DOI: 10.4149/BLL_2023_057

Bratisl Med J 2023; 124 (5)
373 – 379

CLINICAL STUDY

Congenital cytomegalovirus infection – a problem of past, present and future

Ingrid BRUCKNEROVA[1], Dusan DOBOS[1], Michal DUBOVICKY[2], Mojmir MACH[2], Eduard UJHAZY[2], Jana BRUCKNEROVA[3]

Neonatal Department of Intensive Medicine, Faculty of Medicine, Comenius University in Bratislava and National Institute of Children's Diseases, Bratislava, Slovakia. **ingrid.brucknerova@fmed.uniba.sk**

ABSTRACT

AIM: To analyse prenatal and postnatal characteristics, clinical and laboratory findings, results of investigations in the group of 11 newborns with congenital CMV infection, who were hospitalized at Neonatal Department of Intensive Medicine between January 1st 2012 and March 31st, 2022 were included.

RESULTS: Prenatal foetal sonography revealed in patients 5 and 8, positive calcifications in the brain; in patients 6, 9 and 11, isolated ventriculomegaly was found. Neurological examination was clinically negative in patients 1 and 10, changes of muscular tonicity and spontaneous activity were confirmed in the rest of the group. In patients 5 and 10, one-sided positivity of otoacoustic emissions was confirmed. Chorioretinitis with bilateral negative otoacoustic emissions was confirmed in patient 5. Clinical status of patient 11 was complicated by pneumonitis. Three patients were treated with antiviral drugs orally, and 11 newborns had a combination of intravenous and oral form of treatment.

CONCLUSION: The results of analysis will contribute to a society-wide solution of prevention. Monitoring of the frequency of CMV infection in the population with education of the population can decrease the number of affected newborns *(Tab. 4, Ref. 29)*. Text in PDF *www.elis.sk*

KEY WORDS: cytomegalovirus, newborn, therapy, complications.

Abbreviations: CMV – cytomegalovirus, IgM – immunoglobulin M

Introduction

Cytomegalovirus (CMV) is the 5th human herpes virus. The infected person is a source of the infection (1). The virus can be detected in saliva, urine, blood, cervical and vaginal mucus as well as breast milk. Transmission is through transfusion, transplacental, through breast milk or close contact. The special condition is in transplant recipients (2). It multiplies most easily in the epithelial cells of the salivary glands and renal tubules. The lifelong persistence of the virus after overcoming the primary infection in the body is responsible for increased possibility of reactivation under specific conditions.

[1]Neonatal Department of Intensive Medicine, Faculty of Medicine, Comenius University in Bratislava and National Institute of Children's Diseases, Bratislava, Slovakia, [2]Centre of Experimental Medicine SAS, Institute of Experimental Pharmacology and Toxicology, Bratislava, Slovakia, and [3]National Institute for Cardiovascular Diseases, Bratislava, Slovakia

Address for correspondence: Ingrid BRUCKNEROVA, MD, PhD, Prof, Faculty of Medicine, Comenius University in Bratislava, NUDCH, Limbova 1, SK-833 40 Bratislava, Slovakia.
Phone: +421.2.59371232

Acknowledgements: The study was supported by the Ministry of Education, VEGA No. 2/0124/19 and APVV-19-0435.

Congenital form of CMV infection occurs when the pregnant mother is infected mainly during the first trimester (primary infection) (3). Cytomegalovirus passes through placenta and is connected with serious consequences in the foetus. The most severe complication is death of the foetus. The complex investigation of the newborn after delivery in typical case confirms presence of following complications: microcrania, jaundice, petechial haemorrhage due to thrombocytopaenia, enlargement of liver and spleen, calcifications in the brain parenchyma, and investigation of retina confirms presence of chorioretinitis (4). All these findings are typical for a symptomatic form of CMV infection. The danger of an asymptomatic form is that it can manifest later. The child lags behind in psychomotor development and has a hearing impairment.

According to Demmler-Harrison et al (2021), the term asymptomatic expresses no apparent symptoms at birth (5). Some of these patients may have hearing loss later in life. If the newborn is asymptomatic, but has isolated confirmed hearing loss, they propose to use the term asymptomatic with isolated hearing loss.

