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Neonatal and long-term ophthalmological findings in infants with symptomatic and asymptomatic congenital cytomegalovirus infection

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ABSTRACT

Background: Congenital cytomegalovirus (cCMV) infection is responsible of a high burden of neurosensory impairment in children.
Objectives: To report incidence and consequences of ophthalmological abnormalities in infants with cCMV infection and better define their long-term ophthalmological management.
Study design: Infants with cCMV infection were enrolled in a 6-year follow-up. Infants were classified as symptomatic or asymptomatic based on complete clinical, laboratory and instrumental evaluations. All infants underwent funduscopic evaluation in neonatal period, and yearly complete ophthalmological evaluation, including funduscopic, motility and visual acuity assessments.
Results: Forty-eight infants were enrolled, 18/48 (37.5%) symptomatic and 30/48 (62.5%) asymptomatic. Mean duration of follow-up was 34.9 ± 22.2 vs. 34.8 ± 20.1 months (P = 0.98). Funduscopic abnormalities were identified in neonatal period in 7/18 (39%) symptomatic infants and in none of the infants without other clinical and instrumental abnormalities at birth (P < 0.001); chorioretinal scars were the most common finding (5/18 cases, 28%). Strabismus was detected in 1/18 (5.5%) symptomatic infants during the first years of life. Visual impairment at last follow-up evaluation was suspected or detected in 4/18 (22%) symptomatic infants and in none of the asymptomatic infants at birth (P = 0.01). Ophthalmological abnormalities were associated with other signs of central nervous system (CNS) involvement (P < 0.001). No correlation was found with the type of maternal infection.
Conclusions: Ophthalmological abnormalities were common in symptomatic infants though often not associated with long-term visual impairment, and correlated with the presence of CNS involvement. Neonatal and periodical ophthalmological evaluations throughout childhood seem prudential for symptomatic babies. No ophthalmological abnormalities were detected in asymptomatic infants, who might therefore undergo more deferred evaluations.

1. Background

Congenital cytomegalovirus (CMV) infection is the most common congenital viral infection, with an estimated incidence of 0.6-2% of all live births [1,2]. It contributes to a high burden of disease and is recognized as the leading non-genetic cause of sensorineural hearing loss (SNHL) in children [3–6].

Ocular abnormalities and visual impairment have been reported in a high percentage of symptomatic infants with congenital CMV (cCMV) infection, whereas they are considered uncommon in asymptomatic infants [7–11]. These data though are based on few studies, since large follow-up studies have mainly focused on hearing and neurodevelopmental outcomes. This paucity of data has made difficult to reach clear recommendations on the ophthalmological follow-up that should be

Abbreviations: BAERs, auditory brainstem responses; cCMV, congenital cytomegalovirus; CMV, cytomegalovirus; CNS, central nervous system; cUS, cranial ultrasound; GCV, ganciclovir; IUGR, intrauterine growth restriction; MRI, magnetic resonance imaging; SNHL, sensorineural hearing loss; VEPs, visual evoked potentials; VGCV, valganciclovir; WM, white matter

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provided to infants with cCMV infection [12]. Specifically, it is unclear if it should be equally directed to all congenitally infected infants or if it may be adjusted on the basis of the neonatal presentation of CMV infection. Recently, a European panel of experts in the field suggested that, based on the few available studies, ophthalmological follow-up should be provided annually in symptomatic babies at least until children can talk, but not in the asymptomatic babies (article in press). These points are of major interests, both to adequate counsel parents and to have a cost-effective management of infants.

2. Objectives

The aim of this study was to evaluate ophthalmological findings and visual function in the neonatal period and during a long-term follow-up in infants with cCMV infection. The ocular involvement in relation to type and timing of maternal infection was also explored.

3. Study design

All infants with cCMV infection referred to the Outpatient Clinic of the Neonatal Division of St. Orsola-Malpighi Hospital, Bologna, Italy between January 2006 and December 2015 were enrolled in a prospective observational study.

Infants were identified because of suspected/confirmed maternal CMV infection during pregnancy or because of the presence of symptoms consistent with cCMV infection at birth.

Data regarding timing and type (primary vs. non-primary) of maternal infection, neonatal and follow-up evaluations (physical, neurodevelopmental, audiological and ophthalmological assessments) were prospectively collected during routine visits.

The follow-up was scheduled for 6 years: only infants followed for at least 12 months were included.

