Clinical Practice Guidelines for the Management of Congenital Cytomegalovirus Infection in Japan 2023

Executive Summary

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Abstract: Congenital cytomegalovirus (cCMV) infection is the most common congenital infection in developed countries. Although a standard therapy has not yet been established, evidence for the management of cCMV infection has been accumulating. The first edition of the "Clinical Practice Guidelines for the Management of Congenital Cytomegalovirus Infection" was published in Japan in 2023. This summary outlines the clinical questions (CQs) in the guidelines, with reference to the Japanese Medical Information Distribution Service Manual. Overall, 20 CQs with statements regarding prenatal risk assessment, prevention and management at diagnosis (CQs 1-1–1-3), diagnosis (CQs 2-1–2-6), treatment (CQs 3-1–3-7) and follow-up requirements (CQs 4-1–4-4) have been discussed. For each statement, the levels of recommendation, evidence and consensus rates were determined. These guidelines will assist in the management of patients with cCMV infection.

Key Words: guideline, congenital cytomegalovirus infection, symptomatic, asymptomatic, Japan

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Congenital cytomegalovirus (cCMV) infection is caused by transplacental viral transmission from a cytomegalovirus (CMV)-infected mother to the fetus. The incidence in Japan is reported to be 0.31%, with symptomatic disease accounting for 23.9% of cCMV infections (0.07% of all births).[1] In 2022, there were approximately 800,000 births, with an estimated 2500 neonates with cCMV and 560 neonates with symptomatic disease. If 60% of the symptomatic infections and 15% of the asymptomatic infections have sequelae, it is estimated that approximately 630 children will have neurological sequelae. In cases of symptomatic central nervous system (CNS) disorders, treatment with the antiviral drugs ganciclovir and valganciclovir is thought to improve the auditory and psychomotor developmental outcomes; however, there is no standard therapy for indication. In Japan, a recent clinical trial reported the therapeutic efficacy of valganciclovir after 6 months of administration.[2] In Japan, a dry syrup formulation of valganciclovir was approved in March 2023 as an insurance indication for symptomatic cCMV infection.

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METHODS

The "Clinical Practice Guidelines for the Management of Congenital Cytomegalovirus Infection" was developed in accordance with the 2020 Medical Information Distribution Service principles.[3] This guideline includes clinical questions (CQs) and makes recommendations for clinical issues based on a systematic search for relevant evidence. The recommendation evidence levels were assessed as A (strong), B (moderate), C (weak) or D (uncertain). There are 2 patterns of recommendation strength: strongly recommended (notes as recommended, as 1) and weakly recommended (notes as proposed, as 2). The results of the committee members' votes at the recommendation level are also described.

CQs and Statements

The proposed algorithm for the evaluation and management of cCMV infection is illustrated in Figure 1.

Part 1. Prenatal Risk Assessment, Prevention and Management at Diagnosis

CQ1-1

Is raising awareness (information provision) useful for preventing vertical infection during the fetal period?

Statement

The raising of awareness aimed at preventing vertical infection is recommended because it may contribute to increasing the knowledge and awareness of prevention methods, thereby decreasing the frequency of vertical infections. For pregnant

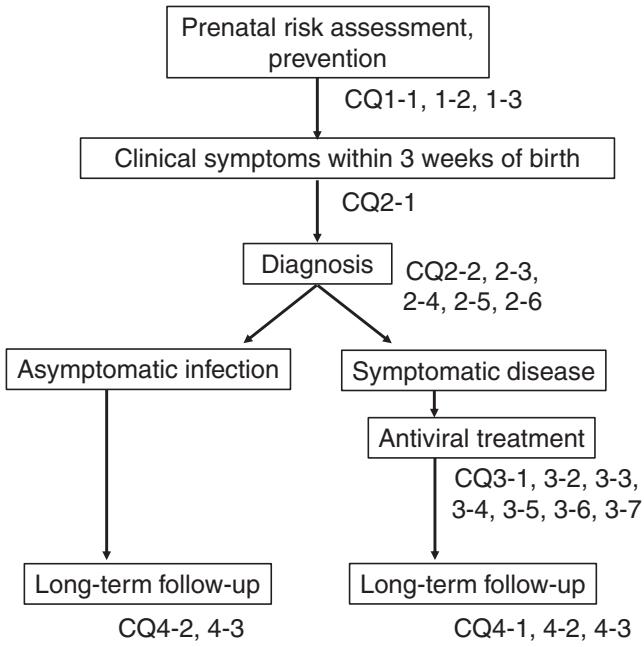

FIGURE 1. Clinical practice algorithm for the management of children with cCMV infection and related clinical issues.

