Eur J Pediatr (2006) 165:773–778
DOI 10.1007/s00431-006-0172-6

ORIGINAL PAPER

Clinical findings and adverse outcome in neonates with symptomatic congenital cytomegalovirus (SCCMV) infection

Ranjit I. Kylat · Edmond N. Kelly · Elizabeth Lee Ford-Jones

Received: 10 February 2006 / Accepted: 25 April 2006 / Published online: 12 July 2006

Abstract
Introduction Congenital cytomegalovirus (CCMV) infection is a common neonatal infection affecting 1% of all live births, 10% of which are symptomatic. Many of these infants have long-term sequelae. The objective is to document the clinical presentation of SCCMV infection in neonates, the frequency of sequelae and severity of adverse neurologic outcomes and risk factors.
Methods A review and analysis of all symptomatic infants diagnosed with SCCMV infection are given. SCCMV was defined as a diagnosis of CCMV infection in the first three weeks of life in the presence of any clinical manifestations. Outcome data from 2 years of age and later are analyzed.
Results There were 104 patients identified as having SCCMV infection and of these 42 cases had definite infection. The common findings at presentation were hepatosplenomegaly 19/42 (45%), thrombocytopenia 21/42 (50%), elevated transaminases 21/42(50%), abnormal cranial US scan 24/41(56%), abnormal head CT scan 29/41 (71%) and abnormal brain MRI 17/19(89%). The risk factors for an adverse outcome including death or deafness or blindness or moderate to severe neurological deficits included an abnormal cranial US scan (OR 8.5), abnormal head CT scan (OR 21) and abnormal brainstem auditory evoked responses (BAER) (OR 8.7).
Conclusions There was only three (7%) patients without any deficits and severely affected infants have been identified with a diverse clinical presentation, reinforcing the importance of CMV as a major public health problem.

Keywords Congenital infection · Cytomegalovirus · Symptomatic congenital CMV infection · Predictors of adverse outcome · Disability · Sensorineural hearing loss · Poor neurodevelopmental outcome

Abbreviations

CMV	Cytomegalovirus
CCMV	congenital CMV
HCMV	Human CMV
ACCMV	asymptomatic CCMV
CT	computed tomography
MRI	magnetic resonance imaging
SCCMV	symptomatic congenital cytomegalovirus
SD	standard deviation
db	decibel
BAER	brainstem auditory evoked responses
CI	confidence intervals
OR	odds ratio
US	ultrasound
HC	head circumference
IUGR	intrauterine growth retardation
SNHL	sensorineural hearing loss
SGA	small for gestational age
HUSS	cranial ultrasound scan
HCT	head computed tomography
EEG	electroencephalogram
AST	Aspartate aminotransferase
SSEP	somatosensory evoked potentials
ALT	Alanine aminotransferase

R. I. Kylat (✉)
Division of Neonatology, Pediatrics Department,
University of Tennessee, Le Bonheur Children's Hospital,
50 N Dunlap St,
Memphis, TN 38103, USA
e-mail: rkylat@gmail.com

R. I. Kylat · E. N. Kelly · E. L. Ford-Jones
Pediatrics Department, University of Toronto,
Toronto, Canada

Introduction

Congenital Cytomegalovirus (CCMV) is the most common cause of congenital infection and is worldwide in distribution; incidence ranges from about 0.2 to 2.5% of live births and around 40,000–80,000 infants with CCMV are born each year in the US [5, 7, 9, 11, 16, 17, 24, 26]. It is caused by Human Cytomegalovirus (HCMV), a ubiquitous virus and like other viruses in the Herpes virus family share properties of latency and reactivation [7, 9, 17]. Cytomegalovirus (CMV) can be vertically transmitted transplacentally and can lead to severe fetal injury, resulting in fetal loss and of those born with CCMV, 10 to 15% will have symptoms at birth and the rest are asymptomatic CCMV (ACCMV) [6, 21].

