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Outcomes of congenital cytomegalovirus disease following maternal primary and non-primary infection

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ABSTRACT

Background: Natural history and long term prognosis of congenital cytomegalovirus (CMV) disease according to maternal primary versus non-primary infection are not clearly documented.
Objective: To investigate clinical, laboratory and neuroimaging features at onset and long term outcome of congenitally CMV-infected patients born to mothers with non-primary infection compared with a group of patients born to mothers with primary infection.
Study design: Consecutive neonates born from 2002 to 2015 were considered eligible for the study. Patients underwent clinical, laboratory and instrumental investigation, and audiologic and neurodevelopmental evaluation at diagnosis and during the follow up.
Results: A cohort of 158 congenitally infected children was analyzed. Ninety-three were born to mothers with primary CMV infection (Group 1) and 65 to mothers with a non-primary infection (Group 2). Eighty-eight infants had a symptomatic congenital CMV disease: 49 (46.2%) in Group 1 and 39 (60%) in Group 2. Maternal and demographic characteristics of patients of Group 1 and Group 2 were comparable, with the exception of prematurity and a 1-min Apgar score less than 7, which were more frequent in Group 2 compared to Group 1. Prevalence of neuroimaging findings did not significantly differ between the two groups. An impaired neurodevelopmental outcome was observed in 23.7% of patients of Group 1 and in 24.6% cases of Group 2. Similarly, the frequency of hearing loss did not differ between the two groups (25.8% versus 26.2%, respectively).
Conclusions: Neurodevelopmental and hearing sequelae are not affected by the type of maternal CMV infection. Preventing strategies should be developed for both primary and non-primary infections.

1. Background

Congenital cytomegalovirus (cCMV) infection is a common cause of neurodevelopmental disabilities [1]. Unlike other perinatal infections as congenital rubella or toxoplasmosis, CMV maternal immunity acquired prior to conception does not ensure a complete protection of fetus from infection [2–6]. Approximately 40% of women experiencing a CMV primary infection during pregnancy will transmit virus to their fetus. Of the infants infected in utero, about 10% will exhibit some symptoms at birth that are consistent with cCMV symptomatic infection [6]. In case of maternal non-primary infection, the risk for fetus to be infected by CMV is around 1% [5,7–9]. Earlier studies showed that maternal immunity to CMV prior to pregnancy can prevent CMV-related fetal damage [10,11]. More recent data have indicated that a preconceptional maternal immunity cannot be viewed as protective in terms of CMV fetal damage and hearing loss [8,12–15]. However, differences in natural history and long term prognosis of cCMV disease according to maternal primary versus non-primary CMV infection are not clearly documented.

2. Objectives

To compare clinical, laboratory and neuroimaging features at onset and long term outcome of patients with cCMV born to mothers with non-primary infection and those born to mothers with primary infection.

Abbreviations: cCMV, congenital cytomegalovirus; HUS, head ultrasound; LSV, lenticulostriated vasculopathy; CT, computed tomography; MRI, magnetic resonance imaging

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3. Study design

3.1. Study population

The study was conducted at the Perinatal Infection Unit of the University Federico II (Naples, Italy), a center with a dedicated multidisciplinary team. Neonates born from 2002 to 2015 with cCMV infection were considered eligible for the study. Infants were referred to our unit because of the presence of cCMV-related symptoms at birth or because of evidence of maternal infection on serologic screening during pregnancy. Diagnosis of cCMV infection was based on virus detection by polymerase-chain reaction assay in neonatal urine samples collected within 2 weeks. Symptomatic cCMV infection was defined in the presence of microcephaly (head circumference < 2 SD below the mean for age and birth weight), seizures, chorioretinitis, hepatosplenomegaly, petechiae, elevated serum transaminase levels, cholestasis, thrombocytopenia (< 10,0000 platelets/mm^3), hearing impairment, and abnormal findings on central nervous system (CNS) imaging evaluation (single or multiple calcifications, ventricolomegaly, cerebral atrophy, white matter or neuronal migration abnormalities) [16]. Isolated lenticulostriated vasculopathy (LSV) detected at Head Ultrasound (HUS) in absence of other abnormalities was not considered as a sign of symptomatic cCMV infection [17]. The study protocol matched the standard care applied in our center to all infants with cCMV infection [18]. Neuroimaging study included HUS and/or brain Computed Tomography (CT) and/or brain Magnetic Resonance Imaging (MRI).

Maternal CMV infections were categorized by analyzing maternal and newborn hospital records. Maternal primary infection was defined in the presence of serocoversion from negative to positive CMV-specific immunoglobulin G (IgG) antibodies during pregnancy; if prior CMV IgG were not available, diagnosis of presumed primary infection was based on presence of CMV–specific immunoglobulin M (IgM) antibodies and a low CMV IgG-avidity. A non-primary infection was defined in the presence of detectable CMV-specific IgG antibodies before pregnancy; if pre-conceptional IgG were not available, a presumed non-primary infection was based on presence of IgG at first antenatal blood sample taken within the first 12 weeks of gestation in absence of specific IgM-antibodies.

