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

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Abstract

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 ($p < 0.001$). Significantly more children in the referred group had hearing loss compared with screened infants ($p = 0.009$). Fifty-one percent of screened children were free of sequelae compared with only 28% of the referred group ($p < 0.003$).

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.

Keywords

hearing loss; sequelae; screening; referred

Congenital cytomegalovirus infection (cCMV) is the most common congenital viral infection affecting 20,000 to 40,000 infants in the United States 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

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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% to 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 CMV screening so that infants at risk for SNHL could be identified early in life. Newborn CMV screening would not only lead to identification of asymptomatic infants but also 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 suggests that neonates with symptomatic cCMV identified on newborn CMV screening have milder disease and their sequelae rates are lower than 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 not enrolled in follow-up (7 died and 2 were lost to follow up). Data on asymptomatic infants from this population has been described in prior published studies.¹⁶⁻¹⁸ Infants were classified as having symptomatic cCMV when 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/mm³), elevated aspartate aminotransferase (AST >80 IU/ml), and direct hyperbilirubinemia (direct bilirubin >2mg/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 two groups based on the way in which they were identified. Newborns were considered to be in the screened group if they were identified by routine virologic screening of all newborns at 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 referred if they were identified by physicians as having cCMV based on findings suggestive of congenital infection in the newborn period that led to virologic testing and referred to us for evaluation and follow-up. Infants in the referred group were born at surrounding regional hospitals during the study period. 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 by 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 three 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 sensorineural hearing loss was defined as having one or more 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} Children were followed every 6 months up to 3 years of age and yearly afterwards. 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 $\pm$ 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, NC). 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 1. Infants in the screened group were more likely to be African American, born prematurely, born to single mothers, and received prenatal care at a public health clinic. The study children in the referred group were more likely to be white, born to married parents, and received prenatal care from a private health care provider. Sex of the newborn, maternal age at delivery (greater than or less than 20 years), and number of previous pregnancies were not different between the two groups.

Table III 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 ($p=0.006$). Jaundice, hepatosplenomegaly, purpura, microcephaly, and small for gestational age also were seen in significantly higher proportion of referred infants. Seizures were seen in 7% of referred infants and 1% of screened infants ($p=NS$). 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 or more findings ($p<0.001$; Table II). Among children who had a single clinical finding at birth in both groups, petechial rash was the most common finding seen in 21/33 (63%) screened infants and 4/8 (50%) of the referred group

($p=NS$). Microcephaly was the next most common single clinical finding seen in 8/33 (24%) screened and 3/8 (38%) referred infants.

Thrombocytopenia occurred significantly more frequently in the referred patients compared with the screened group ($p < 0.001$; 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 two groups.

The long-term outcome for the study children is presented in Table 4. Overall, one-half (36/71) of the screened group was free of sequelae on follow-up, compared with only 28% (24/86) of referred children ($p < 0.003$). Among infants evaluated for sequelae, the referred group was twice as likely to have multiple sequelae compared with the screened group ($p = 0.01$). Referred children were more likely to have SNHL than the screened children, and among those with hearing deficits, children in the referred group were significantly more likely to have bilateral hearing loss. There was no difference, however, in the incidence of progressive or delayed-onset hearing loss between screened and referred infants. Of the children who underwent psychometric testing, a higher proportion of children (28/60, 47%) in the referred group had $IQ < 70$ compared with the screened group (10/40, 25%, $p = 0.03$). Similarly, infants in the referred group were more likely to have seizures compared with the screened group ($p = 0.04$). The presence of motor abnormalities and chorioretinitis was not significantly different between the two groups.

Since SNHL is the most common sequela and hearing outcome was known for most study children, we compared the frequency of SNHL between children with a single clinical finding at birth and those with multiple findings. Significantly fewer infants with a single clinical finding (12/41, 31%) developed SNHL compared with infants with multiple findings (68/129, 53%, $p = 0.02$). Of the 25 infants with petechiae as their only clinical finding at birth, 5 (20%) developed SNHL. None of the 25 infants with petechiae alone on presentation developed motor abnormalities and only one child had low IQ.

Of the 10 infants who died, 7 were not enrolled in the follow-up study. Four of these ten infants (40%) were screened and six (60%) were referred. The clinical and laboratory abnormalities in the deceased infants did not differ significantly between screened and referred populations (data not shown).