women, awareness raising should be conducted as early as possible during pregnancy, and for women who wish to have a baby, awareness raising should be conducted before and after pregnancy. The most common method is to provide all pregnant women with explanatory materials (brochures and videos) that include information on the frequency of congenital infections, effects on the child, routes of infection, and the specific methods of prevention (recommended, moderate evidence: 1B; agreement, 9/9).

Viral shedding after CMV infection continues for months to years, especially in children under 2 years of age, and contact with the child's body fluids (saliva and urine) is a key risk factor for cCMV infection[4] (Table 1). In a study in which prevention education was provided at 12 weeks of gestation, the incidence of pregnant women who were CMV IgM positive and had low IgG avidity (antibody-binding capacity) and were considered to have been first infected in early pregnancy up to 12 weeks of gestation was 0.42% (11/2594 cases), while CMV IgG seroconversion was confirmed in 0.19% (5/2583 cases).[5] The study showed a significant (P = 0.005) decrease in the infection rate per pregnant woman per week. In a study comparing the rate of antibody positivity at delivery between an intervention group in which women who tested negative for CMV IgG antibodies at 11–12 weeks of gestation were offered prevention education and a control group in which no prevention education was offered during pregnancy, the rate was 1.2% (4/331 cases) in the intervention group and 7.6% (24/315 cases) in the control group. This indicated that the rate of positive antibody conversion at delivery was significantly lower than that in the intervention group.[6] The study showed a significant (P < 0.001) reduction in infections after prevention education.

TABLE 1. CMV Infection Prevention Education

Explain that contact with the saliva and urine of children, which may contain CMV, should be avoided during pregnancy
The specific measures include the following:
Hand washing frequently with soap and water for 15–20 s after:
Changing diapers
Feeding a child
Wiping a baby's mucus or drool
Touching a child's toys
Do not share food, drinks or utensils with children
Do not place the pacifier in the child's mouth
Do not share toothbrushes
Avoid contact with saliva when kissing a child
Maintaining toys, counters and areas that may come into contact with saliva or urine

CQ1-2

Is maternal antibody screening useful for assessing the risk of vertical fetal infections?

Statement

It is useful for assessing the risk of vertical transmission from primary infections; however, it is invalid for the assessment of the risk of vertical transmission from nonprimary infections (recommended, strong evidence: 1A; agreement, 9/9).

Serologic tests have been used to diagnose primary infections and screen pregnant women for CMV infection. The serologic findings suggestive of primary infection during pregnancy include (1) CMV IgM positivity, (2) CMV IgG seroconversion, (3) positivity for both CMV IgG and IgM and low IgG avidity or (4) CMV IgM positivity and IgG increase over time.[7–9] In a prospective cohort study of 2193 pregnant women, 3 cCMV infants from pregnant women were diagnosed with primary infection based on IgG seroconversion or low avidity or positive IgM and 7 infants from pregnant women with nonprimary infection with high avidity and IgM negativity.[10]

CQ1-3

What fetal ultrasound findings are suspicious for congenital infection?

Statement

The findings include fetal growth restriction, microcephaly, enlarged ventricles, intracerebral calcifications, periventricular cysts, fetal edema, pleural effusion, ascites, hepatosplenomegaly and intestinal hyperintensity (recommended, weak evidence: 1C; agreement, 9/9).