Symptomatic describes a newborn with one or more symptoms at birth (6). Demmler-Harrison et al (2021), emphasize the category of newborn with primary neurophenotype that involves symptomatic patients with microcephaly (polymicrogyria; cortical dysplasia) and neurologic manifestations at birth. Special category of newborns with CMV infection are not only symptomatic, but they have severe complications or are in life-threatening condition: haemophagocytic lymphohistiocytosis, myocarditis, sepsis-

like disease, needing supportive fluid, electrolyte, nutritional and respiratory therapy and haematological interventions (5).

Newborns who are symptomatic as well as asymptomatic are also at risk of long-term neurodevelopmental problems, mainly sensorineural hearing problems. CMV infection is the leading cause of nonhereditary sensorineural hearing loss (7, 8, 9, 10, 11).

In neonates with severe combined immunodeficiency, the virus disseminates. The most serious complications include interstitial cytomegalovirus pneumonia, cytomegalovirus colitis (in transplant patients), progressive retinitis, encephalitis and oesophagitis, gastrointestinal tract ulcerations (12, 13).

Confirmation of the CMV infection in newborn

When evaluating laboratory findings in a patient with a suspected CMV infection, it should be borne in mind that the production of IgG class antibodies usually begins 1 week later than IgM. If they are positive, it means that the person has been infected. Negativity precludes overcoming the infection. CMV specific IgM antibodies are present within the first two weeks after the development of symptoms and may persist for several months (14). Also, identification of immunoglobulin M (IgM) antibodies in the newborn is suggestive of congenital infection, because IgM antibodies do not cross the placenta (10).

Examination of CMV-IgM detects their negativity or increase. If the concentrations are positive, we still cannot distinguish whether it is a primary infection or a recurrence of the disease.

Increases of the IgG-CMV and IgM-CMV antibodies are typical for primary infection.

Increased IgG-CMV with negative IgM-CMV confirms the presence of disease in the past.

The persistence of high IgG-CMV antibody titres and IgM-CMV positivity is generally a characteristic of reactivation of the infection.

Anti CMV IgG avidity informs the physician about the strength of the binding between antigen and IgG antibodies. The strength of the bond increases as the immune reaction matures. It means the low avidity IgG antibodies point on presence of acute primary infection (15).

If IgG-CMV antibody titres are still high and IgM-CMV are positive it signals reactivation of the infection.

Newborn

CMV virus can be isolated from urine or saliva (PCR; cultivation); and with the DNA PCR test within the first 3 weeks of life. Determination of the number of copies of the viral genome (DNA CMV quantitative) per ml of saliva, blood, bronchoalveolar lavage, urine, or cerebrospinal fluid, informs the neonatologist about the severity of disease in the newborn. The result correlates with the reactivation of infection. After 3 weeks, it is not possible to specify the timing of infection and to confirm whether it is congenital or during delivery or postnatal form (blood transfusion; mother milk) (Tab. 1) (11, 16).

Tab. 1. Diagnostics of congenital ccytomegalovirus infection (11).

CMV infection	Evaluation of investigations	Other
congenital	• detection of CMV via viral culture or PCR in urine, saliva or blood samples obtained within the first three weeks of life, confirmed on repeat testing	• detection of CMV via PCR in the newborn screening dried blood spot: – positive result proves congenital infection – negative result does not exclude congenital infection
possible (testing after 3 weeks of life)	• CMV is detected in urine or saliva samples (via viral culture, or PCR) or CMV IgG antibody is detected in the blood after the first three weeks of life, up to one year of age • one or more signs or symptoms of congenital CMV • other conditions that cause these abnormalities have been ruled out	
negative (not infected)	• negative detection of CMV via viral culture or PCR in urine, saliva or blood samples obtained within the first three weeks of life	

CMV – cytomegalovirus, PCR – polymerase chain reaction

Therapy

It was thought that the use of antiviral agents for a total of six weeks was sufficient for each symptomatic patient with congenital infection 10 years ago. It is recommended to indicate total antiviral therapy at least for 6 months nowadays (17, 18). In a case of serious consequences (retinitis, liver disease) and/or persistent viremia after ruling out the resistance to antiviral therapy, prolongation of antiviral therapy up to 12 months is safe and possible (11, 19). Timely initiation of the antiviral medication is very important. Special attention must be given to patients with primary immunodeficiency.