CCMV is a major cause of central nervous system (CNS) damage leading to sensorineural hearing loss (SNHL), mental retardation and cerebral palsy. In SCCMV, the mortality in the early neonatal period is 30% and the morbidity is devastating, due to its potential to cause cerebral palsy, cognitive impairment (50–80%), SNHL (30–60%), visual impairment (20–35%), neuro-developmental, behavioral and neuromuscular disorders (30–60%) [6, 19, 21, 23]. Treatment of neonates with CCMV infection also remains controversial especially as most of the injury has occurred during fetal life and neuronal damage is irreversible. But as there is significant mortality, progressive injury and long-term neurological sequelae, treatment may be considered in some patients with severe SCCMV infection [3, 14, 15, 22, 25, 27]. The prevalence of congenital CMV and the severity of adverse neurological outcome in this group of infants make this a major public health problem. Because of the paucity of information, we have undertaken a study of SCCMV, to document the diversity of the clinical presentation, describe the range of sequelae and severity of the adverse outcomes.

Methods

Patient population Patients with congenital CMV were identified through the Congenital Infections Clinic, the Cytomegalovirus Registry and a search of the databases at The Hospital for Sick Children, Toronto, which serves as a regional referral hospital to a region having approximately 70,000 births per year. Infants were included if they had definite SCCMV infection which is defined as CMV detected in urine, saliva, secretions or tissue obtained within the first three weeks of life in a newborn with any clinical manifestations of an intrauterine infection and were registered in the database from 1987–2000. CMV was detected by shell vial rapid detection of early antigen fluorescent foci technique (DEAFF) [26]. This study had approval of the institutional ethics and research review board.

Data collection Baseline data obtained included demographic information, maternal, perinatal and neonatal history, clinical information from history, physical examination laboratory, neuro-imaging and neuro-physiological findings. More than 50 variables were collected from patient records. Outcome data included hearing and vision test results, results of developmental and clinical tests, neurological, intellectual, motor function evaluation including Bayley (Psychological Corp, San Antonio, TX, USA) and other tests of cognitive function, and functional level as described in the activities of daily living (ADL) and growth parameters at 1 year, 2 years and, if available, at 5 years of age. Definitions are provided in the Appendix.

The primary outcome was neurodevelopmental and classified as normal or adverse outcome groups. The adverse outcome group was defined as one or more of the following: death, moderate or severe cerebral palsy, moderate or severe developmental delay (Bayley score of <2SD for age (<70) or untestable), blindness or deafness at 2 years of age. Outcome data at later ages are also obtained to obtain a spectrum of severity and also to capture minimal disabilities.

Data description and analysis The clinical, laboratory, neuro-physiological, imaging and outcome data were computed and the data were described using means, medians and standard deviations for continuous variables and percentages for categorical variables. The demographic and clinical characteristics were compared based on their different outcome variables. Fisher's exact or Chi square tests were used to determine significant differences between potential categorical risk factors and outcomes. Univariate and bivariate associations were explored using logistic regression on the variables of potential continuous risk factors to assess their relationship to outcomes. All analyses were performed using the SAS statistical software package (SAS institute, Cary, NC, USA).

Results

Of the 104 patients identified as SCCMV, 42 infants were included. Exclusions were due to misdiagnosis of possible SCCMV, where the diagnosis was not within three weeks of life or difficulty in proving the CMV infection was congenital and not postnatally acquired and when they were asymptomatic. The male:female ratio was 1:1.4. Three patients (7%) died and one child was lost to follow-up. Causes of death were pneumonia and respiratory failure, cyanotic congenital heart disease and unknown in a