The findings suggestive of cCMV include intestinal hyperintensity, ventricular enlargement, intracranial calcifications and fetal growth restriction.[11] In addition, a variety of ultrasound findings have been reported, and their frequency varies among reports (Table 2). Imafuku et al[12] compared ultrasound findings in cases with and without cCMV and found that findings such as fetal

TABLE 2. Ultrasound Abnormalities in Fetal Infection With CMV

Ultrasound Abnormalities	Frequency, %[11]	Frequency, %[12]
Intracranial calcifications	0.6–17.4	-
Microcephaly	14.5	6
Echogenic bowel	4.5–13	13
Fetal growth restriction	1.9–13	9
Subependymal cysts	11.6	-
Cerebral ventriculomegaly	4.5–11.6	6.1
Ascites	8.7	4.2
Pericardial effusion	7.2	1.2
Hyperechogenic kidneys	4.3	-
Hepatomegaly	4.3	3.8
Placentomegaly/placental calcifications	4.3	2.0
Hepatic calcifications	1.4	1.2
Hydrops	0.6	1.2

growth restriction, enlarged ventricles, microcephaly, intracerebral calcifications, pleural effusion, ascites, hepatosplenomegaly and hyperintense intestinal tract were significantly more common in patients with cCMV. In a review by Leruez-Ville et al,[13] 637 cCMV cases were analyzed, of which 35% had abnormal ultrasound findings, with the most common being intestinal hyperintensity (82 cases, 13%).

Part 2. Diagnosis Within 3 Weeks of Birth

CQ2-1

What clinical findings should prompt suspicion of symptomatic infection?

Statement

The clinical findings include small for gestational age (birth weight <−2 standard deviation in weeks of gestation), microcephaly (head circumference <−2 standard deviation in weeks of gestation), petechiae, blueberry muffin rash, jaundice, hepatosplenomegaly, abnormal neurological findings (poor vitality, hypotonia, seizures, poor sucking reflex, etc.) and hearing screening referrals (recommended, weak evidence: 1C; agreement, 9/9).

Luck et al[14] presented the following signs and symptoms of cCMV: hypometropia, microcephaly, petechiae, blueberry muffin rash, jaundice, hepatosplenomegaly and abnormal neurologic findings (poor vitality, hypotonia, seizures and poor sucking reflex). Although several clinical findings of cCMV are nonspecific, some symptoms have been shown to be significantly more common in children with cCMV than in children without cCMV. A meta-analysis by Zhang et al[15] reported a prevalence ratio of 2.3 between cCMV and microcephaly. Messinger et al[16] reported a prevalence ratio of 7.4 for an association between cCMV and microcephaly and 8 for an association between cCMV and seizures.

CQ2-2

What should you do if a maternal antibody test shows suspicion of primary CMV infection?

Statement

It is recommended that the fetal ultrasound be evaluated over time during pregnancy and that appropriate counseling should be provided to the pregnant woman. After delivery, it is recommended that a urine nucleic acid test be performed to confirm the diagnosis of the infant and determine whether the positive case is symptomatic (recommended, weak evidence: 1C; agreement, 9/9).

The risk of cCMV is higher in pregnant women with primary infection, estimated at 30%–40%.[17] Neurologic sequelae, including hearing loss due to fetal infection, are concentrated in cases of infection early in pregnancy. If CMV IgG seroconversion is detected during pregnancy, primary infection is certain; if CMV IgG is positive and antibody titers are unknown earlier in pregnancy, CMV IgM positivity associated with low IgG avidity indicates the primary infection.[17] If a maternal antibody test indicates primary infection, the pregnant woman should receive appropriate counseling and disclosure of the results.[18] After birth, the infant should be examined by a pediatrician to confirm the presence of symptomatic cCMV findings. Urine CMV nucleic acid testing should be performed within 3 weeks of birth to confirm the diagnosis.

CQ2-3

What abnormal findings during pregnancy require urine nucleic acid testing for the baby?