The antiviral treatment in newborns who are clinically asymptomatic without hearing problems is under evaluation nowadays (20).

CMV pregnancy and breast milk

Prenatal diagnostic is possible from the amniotic fluid, because CMV is able to replicate in the foetal kidneys. This is followed by its urinary excretion into amniotic fluid. Revello and Gerna (2002) emphasize the optimal time for performing this investigation is after 21 weeks of gestation and 7 weeks after maternal infection (21). Amniocentesis has prognostic value. If the pregnant mother

Tab. 2. Prenatal and postnatal characteristics.

	Prenatal characteristics	delivery (g. w.)	Postnatal characteristics				
			amniotic fluid	birth weight (g)	birth length (cm)	HC (cm) (‰)	AS
1	**mother** – 1st pregnancy – premature leakage of amniotic fluid	33/s. c.	clear	1850	43	–	7/10
2	**mother** – 2nd pregnancy (1 healthy sibling) – aphasia and visus problems one week before delivery	40 spont.	green	3150	48	33.5	10/10
3	**mother:** – 1st pregnancy (in vitro fertilisation) – CMV infection in pregnancy **foetus:** – IUGR, oligohydramnios – ↓ of placental perfusion	37/s. c.	clear	1850 <3rd	43 <3rd	35.5 >97th	10/10
4	**mother** – 1st pregnancy – respiratory infection	40/s. c.	green	2820 <10rd	48	31.5 <3rd	9/10
5	**mother** – 1st pregnancy – ↑ avidity IgG (80 %) **foetus:** – IUGR – calcifications in brain parenchyma	38+2/ s. c.	clear	1530 <3rd	42 <3rd	30.0 <3rd	9/9
6	**mother** – 1st pregnancy – CMV – IgM, IgG positive **foetus:** 34th g. w. – brain MRI (ventriculomegaly, megacisterna magna)	39 spont.	clear	2490 < 10th	46 <10th	33.0	10/10
7	**mother** – 2nd pregnancy (1 x abortus) – 11th–28th g. w. thrombosis of left lower extremity **foetus:** – 22. g. w. – cheilognathopalatoschisis	37/s. c. (PP)	clear	2600	47	33.5	9/10
8	mother – 2nd pregnancy (in 1st child – CMV) – CMV positivity foetus: – 37+4 g. w. ventriculomegaly periventricular calcifications	38/ spont.	clear	2900 <10th	46	31.5 <10th	10/10
9	**mother** – 2nd pregnancy **foetus:** 2–ventriculomegaly	40+2 spont.	clear	2870 <10th	49	34.0	10/10
10	**mother** – 1st pregnancy **foetus:** – since 20th g. wt. IUGR	37 spont.	clear	2300 <10th	47	30.5 <3rd	9/9
11	**mother** – 2nd pregnancy **foetus:** – 36+2 g. w. – brain MRI: hydrocephalus with hypoplasia of cerebellum	38 spont.	milky	2420 <10th	45 <3rd	31.5 <10th	9/10

AS – Apgar score, PP – pelvic position, spont. – spontaneous, IUGR – intrauterine growth retardation, s. c. – caesarean section, i. v. – intravenous, CMV – cytomegalovirus, IgG – immunoglobulin G, MRI – magnetic resonance imaging, percentile – ‰, HC – head circumference, g. w. – gestational week

had primary CMV infection, there is a greatest risk of transplacental transmission as well as the newborn being infected during delivery or through mothers milk (22). CMV is excreted into breast milk after delivery (viral shedding). Currently mothers milk contains antibodies and active immune particles (23). The knowledge of gestational age and clinical status is most important in making correct decision about breast feeding. Křivohlavová presents that in asymptomatic term newborns the investigation of antibodies or viral particles of CMV is not indicated. Breast milk donation should consider the fact that children of CMV-seronegative mothers should receive CMV-negative milk.

Aim of the work

The aim of the presented work is the analysis of a group of newborns with CMV infection with emphasis on clinical and laboratory results and imaging examinations.

Patients

All patients who are presented were hospitalized at Neonatal Department of Intensive Medicine between January 1st 2012 and March 31st, 2022 included. Prenatal and postnatal characteristics are presented in Table 2. For growth assessment, we used the Intregrowth-21 chart.