Table 1 Clinical characteristics of SCCMV

Characteristics	Result: *N* (%)
Maternal age (*n*=34)	29.2 years±5.4
Maternal ethnicity	
Caucasian	20 (47)
African-American	8 (19.1)
Others (Hispanics, Asian)	12 (29)
Maternal parity—Primiparous	18/41 (44)
Mode of delivery—Vaginal	27 (74)
Prematurity (<37 weeks)	9/42 (21)
Small for gestational age	18/42 (43)
Female	25 (60)
Mean gestational age (Range)	37.5 weeks±3.4 (28–42)
Mean birth weight (Range)	2.56 kg±0.8 (0.6–4.1)
APGAR @ 5 min	7.9±1.4 (5–9)
Petechiae	19/42 (45)
Hepatomegaly (>3 cm below LCM)	19/42 (45)
Splenomegaly (palpable)	19/42 (45)
Microcephaly (<2SD below mean)	15/41 (37)
Early seizures (onset<6 months)	5/38 (13)
Late seizures	6/38 (16)
Hypotonia	8/42 (19)
Early hearing loss	15/40 (38)
Late hearing loss	7/38 (18)
Chorioretinitis	6/42 (14)
Elevated ALT	19/40 (48)
Elevated AST	21/42 (50)
Thrombocytopenia	21/42 (50)
Conjugated hyperbilirubinemia	20/42 (47)
Abnormal BAER	15/41 (38)
Abnormal EEG	14/21 (67)
Abnormal cranial US	24/41 (56)
Abnormal head CT scan	29/41 (71)
Cerebral calcification	21/42 (50)
Abnormal brain MRI	17/19 (89)
Abnormal visual evoked potentials	10/23 (43)
Ventriculomegaly	11/41 (26)
Abnormal SSEP	5/7 (71)

severely impaired older infant who died at home and occurred at ages 2 weeks, 1 month and 6 months, respectively. The clinical characteristics of this cohort are summarised in Table 1. The mean maternal age was 29.2 years±5.4. There were 9 (21%) preterm infants. Hepatosplenomegaly, petechia and microcephaly were the most common initial presenting features. Ophthalmologic findings included cataract in 7% (3/42), corneal opacity in 7% (3/42), retinal hemorrhage in 5% (2/42), retinal scars in 8% (3/38) and Peters' anomaly in 2% (1/42). Other anomalies included Pierre Robin sequence in 2% (1/42), inguinal hernias in 7% (3/42), pneumonitis in 7% (3/42), hypothyroidism, in 2% (1/38), dental enamel defects in 11% (4/38), persistent pulmonary hypertension in 2% (1/42), ventricular septal defect in 5% (2/42), Fallot's tetralogy in 2% (1/42) and complex cyanotic congenital heart disease in 2% (1/42). Abnormalities on imaging included cerebral atrophy, hydrocephalus, pachygyria, periventricular white matter defects, polymicrogyria, lissencephaly, ventriculomegaly, intracranial calcifications, cerebellar asymmetry and hypoplasia and absence of the corpus callosum. Outcomes and severity of neurological deficits are summarised in Table 2. The mean duration of follow-up was 4.3 years±2.3 (Range: 2–13 years). Among those with hearing loss, it was bilateral and moderate to severe (>50 db) in 17/38 (46%). There were 16/38 (43%) patients who had hearing aids and two with cochlear implants and 6 patients who were bedridden or wheelchair bound.

Table 3 summarizes the associations of adverse outcomes with initial presenting signs. Univariate analysis did not show any statistically significant association between the potential risk factors and outcome variables. However bivariate association did show statistically significant associations and there was a significant risk of adverse outcome if there was abnormal BAER (OR 8.7), abnormal head ultrasound (OR 8.5) or abnormal brain CT scan (OR 21.0) at presentation.

Discussion

The common clinical presentations of SCCMV in our cohort include intrauterine growth retardation (IUGR), purpura, jaundice, hepatosplenomegaly, microcephaly, hearing impairment and thrombocytopenia. Reticuloendothelial system signs like hepatosplenomegaly, anaemia, petechiae and lymphadenopathy are transient and differences in incidence are due to the difference in the timing of examination. Similarly, incidence of microcephaly varies (20–50%) if HC was recorded at birth or early in presentation rather than later [1, 6, 13, 26, 19]. It is generally presumed that infants born with SCCMV infection have a poor prognosis as up to 90% of symptomatic infants will have neurological sequelae and the mortality rate can range from 2–30% [6, 19, 26]. A bimodal distribution of intelligence and developmental scores, with one profoundly affected group having a mean IQ of 29 and the other a mean IQ of 92 has also been reported [8].