Statement

Neonatal urine nucleic acid testing is recommended when abnormal fetal ultrasound or magnetic resonance imaging (MRI) findings (fetal growth retardation, microcephaly, enlarged ventricles, intracranial calcifications, periventricular cysts, fetal edema, pleural effusion, ascites, hepatosplenomegaly and intestinal hyperintensity) and CMV IgG seroconversion during pregnancy are noted. Neonatal urine nucleic acid testing should be considered if signs of infection (eg, fever, malaise, anorexia, cough, nasal discharge, sore throat, vomiting and diarrhea) are observed during pregnancy ([1] abnormal fetal findings: recommended, moderate evidence: 1B; agreement, 9/9; [2] serum antibody findings in pregnant women: recommended, moderate evidence: 1B; agreement, 9/9 and [3] signs of infection in pregnant women: suggested, moderate evidence: 2B; agreement, 9/9).

Fetal findings are mainly obtained by ultrasonography and include fetal growth retardation, microcephaly, enlarged ventricles, intracerebral calcifications, periventricular cysts, fetal edema, pleural effusion, ascites, hepatosplenomegaly and intestinal hyperintensity.[8,19] Because ultrasonography may not reveal abnormal fetal findings, fetal MRI, which demonstrates higher diagnostic sensitivity, may be considered when CMV infection is suspected. Urine nucleic acid testing of neonates may be considered if antibody testing suggests a primary CMV infection in the pregnant woman or if flu-like symptoms, such as fever, malaise, anorexia, cough, nasal discharge, sore throat, vomiting or diarrhea, are observed during pregnancy.[8,20]

CQ2-4

If a congenital infection is diagnosed, what laboratory tests should be used to determine symptomatic disease?

Statement

Blood tests (complete blood count, aspartate aminotransferase, alanine aminotransferase, and direct and indirect bilirubin levels), head imaging (MRI and ultrasonography), hearing tests and fundoscopy are recommended (recommended, strong evidence: 1A; agreement, 9/9).

It has been reported that 56% of cCMV cases found to be asymptomatic on physical examination were diagnosed as symptomatic by blood tests, head imaging, audiometry and fundus examination.[21] It is necessary to look for abnormal head imaging findings, sensorineural hearing loss and retinochoroiditis (Table 3). Blood tests may reveal cytopenia including thrombocytopenia, as well as elevated aspartate aminotransferase/alanine aminotransferase and direct and indirect bilirubin levels.[22] Because MRI is more sensitive than ultrasonography in the detection of abnormal findings in the CNS, MRI is recommended in addition to ultrasonography, as it is easier to perform.[23]

TABLE 3. Clinical Features of Symptomatic cCMV Disease

Clinical Manifestations	Laboratory Findings During the Screening Process
Microcephaly	Leukopenia (neutropenia), anemia, thrombocytopenia
Hepatosplenomegaly, jaundice	Elevated serum AST/ALT, direct/indirect hyperbilirubinemia
Petechiae, blueberry muffin rash	Neuroimaging (MRI, ultrasound): hydrocephalus, ventricular dilatation, white matter abnormalities
Abnormal neurological findings (lethargy, hypotonia, seizures, and poor sucking reflex)	Hearing test: sensorineural hearing loss
Small for gestational age	Fundoscopy: chorioretinitis
	Cerebrospinal fluid: pleocytosis, positive CMV DNA

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase.

CQ2-5

What should we do for newborns who failed hearing screening?

Statement

It is recommended that urine samples should be collected within 21 days of birth for nucleic acid testing. Simultaneously, a referral to an otorhinolaryngologist should be requested to perform further examinations (recommended, moderate evidence: 1B; agreement, 9/9).

CMV is a leading cause of childhood hearing loss, next to hereditary hearing loss,[24] which is estimated to consist of approximately 10%–20% of all children with hearing loss.[25]

The specimens should be collected within 21 days of birth, and urine sample is preferred.[14] Nucleic acid amplification is recommended because of its cost-effectiveness.[26] In Japan, CMV nucleic acid amplification with urine has been covered by the universal health insurance since 2018. Since the evidence for antiviral therapy is limited to starting within 2 months, it is necessary to simultaneously conduct testing and referral to otolaryngologists once the neonate fails the hearing screening.

CQ2-6

Is it useful to diagnose cCMV using preserved samples from children older than 3 weeks of age?

Statement

Dried blood spots or dried umbilical cords (DUCs) are useful for detecting CMV DNA when cCMV is suspected (suggested, weak evidence: 2C; agreement, 9/9).