Results

Results of laboratory findings, ophthalmologic investigation of retina, sonography of brain and analysis of treatment are described in Tables 3 and 4.

CMV infection was confirmed in all patients by CMV-PCR in urine and blood. Patient 1 was admitted to our department for treatment due to a change in the brain parenchyma and positive verification of CMV infection at the age of 2 months. In patient 4, who was admitted for treatment on 23rd day of life, although congenital CMV infection with low viral load (serum CMV-PCR) was confirmed already on 4th day of life.

Discussion

Consequences of CMV infections during pregnancy are caused by the ability of CMV to pass through placenta. The earlier prenatal origin of infection is present, the worst spectrum of complications is detected either prenatally, but in the majority of cases after delivery only.

Analysis of the history of mother and current pregnancy is important. CMV infection was confirmed by serology in our group. We found positive results in 4 mothers. After seropositivity of the pregnant mother (the presence of IgM antibodies supposes primary infection; IgM antibodies can persist for several months), test of anti CMV IgG avidity is advised (1, 17). This result in pregnant women brings us information about duration of CMV infection. The higher the result of anti CMV IgG avidity, the longer duration of infection during pregnancy (more than 6 months). The low avidity anti CMV IgG pointed on primary infection, that had

Tab. 3. Appearance and results of investigations.

Age at admission		Results of investigations				
		TRO	Retina	Brain	Liver	Spleen
1	2 months	N	negative	– asymmetry of ventricles – IVH 1st–2nd grade	hepatopathy	
2	32 hours	↓	negative	– fronto–parietal hyperechogenicities l. dx. – subependymal cysts l. sin.	– CH – subcapsular haematoma	>>
3	3 days	↓	coloboma maculae luteae o. sin.	– hypoxic periventricular changes – periventricular calcifications	– CH	
4	23 days	N	negative	– periventricular cysts – IVH 1st grade	negative	
5	2 hours	↓	– chorioretinitis peracta o. u. – maculopathia o. u.	– hyperechogenicities in basal ganglia and thalami – periventricular calcifications – IVH 2nd grade	– CH – > liver	>
6	3 hours	N	negative	– lissencephaly – ventriculomegaly of lateral ventricles – MRI – cerebellar hypoplasia		
7	6 days	N	negative	– negative		
8	5 days	↓	negative	– ventriculomegaly of lateral ventricles – multiple periventricular calcifications	– CH – > liver	>>
9	5 days	N	haemorrhagiones intraretinales o. sin.	– asymmetric dilatation of lateral ventricles – IVH	– CH	
10	5 days	N	negative	– calcifications in lateral ventricles and supratentorial – ventriculomegaly of lateral ventricles		
11	3 days	N	– haemorrhagiones maculae luteae praec. o. sin. et retinae o. u.	– >> dilatation of lateral ventricles (l. dx. > l. sin.) – cystic dilatation in posterior fossa – periventricular and subependymal calcifications	– CH	

N – normal, IVH – intraventricular haemorrhage, gr. – grade, AST – aspartate aminotransferase, MRI – magnetic resonance imaging, Thrombocytes – TRO, l. sin. – on the left side, l. dx. – on the right side, CH – conjugated bilirubinaemia

Tab. 4. Characteristics of patients.

	Clinical status at admission/neurological status	Otoacoustic emission	Others	Therapy
1	– negative	Positive bilateral		– GAN (i. V.) – VAN (per os)
2	– hypertonicity – irritability	–		– GAN (i. V.) – VAN (per os)
3	– axial hypotonicity	Negative bilateral	Retinitis oculi sinistri	– GAN (i. V.) – VAN (per os)
4	– microcrania	Negative bilateral		– GAN (i. V.) – VAN (per os)
5	– microcrania – irritability	Left: positive Right: negative		– GAN (i. V.) – VAN (per os)
6	– axial hypotonicity – acral hypertonicity – hyperexcitability	Negative bilateral		– GAN (i. V.) – VAN (per os)
7	– maculopapulous exanthema – cheilognathopalatoschisis l. sin. – deformity of the nose	Negative bilateral		– GAN (i. V.) – VAN (per os)
8	– microcrania – lethargy	Negative bilateral		– VAN (per os)
9	– tremor	Positive bilateral		– VAN (per os)
10	– negative – microcrania	Left: positive Right: negative		– VAN (per os)
11	– microcrania – axial hypotonicity – acral hypertonicity – convergent strabismus – generalised convulsions	Negative bilateral	Pneumonitis (positive lavage)	– VAN (per os) – GAN (i. V.) – VAN (per os)