The mortality of 7% represents in-hospital mortality, but as loss to follow-up was small, it would not be expected to increase significantly and 71% of this cohort had 1 or more adverse outcome. The reasons for these differences in reported outcomes include variation in choice and timing of endpoints use of either motor assessment or cognitive assessment. Infants referred to tertiary centers, as in our study, are a highly selected population and severely affected infants are more likely to be included. Prospective ascertainment and follow-up of infants also suffers from selection bias as universal screening is not generally performed.

Table 2 Outcome and neurological deficits in SCCMV infection

Clinical finding and deficits (minimum 2 years of age)	*N*=38 (%)
Early hearing loss	15 (38)
Late hearing loss	7 (18)
Moderate/severe hearing loss	17 (45)
Visual loss (cortical=3)	4 (11)
Bayley<2SD / cognitive deficit	27 (71)
Mild motor deficit	9 (25)
Moderate motor deficit	12 (31)
Severe motor deficit	10 (26)
Deaths	3/42 (7)
Abnormal ophthalmologic exam	19 (50)
Developmental delay	32 (84)
Institutionalized	9 (25)
G-tube placement	9 (25)
Speech delay	30 (79)
Hearing aids	16 (42)
Cochlear implants	2 (5)
Bedridden or wheelchair bound	6 (16)

The present study extends the findings of other cohort studies which are limited by follow-up periods to 1 or 2 years or single follow-up visits or lack of detailed evaluations [2, 4, 6, 8, 19]. Long term follow-up is essential as some of the major neurological deficits improve with time and other deficits like cognitive, learning disabilities, dyslexia, hyperactivity-inattention syndromes and behavioral difficulties become apparent as children grow older, at school age or later. SNHL not identified by early testing can be found at a later age and pre-existent SNHL can worsen suggesting progressive neural damage. Our series shows that early SNHL was seen in 38% and later loss detected in a further 18%. This compares with an earlier study, which detected early SNHL at birth in 5.2% of all infected children, including ACCMV, but late-onset disease at 6 years in 15.4% of children [10]. The risk factors for an adverse outcome included abnormalities on neuroimaging and BAER at presentation.

Infection in utero can occur in 35–40% of cases after primary infection and it is also more severe but CCMV occurs in 1–2% of pregnant women with previous infection due to chronic infection, reactivation or reinfection with a new strain. Although controversial, there are groups advocating pre-conceptional screening, so that the sero-negative pregnant woman can be monitored closely for sero-conversion and for amniotic fluid HCMV [7, 12, 17].

To prognosticate, retrospectively, in SCCMV it is helpful in determining the sero-status of mothers during pregnancy from stored blood samples, but in view of the length of time spread it was not possible in this cohort. Ganciclovir has now been shown to prevent hearing deterioration at 6 months of age when treatment was started in the neonatal period and continued for at least 6 weeks but the need for intravenous access, prolonged duration, costs and adverse effects need to be considered [14, 25]. From a public health perspective, it is imperative that we focus on prevention of CCMV and, apart from hygiene and the detection of pre-conceptional immunity, an effective vaccine is the most important element. The cost and burden of SCCMV can be reduced markedly only if a safe and effective vaccine is developed. Currently, work is being done on recombinant Towne strains, gB glycoprotein, Vactor and DNA vaccines [12, 18, 20].

In this cohort of SCCMV, we have identified a diverse presentation with very severe neurological outcome and some children who have progressive deficits. This study consequently reinforces the need for all children with CCMV to have long term follow up at least till their school years, when more comprehensive assessments can be done. The major challenge for primary care physicians will be to ensure this long term follow up.

Table 3 Bivariate association of adverse outcome and initial presenting signs

	Normal (*N*=12)	Adverse (*N*=30)	Fisher's exact or Chi-square test	Odd's ratio
Microcephaly	4	11	*P*=0.3	
Splenomegaly	9	10	*P*=0.5	
Chorioretinitis	2	4	*P*=0.6	
Thrombocytopenia	8	13	*P*=0.4	
Abnormal AST	10	11	*P*=0.5	
Abnormal BAER	1	14	*P*<0.01	8.7 (1.5–48)
Abnormal HUSS	4	20	*P*<0.01	9 (1.6–55)
Abnormal CT	3	27	*P*<0.001	21 (2.5–195)
Abnormal EEG	2	12	*P*=0.09	
Abnormal MRI	3	14	*P*=0.3	