Situations in which the diagnosis of cCMV should be considered after 3 weeks of age include (1) when the infant was symptomatic at birth but was not diagnosed with cCMV and (2) when the symptoms were apparent subsequently. In such cases, both dried blood spots and DUC can be used for retrospective diagnosis,[27] although negative results cannot exclude cCMV owing to their insufficient sensitivity. In a study of DUC among students at a school for the deaf in Japan, 3 of 26 (12%) were CMV DNA-positive, suggesting that a significant number of cases of hearing loss with cCMV remain undiagnosed.[28]

Part 3. Treatment

CQ3-1

Is oral valganciclovir effective for symptomatic cCMV disease?

Statement

In cases of symptomatic infection, oral valganciclovir is effective in improving the auditory and neurological prognoses and controlling symptom progression ([1] auditory prognosis: recommended, moderate evidence: 1B; agreement, 9/9 and [2] neurological prognosis: suggested, uncertain evidence: 2D; agreement, 9/9).

In a systematic review of 682 patients in 18 references by De Cuyper et al,[29] ganciclovir/valganciclovir treatment improved hearing (odds ratio, 7.72; 95% CI 3.08–19.34) and prevented hearing deterioration (odds ratio, 0.23; 95% CI 0.10–0.57). A phase III, multicenter, open-label, single-arm study of oral valganciclovir was conducted in Japan in February 2020.[2,30] At 6 months, the auditory brainstem response showed no progression of hearing loss in 24 of 24 (100%) patients in the dominant ear. There is insufficient evidence for preterm infants, low-birth-weight infants or when treatment is initiated after the neonatal period. Notably, treatment is not currently recommended for asymptomatic cCMV infants.

CQ3-2

What symptoms are eligible for oral valganciclovir therapy?

Statement

Oral valganciclovir therapy is recommended to improve the long-term prognosis in patients with hearing impairment and CNS involvements (such as microcephaly, intracranial calcifications, chorioretinitis and abnormal findings on head MRI, including white matter lesions). Oral therapy is recommended for active infections of moderate severity (eg, hepatosplenomegaly, petechial hemorrhage, pneumonia, abnormal liver function, thrombocytopenia, leukopenia and anemia; [1] hearing impairment: recommended, moderate evidence: 1B; agreement, 9/9; [2] CNS disorders: recommended, weak evidence: 1C; agreement, 9/9 and [3] active moderate infections: recommended, uncertain evidence: 1D; agreement, 9/9).

Case reports and clinical trials of oral antiviral therapy have been reported worldwide, showing its efficacy in improving hearing.[29] Regarding CNS disorders, a randomized phase III study of 6-week intravenous ganciclovir by Oliver et al[31] showed that the mean number of developmental delays in the ganciclovir-treated and untreated groups was 4.46 and 7.51, respectively, at 6 months of age ($P = 0.02$) and 10.06 and 17.14, respectively, at 12 months of age ($P = 0.007$). Kimberlin et al[32] also reported on 96 children with cCMV randomized to 6-week and 6-month treatment periods and compared their prognoses. Regarding the neurological prognosis, the 6-month group showed improved neurodevelopmental scores on the Bayley Scales of Infant Development Test, Third Edition, at 24 months of age compared with the 6-week group. They were significantly better in the language composite component ($P = 0.004$) and receptive communication ($P = 0.003$).

CQ3-3

When should a patient receive oral valganciclovir treatment?

Statement

Oral medication should be started within 2 months of life, and the treatment duration should be 6 months (recommended, moderate evidence: 1B; agreement, 9/9).

In a review article, Lim and Lyall[33] recommended starting treatment within the first month of life because treatment with oral valganciclovir after the first month of life has not been well reported. Morioka et al[2] conducted a clinical trial on cCMV within the first 2 months of life. Based on the above, starting treatment with valganciclovir within 2 months of birth is recommended, and starting treatment within 1 month of birth is a stronger recommendation because the level of evidence is stronger. Regarding the duration of treatment with oral valganciclovir, Kimberlin et al[32] randomized cCMV to 6 weeks or 6 months of treatment and reported the superiority of 6 months of treatment in terms of the auditory and neurological outcomes. Garofoli et al[34] reported that long-term oral valganciclovir therapy was a risk for resistance.