SD – standard deviation, GAN – ganciclovir, VAN – valganciclovir, i. v. – intravenous

begun two to four months earlier (15). In our group of patients, only in one case (patient 5) this investigation was performed. The result confirmed duration of infection of more than 6 months during pregnancy. This result is in agreement with conclusions of Sheffield et al (2021.

A detailed history of the patient can be a source of important information, including the number of siblings. In connection with CMV infection, it is useful to know whether the mother also takes care of other children of preschool age (1). We detected 4 siblings in 4 mothers in our group of patients, three of them were healthy (patient 2, patient 9, patient 11), and CMV infection was detected in one sibling (patient 8).

Prenatal foetal sonography revealed in two cases positive calcifications in brain (patient 5, patient 8) and in 3 cases isolated ventriculomegaly (patient 6, patient 9, patient 11). Different findings on postnatal brain sonography were confirmed. The presence of calcifications in the brain were confirmed in patient 3 and patient 10 postnatally.

From the total number of patients (n = 11), one was a premature newborn (patient 1) and 10 were term newborns (patients 2–10). Eight term newborns were prenatally hypotrophic comparing them with Intergrowth-21, out of these eight, two of them were under 3rd percentile and in 6 cases the birth weight was under 10th percentile. Using information about values of Apgar scoring system no patient was asphyxiated.

CMV infection was confirmed in all patients by CMV-PCR in urine and blood. In 10 patients, congenital infection was diagnosed within 3 weeks of life. Patient 1 may have a congenital or postnatally acquired CMV infection, as the diagnosis was confirmed in 2 months after routine USG brain monitoring revealed newly developed parenchymal changes typical for CMV etiology. Clinically, the patient was asymptomatic, and the first postnatal USG of the brain was negative, except for the finding of a minor grade 1 IVH, without any suspicion of CMV-specific changes. This case underlines the importance of postnatal monitoring of premature neonates. This patient also represents a group of asymptomatic neonates without a risk history (other than prematurity) in whom screening for CMV infection would allow early diagnosis and treatment.

Neurological examination was clinically negative in two newborns (patient 1, patient 10). All others had confirmed changes of muscular tonicity and spontaneous activity. The value of head circumference of each patient was evaluated using the Intergrowth-21. The value under 10th percentile was present in 2 newborns (patient 8 and 11), and in 3 patients (patient 4, 5, 10) the value was under 3rd percentile. One value was above 97 percentile, four newborns had normal values and in one case this information was not mentioned. From this group of patients only patient 4 did not have clinical signs of neurological impairment. The primary neurophenotype form of CMV infection described by Demmler-Harrison et al (2021) as combination of microcrania, and presence of neurological signs was confirmed in three term newborns (patient 5, patient 8, patient 11).

Results of otoacoustic emissions were bilaterally positive only in patients 1 and 9. One patient did not have investigation of otoacoustic emissions during his stay at department (investigation was planned in out-patient department). In patient 5 and 10 only one-sided positivity was confirmed. The rest of newborns had negative results. These results are in correlation with described typical complication, to which belongs sensorineural hearing loss (10, 11).

Chorioretinitis in CMV is a predictor of poor neurological outcome (24). Sometimes it can require additional local treatment. Ophthalmologic investigation of retina revealed retinitis together with bilateral negative otoacoustic emissions only in patient 3. According to long-term ophthalmologic follow up chorioretinitis in this patient with CMV infection responded well to systemic therapy.

Clinical status of patient 11 was complicated by pneumonitis. This newborn had negative immunological investigation.

In the treatment of our newborns we used intravenous ganciclovir and/or oral valganciclovir. The therapy was enriched with hepatoprotective drugs and vitamins. The duration of antiviral therapy has changed over the years (6, 18). Our patients with confirmed CMV infection have been treated for 6 months since 2016. We respect the conclusions of scientific evaluations and the recommendations of UpToDate 2022, nowadays (11).