3.1. Definition and monitoring of cCMV infection

Maternal primary infection was diagnosed based on clinical and laboratory history and CMV IgM-positive and low/moderate CMV IgG avidity results as well as positive DNAemia and/or seroconversion for CMV. Maternal non-primary infection was diagnosed, within the first 16 weeks of gestation, according to blot-confirmed IgM-positivity with high avidity CMV IgG and presence of CMV DNA in blood and/or urine and/or saliva [13].

cCMV infection was diagnosed by CMV detection in urine within the first three weeks of life by viral culture until 2012 and by real-rime Polymerase Chain Reaction (PCR) from 2012 to 2015; for infants who were referred to our Center beyond the third week of life, cCMV infection was diagnosed by detection of CMV-DNA by real-time PCR on the Guthrie card stored at 48 h of life.

Blood viral load was assessed on whole blood using real-time PCR, and expressed as number of copies/mL, as previously described [13].

All infants underwent a complete clinical, laboratory and instrumental evaluation during the first month of life to define the infection as symptomatic or asymptomatic.

Infants were considered symptomatic if showing: intrauterine growth restriction (IUGR), hepatomegaly, splenomegaly, petechiae, thrombocytopenia, elevated serum transaminases, jaundice with conjugated hyperbilirubinemia, central nervous system (CNS) involvement (as denoted by microcephaly, seizures or other neurological signs, neuroimaging abnormalities consistent with CMV infection detected by cranial ultrasound [cUS] and/or Magnetic Resonance Imaging [MRI], ophthalmological abnormalities detected by funduscopic examination or SNHL detected by Brainstem Auditory Evoked Responses [BAERs]). SNHL was defined as a threshold > 20 dB for pure tones, confirmed at two consecutive BAERs, and after exclusion of middle ear disorders. Infants were considered asymptomatic if clinical, laboratory and instrumental evaluations were all normal at birth.

Neonates with CNS involvement were treated with intravenous ganciclovir (GCV) or oral valganciclovir (VGCV) for at least 6 weeks, after informed consent from parents or legal guardians was obtained.

3.2. Ophthalmological evaluation

All ophthalmological examinations were adapted to the age of the patient and performed by experienced ophthalmologists.

Dilated funduscopic examination with cycloplegic refraction was performed at birth, 1, 3, 6 and 12 months and then annually. Cycloplegia was obtained with a single instillation of a solution of tropicamide/phenylephrine hydrochloride.

Visual function was defined according to the *International Classification of Diseases, 10th Revision*: blindness was defined as a corrected visual acuity of $< 1/20$ (or corresponding visual field loss) in the better eye, and low vision corresponded to a best corrected visual acuity of $< 3/10$ but $\geq 1/20$ in the better eye [14]. For the purpose of this study also unilateral findings were reported. For younger preverbal infants, visual function was estimated on the basis of the fixation behavior, considering a moderate impairment as a poor but demonstrable fixation and a severe visual impairment as no demonstrable fixation behavior. Measurement of visual acuity with optotypes was used in older children.

All infants received motility examination and testing of anterior segment.

Infants with funduscopic abnormalities and/or abnormal visual function underwent visual evoked potentials (VEPs). VEPs were elicited using a flash stimulus and/or a pattern-reversal stimulus and recorded at the scalp over the occipital cortex. The VEPs waveform was analyzed for both amplitude and latency of onset of a peak after stimulus.

A complete ophthalmological examination was performed yearly until 6 years.

3.3. Statistical methods

Statistical analyses were conducted using IBM SPSS software version 20. Categorical data were summarized using frequency counts and percentages. The chi-square test or Fisher's exact test were used for comparison between groups for categorical data. For continuous data, data distribution was checked for normality by the Shapiro-Wilk test. Being data normally distributed, the T-test was used to compare mean ($\pm$ standard deviation) between groups. The Mann-Whitney test was used to compare blood viral load between groups. P-values < 0.05 were considered statistically significant.

4. Results

Forty-eight infants with cCMV infection were enrolled, including 18/48 (37.5%) symptomatic and 30/48 (62.5%) asymptomatic infants (Table 1).

In the symptomatic group 11/18 infants (61%) were born to mothers with a primary CMV infection, diagnosed during the first trimester of pregnancy in 6/11 (55%) cases and during the second trimester in the other 5/11 (45%) cases. Instead, 5/18 (28%) infants were born to mothers with a non-primary CMV infection. For two infants, maternal serology during pregnancy was not available.

In the asymptomatic group 27/30 (90%) infants were born to mothers with a primary CMV infection, diagnosed during the first trimester in 6/27 (22%) cases, during the second trimester in 11/27 (41%) cases and during the third trimester in 10/27 (37%) cases. Instead, 3/30 (10%) infants were born to mothers with a non-primary CMV infection.

Mean gestational age, birth weight and age at the last evaluation were similar between groups (Table 1).

Blood viral load was available for 13/18 (72%) symptomatic infants and for 22/30 (73%) asymptomatic infants. Blood viral load at birth was significantly higher in symptomatic as compared with