ. Overview of cytomegalovirus infections in children. Edwards MS, Weisman LE (eds). Available from: www-uptodate-com (Accessed date: 12 December 2021).[CrossRef]*
6. *Caliendo AM. Overview of diagnostic tests for cytomegalovirus infection. Hirsch MS (eds). Available from: www-uptodate-com (Accessed date: 12 December 2021). [CrossRef]*
7. *Chou S. Newer methods for diagnosis of cytomegalovirus infection. Rev Infect Dis 1990;12(Suppl 7):S727. [CrossRef]*
8. *Eggers M, Bäder U, Enders G. Combination of microneutralization and avidity assays: improved diagnosis of recent primary human cytomegalovirus infection in single serum sample of second trimester pregnancy. J Med Virol 2000;60(3):324. [CrossRef]*
9. *Lazzarotto T, Ripalti A, Bergamini G, Battista MC, Spezzacatena P, Campanini F, et al. Development of a new cytomegalovirus (CMV) immunoglobulin M (IgM) immunoblot for detection of CMV-specific IgM. J Clin Microbiol 1998;36(11):3337. [CrossRef]*
10. *Grangeot-Keros L, Mayaux MJ, Lebon P, Freymuth F, Eugene G, Stricker R, et al. Value of cytomegalovirus (CMV) IgG avidity index for the diagnosis of primary CMV infection in pregnant women. J Infect Dis 1997;175(4):944. [CrossRef]*
11. *Leruez-Ville M, Sellier Y, Salomon LJ, Stirnemann JJ, Jacquemard F, Ville Y. Prediction of fetal infection in cases with cytomegalovirus immunoglobulin M in the first trimester of pregnancy: a retrospective cohort. Clin Infect Dis 2013;56(10):1428. [CrossRef]*
12. *Kanengisser-Pines B, Hazan Y, Pines G, Appelman Z. High cytomegalovirus IgG avidity is a reliable indicator of past infection in patients with positive IgM detected during the first trimester of pregnancy. J Perinat Med 2009;37(1):15. [CrossRef]*
13. *Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol 2007;17(4):253. [CrossRef]*
14. *Ornoy A, Diav-Citrin O. Fetal effects of primary and secondary cytomegalovirus infection in pregnancy. Reprod Toxicol 2006;21(4):399. [CrossRef]*
15. *Staras SA, Dollard SC, Radford KW, et al. Seroprevalence of cytomegalovirus infection in the United States, 1988-1994. Clin Infect Dis 2006;43(9):1143. [CrossRef]*
16. *Mussi-Pinhata MM, Yamamoto AY, Moura Brito RM, de Lima Isaac M, de Carvalho Oliveira PF, Boppana S, et al. Birth prevalence and natural history of congenital cytomegalovirus infection in a highly seroimmune population. Clin Infect Dis 2009;49(4):522. [CrossRef]*
17. *Fowler KB, Ross SA, Shimamura M, Ahmed A, Palmer AL, Michaels MG, et al. Racial and ethnic differences in the prevalence of congenital cytomegalovirus ınfection. J Pediatr 2018;200:196. [CrossRef]*
18. *Türkiye Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Uzmanlık Derneği (EKMUD). Sitomegalovirüs Tanı, Tedavi Uzlaşı Raporu, Nisan 2020. Şencan İ, Taşbakan MI, Çağ Y (eds). Available from: https://www.ekmud.org.tr (Accessed date: 12 December 2021).*
19. *Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med 1992;326(10):663. [CrossRef]*
20. *Fowler KB, McCollister FP, Dahle AJ, Boppana S, Britt WJ, Pass RF. Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. J Pediatr 1997;130(4):624. [CrossRef]*
21. *Demmler-Harrison GJ. Congenital cytomegalovirus infection: Management and outcome. Edwards MS, Weisman LE (eds). Available from: www-uptodate-com (Accessed date: 12 December 2021). [CrossRef]*
22. *Dreher AM, Arora N, Fowler KB, et al. Spectrum of disease and outcome in children with symptomatic congenital cytomegalovirus infection. J Pediatr 2014;164(4):855. [CrossRef]*
23. *Jin HD, Demmler-Harrison GJ, Coats DK, Paysse EA, Bhatt A, Edmond JC, et al. Long-term Visual and Ocular Sequelae in Patients With Congenital Cytomegalovirus Infection. Pediatr Infect Dis J 2017;36(9):877. [CrossRef]*
24. *American Academy of Pediatrics. Cytomegalovirus Infection. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH (eds). Red Book: 2021 Report of the Committee on Infectious Diseases. 32nd ed. Itasca, IL: American Academy of Pediatrics: 2021; 94-300.*
25. *Rawlinson WD, Boppana SB, Fowler KB, Kimberlin DW, Lazzarotto T, Alain S, et al. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. Lancet Infect Dis 2017;17:e177-e188. [CrossRef]*