CQ3-4

When should intravenous ganciclovir be used?

Statement

We suggest that intravenous ganciclovir should be the treatment of choice for patients with difficulty in taking oral valganciclovir (suggested, weak evidence: 2C; agreement, 9/9).

There are no established criteria for selecting cases of intravenous ganciclovir in symptomatic children with cCMV. In cases where the oral administration of valganciclovir is difficult, intravenous ganciclovir may be preferable over no treatment.

CQ3-5

What are the most common adverse effects associated with oral valganciclovir?

Statement

Treatment should be administered while monitoring for neutropenia, a common adverse effect (recommended, strong evidence: 1A; agreement, 9/9).

The most common adverse effects associated with oral valganciclovir have been reported in human clinical trials, including neutropenia, thrombocytopenia, abnormal liver function, and anemia.[35] The UK cCMV practice guidelines by Kadambari et al[36] recommend weekly monitoring of neutropenia during antiviral therapy, stopping treatment if neutrophils <500/mm^3 and resuming treatment when neutrophils >750/mm^3 have recovered. Weekly assessments of liver and kidney function are also recommended. In basic animal studies, high-dose ganciclovir administration has been reported to cause reversible sperm and testicular damage, as well as carcinogenesis; however, there are no long-term prognostic data in humans.[37]

CQ3-6

What are the measures of therapeutic efficacy in oral valganciclovir therapy?

Statement

The recommended end points include changes in the CMV DNA levels in the blood during treatment, post-treatment hearing, and developmental prognosis (recommended, weak evidence: 1C; agreement, 9/9).

The therapeutic effects of intravenous ganciclovir or oral valganciclovir have been shown in randomized controlled trials in humans to improve hearing impairment at 6 and 12 months of age and psychomotor developmental delay[32,38] at 6 and 12 months of age in the ganciclovir/valganciclovir treatment group compared with placebo.[31] Nonrandomized controlled trials have also shown that the CMV viral load in whole blood is significantly reduced at 6 months after treatment initiation compared to the baseline.[3,32] Kido et al[39] retrospectively evaluated the association between the changes in whole blood or urine viral load and hearing prognosis up to 8 weeks after treatment initiation in children with cCMV treated with oral valganciclovir. They reported no difference in the change of whole blood or urine viral load between the deaf and nondeaf groups at the corrected 6-month time point.

CQ3-7

Is it useful to switch antiviral drugs if the therapeutic effect of oral valganciclovir is insufficient?

Statement

A change in antiviral medication is recommended if valganciclovir resistance has been confirmed (suggested, weak evidence: 2C; agreement, 9/9).

Regarding drug-resistant viruses, a review article on antiviral therapy for children with cCMV reported drug resistance in less than 4% of cases.[40] In CMV, drug-resistant mutations are known to cluster in the *UL97* and *UL54* genes; however, foscarnet may be useful for the *UL97* mutation, while the *UL54* mutation may be foscarnet resistant.[36] Based on studies of transplant cases, (1) high viral load, (2) prolonged ganciclovir/valganciclovir administration and (3) suboptimal drug dosing are considered to be risk factors for the emergence of drug resistance.[41]

Part 4. Follow-up Requirements

CQ4-1

What evaluations are necessary for the long-term follow-up of patients treated with oral valganciclovir?

Statement

The long-term follow-up of treated cases is recommended for psychomotor developmental assessment up to 6 years of age and hearing assessment up to 18 years of age (psychomotor developmental assessments over 2 years and hearing assessments over 6 years of age are particularly useful; recommended, moderate evidence: 1B; agreement, 9/9).

