Spectrum of Disease and Outcome in Children with Symptomatic Congenital Cytomegalovirus Infection

A. Mackenzie Dreher, MD[1], Nitin Arora, MD[1], Karen B. Fowler, DrPH[1,2], Zdenek Novak, MD[1], William J. Britt, MD[1,3], Suresh B. Boppana, MD[1,3], and Shannon A. Ross, MD, MSPH[1,3]

Objective To evaluate differences in presentation and outcomes in children with symptomatic congenital cytomegalovirus (cCMV) identified on newborn screening (screened group) and those identified based on clinical findings at birth (referred group).

Study design Data on 178 infants with symptomatic cCMV were analyzed. Demographic characteristics, clinical and laboratory findings documented in the nursery, and sequelae data were compared between the screened and the referred groups using χ^2 or Fisher exact test.

Results Two or more clinical findings were detected at birth in 91% of referred infants, and only 58% of screened infants ($P < .001$). Significantly more children in the referred group had hearing loss compared with screened infants ($P = .009$). Fifty-one percent of screened children were free of sequelae compared with only 28% of the referred group ($P < .003$).

Conclusions Infants with symptomatic cCMV identified based on clinical suspicion have more severe disease at birth and more commonly have sequelae than those identified on newborn screening. Inclusion of referral infants in many previous reports may have overestimated the severity of disease because of selection bias. Defining the complete spectrum of symptomatic disease due to cCMV and providing precise estimates of disease burden can only be gathered from large newborn screening studies. *(J Pediatr 2014;164:855-9)*.

Congenital cytomegalovirus (cCMV) infection is the most common congenital viral infection, affecting 20 000-40 000 infants in the US annually.[1] Only 10%-15% of the infected infants have clinical abnormalities at birth (symptomatic infection).[2] However, not all symptomatic infants are recognized to have cCMV in the nursery because findings at birth sometimes are subtle and nonspecific. Infants with symptomatic cCMV are more likely to have long-term sequelae with estimates of adverse outcomes ranging from 50% to 90% compared with 10%-15% of infants with cCMV without clinical abnormalities (asymptomatic infection).[2-11] Common sequelae include sensorineural hearing loss (SNHL), cognitive and motor deficits, seizures, and chorioretinitis. Although long-term outcome in children with cCMV has been described previously, there are limited data on infants with symptomatic cCMV identified by newborn screening.[12-14]

There has been increased interest in newborn cytomegalovirus (CMV) screening so that infants at risk for SNHL could be identified early in life. Newborn CMV screening would lead to identification of asymptomatic infants as well as symptomatic infants with milder or nonspecific clinical findings who would have been missed without screening. The outcome data from natural history studies that included predominantly infants detected based on obvious clinical findings of cCMV may not accurately represent the spectrum of the disease due to selection bias. Limited data suggest that neonates with symptomatic cCMV identified on newborn CMV screening have milder disease and their sequelae rates are lower than those in the published data from studies that included children who were primarily identified based on clinical suspicion in the nursery.[15] To evaluate the differences in clinical findings at birth and outcome among symptomatic infants with cCMV identified on newborn screening and those based on clinical suspicion, we analyzed the data from a long-term follow-up study of children evaluated at the University of Alabama at Birmingham (UAB) Hospitals between 1980 and 2002.

Methods

The study population consisted of 178 children with symptomatic cCMV enrolled in a longitudinal follow-up study. An additional 9 children were found to have cCMV but were not enrolled in follow-up (7 died and 2 were lost to follow-up). Data on asymptomatic infants from this population have been described in previous published studies.[16-18] Infants were classified as having symptomatic cCMV when

AST	Aspartate aminotransferase
cCMV	Congenital cytomegalovirus
CMV	Cytomegalovirus
SNHL	Sensorineural hearing loss
UAB	University of Alabama at Birmingham

From the Departments of [1]Pediatrics, [2]Epidemiology, and [3]Microbiology, the University of Alabama at Birmingham, Birmingham, AL

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they were positive for CMV within the first 3 weeks of life and had any findings suggestive of congenital infection, including jaundice, petechiae, purpura, hepatosplenomegaly, seizures, chorioretinitis, and microcephaly.[2] Laboratory findings considered abnormal included thrombocytopenia (platelets <100 000/mm^3), elevated aspartate aminotransferase (AST >80 IU/ml), and direct hyperbilirubinemia (direct bilirubin >2 mg/dL). Clinical and laboratory findings documented in the newborn nursery were recorded on a standard case report form for all children with cCMV during the study period from the birth records, and this information was used to classify infected children as symptomatic.[2]