Infants were included in the study in the presence of certain classification of maternal CMV infection, complete data at diagnosis and during the observation period, and if the follow up was > 1 year. Patients with other perinatal infections or other chronic concomitant diseases were excluded.

The study was approved by the Ethical Committee of our Institution (protocol number 274/16).

3.2. Hearing and neurodevelopmental assessment

Audiological evaluation was performed every 3–6 months until the age of three years, and every 6–12 months later. Hearing function was evaluated at birth by auditory brainstem evoked responses (BAERs) test and during the routinely follow up by age-specific tests. Hearing thresholds were: 21–40 dB for mild hearing loss, 41–70 dB for moderate hearing loss, and > 70 dB for severe hearing loss [19].

Hearing loss was considered as sensorineural if the air-bone gap was less than 10 dB. Tympanometry was routinely performed in all cases to exclude middle ear disorders.

Neurodevelopmental examination was performed by using the Griffiths Mental Developmental Scales (version extended revised GMDS-ER 0–2 and 2–8) and by Denver test. The ages of posture-motor control milestone acquisition were carefully recorded for each child. Cognitive impairment in children aged ≥30 months was assessed by the Wescheler Scale, while behavioral problems in children aged ≥18 months were investigated by the Child Behavior Checklist (CBCL). An impaired neurological outcome was defined in the presence of developmental/cognitive impairment (DQ/IG < 70), motor delay requiring rehabilitation, epilepsy and behavioral/emotional problems (affective problems, attention deficit/hyperactivity and oppositional behavior). Severe mental retardation was defined in the presence of global IQ < 50. Sensorineural hearing loss and visual impairment were not included in the neurodevelopmental outcome but they were independently analyzed.

3.3. Statistical analysis

All data were recorded on a standardized case report form. Statistical analysis was performed using the Statistical Package for Social Science (SPSS). The chi square and the Fisher exact test were used to assess statistical significance of demographic characteristics, clinical data, and outcomes. P values < 0.05 were deemed as statistical significant.

4. Results

During the study period, 224 patients with cCMV were identified. Sixty-six children were excluded from the analysis because of the unavailability of preconceptional and/or prenatal maternal CMV exams. Of the remaining 158 patients, 93 (59%) were born to mothers with a primary CMV infection (Group 1) and 65 (41%) to mothers with a non-primary infection (Group 2) (Table 1). The reasons of cCMV-screening in newborns of non-primary infection group were presence of symptoms at birth in the majority of cases (39/65, 60%), abnormal findings on fetal US in 3 (4.6%) cases (intrauterine growth restriction in all cases), history of maternal immunosuppression in 2 (3.1%) cases. In the remaining 21 (32.3%) patients the diagnosis of cCMV was performed because of newborn CMV screening. No mothers in Group 1 and two (3.1%) mothers in Group 2 had immunosuppression during the pregnancy (p = 0.08). Immunosuppression was due to the need of high dose of steroids because of maternal multiple sclerosis in both cases. Eighty-eight infants were classified as having a symptomatic cCMV infection: 49/93 (46.2%) patients of Group 1 and 39/65 (60%) of Group 2. Signs and symptoms at diagnosis in the two groups of patients are presented in Table 2.

The majority of patients (n = 140, 88.6%) received more than one neuroimaging study (three neuroimaging studies in 116 cases). The prevalence of abnormal findings differed according to the type of neuroimaging exam, being LSV the most frequent finding detected by HUS, calcifications by CT, and white matter disease, callosal and

Table 1
Characteristics of patients with cCMV born to mothers with CMV primary and non-primary infection.

Features	Group 1: maternal primary infection (n = 93)	Group 2: maternal non-primary infection (n = 65)	P
Male, n	46 (49.5)	31 (47.7)	0.8
Age at last observation (years)	3.8 ± 2.6	3.6 ± 2.4	0.5
Abnormal findings on fetal US[a]	9/70 (12.8)	12/54 (22.2)	0.2
Mean gestational age at delivery	38 ± 2.6	35.9 ± 4.2	0.002
Preterm infants[b]	13 (14)	24 (37)	0.0008
Infant with a 1-min Apgar score < 7	4 (4.3)	12 (18.5)	0.008
Patients small for gestational age[c]	15 (16.1)	15 (23.1)	0.2

Values are expressed as numbers and percentages or mean and standard deviation (SD), as appropriated.

[a] Not available in all cases.

[b] Prematurity was defined in case of gestational age less than 37 weeks.

[c] Patients small for gestational age were classified in case of a birth weight below the 10th percentile conditional on gestational age and sex.

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