Adverse outcome group was defined as one or more of the following: death, moderate or severe cerebral palsy, moderate or severe developmental delay (Bayley score of <2SD for age (<70) or untestable), blindness or deafness at two years of age

Appendix

Definitions

Sensorineural Hearing Loss: unequivocal failed or >30 db hearing loss on two or more age-appropriate audiologic tests (soundfield or pure tone audiometry) and middle ear disease ruled out or use of hearing aids in one or both ears

Visual impairment: blindness in one or both eyes or the need for corrective lenses

Blindness: visual acuity in both eyes of less than 6/60

Abnormal ophthalmologic exam: chorioretinitis, retinal scars, cataracts and other anomalies, like high myopia, strabismus, glaucoma, corneal opacities

Neuro-developmental delay: delay of more than 2SD below the mean for age (<70) when assessed by the Bayley Scales of Infant Development or equivalent scale

Abnormal CT scan of brain: cortical atrophy, cortical dysgenesis/dysplasia, moderate to severe ventriculomegaly/ hydrocephalus, cerebellar hypoplasia/asymmetry, migration abnormalities, intracranial calcifications (any one). Isolated abnormalities like subependymal, choroidal cysts, cephalhematoma were not included as an abnormal scan

Abnormal head ultrasound scan of brain: moderate to severe ventriculomegaly/hydrocephalus intracranial calcifications (any one). Presence of subependymal and choroidal cysts were also noted but not included as abnormal scan

Abnormal MRI scan of brain: the presence of any of the following: cortical atrophy, cortical dysgenesis, moderate to severe ventriculomegaly/ hydrocephalus, cerebellar hypoplasia/asymmetry, migration abnormalities, intracranial calcifications, pachygyria, lissencephaly (any one)

Abnormal EEG: abnormal background activity, assymmetric background activity, burst suppression or focal abnormality or if electrographical seizures, rolandic sharp waves (any one)

Cerebral Palsy: nonprogressive central nervous system disorder characterised by abnormal motor tone in at least one extremity and a decreased range or abnormal control of movement or posture, accompanied by neurologic signs

Microcephaly: HC<2SD below mean for age

SGA: birth weight<2SD below mean for gestational age

SCCMV infection: CMV detected in urine, saliva, secretions or tissue obtained within the first three weeks of life in a newborn with any clinical manifestations of an intrauterine infection including one or more of the following: petechiae or purpura, splenomegaly, hepatomegaly, jaundice at birth, microcephaly (<2SD), chorioretinitis, unexplained neurologic abnormalities, seizures, small for gestational age (SGA) or intrauterine growth retardation (<2SD), intracranial calcifications, hearing impairment, thrombocytopenia<100,000 mm^3, alanine aminotransferase (ALT) >100 IU/dl, aspartate aminotransferase (AST)>100 IU/dl, conjugated hyperbilirubinemia>3 mg/dl