Deterioration of the clinical condition may occur during oral antiviral therapy. Therefore, it is necessary to think not only about the side effects of treatment (blood count: leukopoenia, thrombocytopenia, haemolytic anaemia, hepatic enzymes, conjugated bilirubin, viral load in the blood), but also about the possible complications of CMV infection (pneumonia, myocarditis, etc.). If the viral load decreases and the clinical condition worsens, we think about the consequences of treatment. Therefore, treatment may need to be interrupted for a short time. If the degree of viral load in the blood increases, we must reconsider the form of administration of antivirals, respectively, development of resistance to treatment and consider second line agents such as foscarnet, or cidofovir (25, 26). In patient 11 the worsening of his clinical status was successfully reversed by switching the form and route of administration from oral valganciclovir to intravenous ganciclovir.

Conclusion

Every newborn's investigation must be comprehensive. It is based on the detection of deviations and anomalies from the physiological state. The complications associated with prenatally overcoming the CMV infection are diverse. The distribution of neonates with proven CMV infection is based on the range of consequences that can occur. The most serious complications occur when a pregnant woman is infected during the first trimester. Irreversible damage of brain parenchyma together with sensorineural hearing loss and vision impairment can significantly affect an individual's quality of life.

We believe that even though it is a small set of presented patients, the results will contribute to a society-wide solution of prevention. Regular monitoring of the frequency of CMV infection in the population together with education of the population (to prevent direct transmission of CMV through saliva: contact with newborn, pacifier, utensils) can decrease the number of affected newborns. An interprofessional approach to early intervention is necessary. Examination of the newborn's urine or saliva is proving to be a promising option for early detection of CMV infection. We can only assume that it will be a part of routine neonatal screening in the future (27, 28). We can also use the dry blood sample that is a part of neonatal screening in a case of uncertain results of the infection onset. The incorporation of a detailed foetal anatomy scan into first-trimester screening algorithms can be very useful also (29). CMV infection is a problem of past, present and future.

References

1. Akpan US, Pillarisetty LS. Congenital cytomegalovirus infection. Stat Pearls 2022. https://www.ncbi.nlm.nih.gov/books/NBK541003/.

2. Tasoujlu M, Khalafkhany D, Makhdoomi K, Motazakker M. Cytomegalovirus UL97 ganciclovir resistance mutations in kidney transplant recipients. Bratisl Med J 2022; 123 (7): 518–522.

3. Picone O, Vauloup-Fellous C, Cordier AG, Guitton S, Senat MV, Fuchs F, Ayoubi JM, Grangeot Keros L, Benachi A. A series of 238 cytomegalovirus primary infections during pregnancy: description and outcome. Prenat Diagn 2013; 33 (8): 751–758.

4. Tahotná A, Brucknerová J, Brucknerová I. Literary review of zika virus infection from a newborn point of view. TORCH or TORZiCH? Interdisciplinary Toxicol 2018; 11 (4): 241–246.

5. Demmler-Harrison GJ, Edwards MS, Weisman LE, Armsby C. Congenital cytomegalovirus infection: management and outcome. 2021. https://www.uptodate.com/contents/congenital-cytomegalovirus-infection-management-and-outcome

6. Lazzarotto T, Gabrielli L, Lanari M, Guerra B, Bellucci T, Sassi M et al. Congenital cytomegalovirus infection: recent advances in the diagnosis of maternal infection. Hum Immunol 2004; 65: 410–415.

7. Ahlfors K, Forsgren M, Ivarsson SA, Harris S, Svanberg L. Congenital cytomegalovirus infection: on the relation between type and time of maternal infection and infant's symptoms. Scand J Infect Dis 1983; 15: 129–138.

8. McCarthy M, Auger D, Whittemore SR. Human cytomegalovirus causes productive infection and neuronal injury in differentiating fetal human central nervous system neuroepithelial precursor cells. J Hum Virol 2000; 3: 215–228.

9. Bissinger AL, Sinzger C, Kaiserling E, Jahn G. Human cytomegalovirus as a direct pathogen: correlation of multiorgan involvement and cell distribution with clinical and pathological findings in a case of congenital inclusion disease. J Med Virol 2002; 67: 200–206.