Since neurological sequelae are observed in 40%–80% of cases of symptomatic cCMV, and progressive or delayed sensorineural hearing loss and developmental delay are possible,[40] specialized follow-up in infancy with or without antiviral treatment is considered necessary. However, there is no international standardization of the content and duration of follow-up. The expert consensus of the European Society for Pediatric Infectious Diseases has provided specific suggestions for the treatment of cases with valganciclovir: (1) hearing tests every 3–6 months until 1 year of age, every 6 months until 3 years of age and every 12 months until 6 years of age; (2) developmental assessments at least until 2 years of age and (3) ophthalmologic examinations until 5 years of age.[14] In a review article in *Lancet Infectious Diseases*, the consensus recommends ophthalmologic examination, audiologic evaluation and developmental assessment for patients treated with valganciclovir, with audiologic testing every 6 months until 3 years of age and then annually until adolescence (10–19 years of age).[42]

CQ4-2

Is auditory follow-up useful?

Statement

Both symptomatic and asymptomatic children should be regularly evaluated for hearing and balance every 6 months until the age of 3 years, annually until 6 years of age and then at least until 18 years of age (recommended, moderate evidence: 1B; agreement, 9/9).

The incidence of hearing impairment immediately after birth was 7.5% for cCMV, 27.4% for symptomatic cCMV, and 5.6% for asymptomatic cCMV,[43] with a higher incidence in symptomatic cCMV. Three universal screening studies[44–46] found hearing impairment in 33.3%–54.5% of symptomatic cCMV and 5%–21% of asymptomatic cCMV cases. Cannon et al[43] found that 27.4% of symptomatic cCMV cases developed hearing loss between birth and 3 months of age, 3.2% by 9 months, 3.2% by 24 months and 4.8% by 72 months, resulting in 38.6% of cases with hearing loss by 72 months. However, for asymptomatic cCMV, the authors report that 5.6% of cases will develop hearing loss by 3 months of age, another 1% by 9 months, 1% by 24 months and 5.3% by 72 months, for a total of 12.2% by 72 months.[43] The 2015 International CMV Conference recommended that hearing tests should be performed every 6 months until 3 years of age and then annually until adolescence at 10–19 years of age.[42]

CQ4-3

Is ophthalmologic follow-up useful in asymptomatic children?

Statement

For children without fundus lesions on ophthalmologic screening at birth, ophthalmologic consultations at 6 months and 1 year of age are useful. Thereafter, we suggest a consultation at the onset of clinical symptoms (suggested, weak evidence: 2C; agreement, 9/9).

Abnormal ophthalmic findings of cCMV are more common in symptomatic children, with 5%–30% presenting with chorioretinitis, peripheral retinal scars, optic nerve atrophy, cataracts, corneal opacities and strabismus.[47] It is important to identify these

conditions early in life and provide appropriate ophthalmic management.

In an observational study by Jin et al,[48] 19.5% of symptomatic children had chorioretinal scars, 11.7% had optic nerve atrophy, 14.3% had cortical visual impairment and 23.4% had strabismus, whereas no visual impairment was observed in asymptomatic children or controls. It was observed that 28% of symptomatic children had chorioretinal scars, whereas asymptomatic children had no fundus abnormalities; 22% of symptomatic children had visual impairments at the last examination, whereas asymptomatic children did not.[49] In addition, a relationship between CNS abnormalities and long-term visual prognosis has been suggested.

CQ4-4

Is it useful to follow psychomotor development in asymptomatic children?

Statement

As with symptomatic children, psychomotor assessment up to 6 years of age is recommended (psychomotor assessment beyond 2 years of age is particularly useful; suggested, weak evidence: 2C; agreement, 9/9).

In asymptomatic cCMV, neurological abnormalities, including hearing loss, appear late even if the child is asymptomatic at birth (including cases in which only sensorineural hearing loss is present), leaving sequelae in 10%–15% of cases.[40,50] Therefore, a follow-up after diagnosis is necessary even in asymptomatic children. However, there is no international standardization of the content and the duration of follow-up. Hearing and developmental tests in infancy have been suggested for the follow-up of children with cCMV, regardless of the symptoms at birth. The expert consensus of the European Society for Pediatric Infectious Diseases recommends (1) hearing testing every 3–6 months until 1 year of age, every 6 months until 3 years of age and every 12 months until 6 years of age and (2) developmental testing until at least 1 year of age (and up to 2 years of age if possible).[14]

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