Enrolled symptomatic infants were categorized into 2 groups based on the way in which they were identified. Newborns were considered to be in the screened group if they were identified through routine virological screening of all newborns at a UAB hospital (1980-2002) and a smaller subset of newborns at a private community hospital (1980-1996) and had findings consistent with symptomatic cCMV at birth. Infants were considered to be referred if they were identified by physicians as having cCMV based on findings suggestive of congenital infection in the newborn period that led to virological testing and were referred to us for evaluation and follow-up. Infants in the referred group were born at surrounding regional hospitals during the study period. The study was approved by the UAB Institutional Review Board and Informed consent was obtained from parents or legal guardian of the infants enrolled in the study.

Congenital infection in the referred patients was confirmed by the isolation of virus in our laboratory within the first 3 weeks of life. Newborn CMV screening was carried out by testing urine or saliva specimens from infants using culture-based methods. Between 1980 and 1990, newborns were screened for CMV by testing urine samples using the standard tube culture method.[19] The screening protocol was modified in January 1990 to include testing of newborn saliva specimens.[9,20] Beginning in January 1993, newborn saliva samples were tested for CMV via a rapid culture method for the detection of early antigen fluorescent foci.[9]

Children enrolled in the study were followed in a multidisciplinary clinic at UAB as part of a natural history study. Serial audiologic, visual, and neurologic examinations were performed using previously described protocols.[21] Patients were evaluated quarterly during their first year, twice yearly until 3 years of age, and then yearly through the completion of the study.[3] Audiologic evaluations were performed in the newborn period and every 6 months until 24 months of age and then annually. SNHL was defined as air conduction thresholds >25 dB on auditory brainstem response audiometry or >20 dB on behavioral audiometric evaluations appropriate for child's developmental level in conjunction with normal bone conduction thresholds and normal middle ear function.[21,22] Delayed SNHL was defined as having ≥1 hearing evaluations with normal threshold documented for each ear before SNHL was detected.[16] Developmental and intellectual evaluations were administered using standard psychometric tests appropriate for age, perceptual function, and physical abilities[16,21]. The protocol for the follow-up of children with cCMV remained the same during the study period. The average length of follow-up of was 4.6 ± 3.77 years (mean ± SD) and did not differ between screened and referred infants.

The demographic data, newborn clinical findings, and follow-up data were maintained in SAS 9.3 for Windows data sets (SAS Institute, Cary, North Carolina). The demographic, newborn clinical characteristics, and sequelae data were compared between the referred and screened group of children, and statistical significance was determined using χ^2 or Fisher exact test, where appropriate.

Results

Of the 178 children with symptomatic cCMV enrolled in follow-up between January 1980 and January 2002, 78 infants were identified on newborn virologic screening and the remaining 100 infants were referred from other hospitals. The demographic characteristics were compared between screened and referred children, and the results are shown in Table I. Infants in the screened group were more likely to be African American, born prematurely, and born to single mothers and to have received prenatal care at a public health clinic. The study children in the referred group were more likely to be white and born to married parents and to have received prenatal care from a private health care provider. Sex of the newborn, maternal age at delivery (>20 or ≤20 years), and number of previous pregnancies did not differ between the 2 groups.

Table II shows a comparison of newborn clinical findings between the screened and referred groups. Petechiae was the most common finding in both groups, but a significantly higher proportion of referred infants (74%) than screened infants (55%) had this finding (P = .006). Jaundice, hepatosplenomegaly, purpura, microcephaly, and small for gestational age also were seen in significantly higher proportions of referred infants. Seizures were seen in 7% of referred infants and 1% of screened infants (P = nonsignificant). A significantly higher proportion of screened infants had only a single clinical finding compared with the referred group, who were more likely to have ≥2 findings (P < .001; Table II). Among children who had a single clinical finding at birth in both groups, petechial rash was the most common finding seen in 21 of 33 (63%) screened infants and 4 of 8 (50%) of the referred group (P = nonsignificant). Microcephaly was the next most common single clinical finding seen in 8 of 33 (24%) screened and 3 of 8 (38%) referred infants.

Thrombocytopenia occurred significantly more frequently in the referred patients compared with the screened group (P < .001; Table III). Among the children with neuroimaging studies, there was no difference in the proportion of subjects with abnormal imaging findings, including intracranial calcifications, between the 2 groups.

The long-term outcome for the study children is presented in Table IV. Overall, approximately one-half (36 of 71) of the