10. Johnson KE, Weisman LE, Edwards MS, Armsby C. Overview of TORCH infections. 2021. https://www.uptodate.com/contents/overview-of-torch-infections

11. Demmler-Harrison GJ, Edwards MS, Weisman LE, Armsby C. Congenital cytomegalovirus infection: Clinical features and diagnosis. 2022. https://www.uptodate.com/contents/congenital-cytomegalovirus-infection-clinical-features-and-diagnosis

12. Miquel CPV, Mejias A, Ramilo O, Ardura MI, Sánchez PJ. Cytomegalovirus meningitis in an infant with severe combined immunodeficiency. J Pediatr 2016; 173: 235–237.

13. Caliendo AM, Hirsch MS, Bond S. Overview of diagnostic tests for cytomegalovirus infection. 2021.

14. Chou S. Newer methods for diagnosis of cytomegalovirus infection. Rev Infect Dis 1990; 12 Suppl 7: S727.

15. Sheffield JS, Boppana SB, Wilkins-Hang L, Hirsch MS, Barss VA. Cytomegalovirus infection in pregnancy2022. https://www.uptodate.com/contents/cytomegalovirus-infection-in-pregnancy

16. Pass RF. Cytomegalovirus infection. Pediatr Rev 2002; 23 (5): 163–170.

17. Lazzarotto T, Varani S, Spezzacatena P, Gabrielli L, Pradelli P, Guerra B et al. Maternal IgG avidity and IgM detected by blot as diag-

nostic tools to identify pregnant women at risk of transmitting cytomegalovirus. Viral Immunol 2000; 13: 137–141.

18. Kimberlin DW, David W, Sarah S. Long, Brady MT, Jackson MA (eds). Red book: 2015 Report of the Committee on Infectious Diseases/ Committee on Infectious Diseases, 30th ed. Elk Grove: American Academy of Pediatrics. J Pediatr 2016; 169: 316–317.

19. Amir J, Wolf DG, Levy I. Treatment of symptomatic congenital cytomegalovirus infection with intravenous ganciclovir followed by long-term oral valganciclovir. Eur J Pediatr 2010; 169 (9): 1061.

20. Asymptomatic Congenital CMV Treatment. https://clinicaltrials.gov/ct2/show/NCT03301415 (Accessed on May 20, 2022).

21. Revello MG, Gerna G. Diagnosis and management of human cytomegalovirus infection in the mother, fetus, and newborn infant. Clin Microbiol Rev 2002; 15 (4): 680–715.

22. Bhide A, Papageorghiou AT. Managing primary CMV infection in pregnancy. Br J Obstet Gynaecol 2008; 115: 805–807.

23. Křivohlavá R. Cytomegalovirus a kojení. Neonatologické listy 2018; 24 (2): 3–6.

24. Burny W, Liesnard C, Donner C, Marchant A. Epidemiology, pathogenesis and prevention of congenital cytomegalovirus infection. Expert Rev Anti Infect Ther 2004; 2: 881–894.

25. Mareri A, Lasorella S, Lapadre G, Maresca M, Tambucci R, Nigro G. Anti-viral therapy for congenital cytomegalovirus infection: pharmacokinetics, efficacy and side effects. J Matern Fetal Neonatal Med 2015; 29 (10): 1657–1664.

26. Hakki M. Moving past ganciclovir and foscarnet: advances in CMV therapy. Curr Hematol Malig Rep 2020; 15: 90–102.

27. Andrlova L, Kandar R. The dried blood spot sampling method in the laboratory medicine. Bratisl Med J 2019; 120 (3): 223–234.

28. Dollard SC, Dreon M, Hernandez-Alvarado N, Amin MM, Wong P. et al. Sensitivity of dried blood spot testing for detection of congenital cytomegalovirus infection. JAMA Pediatr 2021; 175 (3): e205441.

29. Kornanova E, Dugatova M, Vaclavova Z, Borovsky M. Fetal anatomy scan with integrated nuchal transparency and combination of PAPP-A and fβhCG for prediction of aneuploidy. Bratisl Med J 2022; 123 (4): 299–303.

Received November 28, 2022.
Accepted December 8, 2022.