References

1. Ahlfors K, Ivarsson SA, Bjerre I (1986) Microcephaly and congenital cytomegalovirus infection: a combined prospective and retrospective study of a Swedish infant population. Pediatrics 78(6):1058–1063
2. Ahlfors K, Ivarsson SA, Harris S (1999) Report of a long-term study of maternal and congenital cytomegalovirus infection in Sweden. Review of prospective studies available in the literature. Scand J Infect Dis 31(5):443–457
3. American Academy of Pediatrics (2003) Cytomegalovirus. In: Pickering LK (ed) Red book: report of the committee on infectious diseases, 26th edn. American Academy of Pediatrics, Elk Grove Village, Illinois, pp 59
4. Bale JF, Blackman JA, Sato Y (1990) Outcome in children with symptomatic congenital cytomegalovirus infection. J Child Neurol 5(2):131–136
5. Barbi M, Binda S, Primache V, Clerici D (1998) Congenital cytomegalovirus infection in a northern Italian region. NEOCMV Group. Eur J Epidemiol 14(8):791–796
6. Boppana SB, Pass RF, Britt WJ, Stagno S, Alford CA (1992) Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. Pediatr Infect Dis J 11(2):93–99
7. Burny W, Liesnard C, Donner C, Marchant A (2004) Epidemiology, pathogenesis and prevention of congenital cytomegalovirus infection. Expert Rev Anti Infect Ther 2(6):881–894
8. Conboy TJ, Pass RF, Stagno S, Alford CA, Myers GJ, Britt WJ, McCollister FP, Summers MN, McFarland CE, Boll TJ (1987) Early clinical manifestations and intellectual outcome in children with symptomatic congenital cytomegalovirus infection. J Pediatr 111(3):343–348
9. Demmler GJ (1994) Congenital cytomegalovirus infection. Semin Pediatr Neurol 1(1):36–42
10. Fowler KB, McCollister FP, Dahle AJ, Boppana S, Britt WJ, Pass RF (1997) Progressive and fluctuating sensorineural hearing loss in children with asymptomatic congenital cytomegalovirus infection. J Pediatr 130(4):624–630
11. Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA (1992) The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med 326(10):663–667
12. Griffiths PD (2002) Strategies to prevent CMV infection in the neonate. Semin Neonatol 7(4):293–299
13. Ivarsson SA, Jonssson K, Jonsson B (2003) Birth characteristics and growth pattern in children with congenital cytomegalovirus infection. J Ped Endocrin 16(9):1233–1238
14. Kimberlin DW, Lin CY, Sanchez PJ, Demmler GJ, Dankner W, Shelton M, Jacobs RF, Vaudry W, Pass RF, Kiell JM, Soong SJ, Whitley RJ, National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group (2003) Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. J Pediatr 143(1):16–25
15. Michaels MG, Greenberg DP, Sabo DL, Wald ER (2003) Treatment of children with congenital cytomegalovirus infection with ganciclovir. Pediatr Infect Dis J 22(6):504–509
16. Morita M, Morishima T, Yamazaki T, Chiba S, Kawana T (1998) Clinical survey of congenital cytomegalovirus in Japan. Acta Paediatr Jpn 40(5):432–436

17. Pass RF (2001) Cytomegalovirus infection. In: Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, Straus SE (ed) Field's virology, 4th edn. Lippincott-Williams & Wilkins, Philadelphia, PA, pp 2675–2705
18. Pass RF, Burke RL (2002) Development of cytomegalovirus vaccines: prospects for prevention of congenital CMV infection. Semin Pediatr Infect Dis 13(3):196–204
19. Pass RF, Stagno S, Myers GJ, Alford CA (1980) Outcome of symptomatic congenital cytomegalovirus infection: results of long-term longitudinal follow-up. Pediatrics 66(5):758–762
20. Plotkin SA (2004) Congenital cytomegalovirus infection and its prevention. Clin Infect Dis 38(7):1038–1039
21. Ramsey MEB, Miller E, Peckhan CS (1991) Outcome of confirmed symptomatic congenital cytomegalovirus infection. Arch Dis Child 66(9):1068–1069
22. Revello MG, Gerna G (2002) Diagnosis and management of human cytomegalovirus infection in the mother, fetus, and newborn infant. Clin Microbiol Rev 15(4):680–715
23. Rivera LB, Boppana SB, Fowler KB, Britt WJ, Stagno S, Pass RF (2002) Predictors of hearing loss in children with symptomatic congenital cytomegalovirus infection. Pediatrics 110(4):762–767
24. Ross SA, Boppana SB (2005) Congenital cytomegalovirus infection: outcome and diagnosis. Semin Pediatr Infect Dis 16(1):44–49
25. Schleiss MR (2005) Antiviral therapy of congenital cytomegalovirus infection. Semin Pediatr Infect Dis 16(1):50–59
26. Stagno S (2001) Cytomegalovirus. In: Remington JS, Klein JO (ed) Infectious diseases of the fetus and newborn infant, 5th edn. Saunders Philadelphia, PA, pp 389–424
27. Whitley RJ (2004) Congenital cytomegalovirus infection: epidemiology and treatment. Adv Exp Med Biol 549:155–160