DISCUSSION

Studies estimating long-term outcome in children with symptomatic cCMV have reported varying rates of sequelae from 35% to 100%.^{2-5, 15, 23} The findings from the current study demonstrate that among children with confirmed cCMV, the sequelae rates vary significantly based on the clinical presentation at birth and whether infants were identified by newborn screening or by clinical suspicion. The proportion of children with various newborn clinical findings in the referred group was similar to the previously published data.^{2, 4, 6} In contrast, the proportion of screened infants with multiple clinical abnormalities was significantly lower than previously reported.^{2, 3} Except for seizures, at birth all of the clinical findings were significantly more frequent in children in the referred group than those in the screened group. Since only 8/178 children had seizures, the lack of significant difference between the two groups could be due to the small number of infants with this finding. The increased frequency of prematurity in the screened group is likely related to the underlying characteristics of the screened population. The mothers of screened infants consisted predominantly of low income, single, African American women with higher rates of preterm deliveries.²⁴⁻²⁶

Along with more severe clinical disease at birth, children in the referred group also had a higher frequency of sequelae. Early studies of natural history of cCMV have reported that 50% to 90% of symptomatic infants develop sequelae.^{2, 4, 27} However, a recent review found the frequency of sequelae to be 40-58%.¹⁵ The differences in sequelae rates among the published reports may be attributable to inclusion in more recent studies of infants identified from newborn screening compared with early studies that included predominantly infants identified based on clinical suspicion.¹² Our finding that the percentage of children with >1 sequelae in the screened group was 21% compared with 42% in the referred group is consistent with this possibility.

SNHL is the most common sequelae of cCMV infection. Past studies have shown that approximately 22% to 65% of infants with symptomatic cCMV develop SNHL. It has been estimated that infants with symptoms at birth are 6 times more likely than those without symptoms to develop SNHL.^{8, 18} We found that 36% of children in the screened group developed hearing loss, which is at the lower end of prior estimates compared with 55% of referred infants. It is noteworthy that the incidence of SNHL in symptomatic infants with petechiae alone at birth was only 20%, which is similar to the rates of SNHL observed in children with asymptomatic cCMV.²¹ These findings argue in support of screening all newborns for cCMV. In addition to missing infants with asymptomatic cCMV, without newborn CMV screening, most infants with milder disease at birth would not be identified. Although the sequelae rates in children with cCMV identified on newborn screening were lower compared with the referred group, these children are still at significant risk for SNHL. Therefore, identifying these children early will allow appropriate evaluation, management, and early intervention measures to improve outcome.

Our study has some limitations. Not all infants underwent neuroimaging and laboratory evaluations because the initial evaluation and management of these infants was at the discretion of physicians caring for the infants in the newborn nursery. The absence of a standard evaluation protocol in the newborn period resulting in missing laboratory and imaging data for some of the infants raises the possibility that those undergoing a more thorough evaluation may have more severe disease than those who did not. Despite this limitation, significant differences were observed between the two groups in the frequency of clinical findings, elevated serum AST level and thrombocytopenia and long term sequelae. There were significant differences in demographic features between the two groups. These differences stemmed primarily from the fact that most infants in the screened group were born at a public hospital whereas most referred children were born at private hospitals. It is noteworthy that based on demographic characteristics the screened children would be expected to have poor outcomes²⁸, however we found better outcomes in these children compared with the referred group. This finding suggests that outcomes in children with cCMV are more likely based on the severity of newborn disease than underlying demographic characteristics. As there is increasing interest in screening all newborns for CMV, it is likely that more symptomatic infants with milder clinical disease will be identified and these children may be at a lower risk for sequelae than those infants diagnosed because of clinical suspicion.

Data presented here demonstrate that infants with multiple clinical findings at birth are at much higher risk for an adverse outcome when compared to those with a single clinical finding. This information is important for counseling parents and for future natural history and antiviral treatment studies. We anticipate that ongoing large newborn screening studies such as the NIDCD CMV and Hearing Multicenter Screening (CHIMES) study will provide more precise data that will allow for a better prediction of long-term outcome in children with cCMV. Finally, it could be useful to consider manifestations of cCMV in the newborn period as a continuum of disease and not limit the classification of cCMV to symptomatic or

asymptomatic infection. Therefore, a less rigorous categorization of infants with cCMV could permit not only more informative stratification of infected children in terms of the risk for the development of sequelae but also suggest different mechanisms of disease leading to different clinical findings and long term outcomes.

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Abbreviations

cCMV	Congenital cytomegalovirus
CT	computed tomography
SNHL	sensorineural hearing loss
UAB	The University of Alabama at Birmingham
AST	Aspartate Aminotransferase

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Table 1

Demographic characteristics of newborns with symptomatic congenital CMV infection identified based on newborn screening (screened) or clinical suspicion (referred)

	Screened (N= 78)	Referred (N= 100)	P-value
No (%)			
Female sex	36 (46)	44 (44)	NS
Race			
Black	59 (77)	27 (27)	<0.001
White	18 (23)	73 (73)	
Hispanic	1 (1)	0	
Premature Birth (< 37 weeks gestation)	27 (35)	21 (21)	0.04
Single Mother	54 (70)	35 (35)	<0.001
Maternal Age ≥ 20	46 (59)	46 (46)	NS
Prenatal Care			
Private	11 (14)	77 (77)	<0.001
Public Health Clinic	64 (82)	21 (21)	
None	3 (4)	1 (1)	
Insurance			
Private	11 (14)	48 (48)	<0.001
Medicaid	61 (79)	34 (34)	
None	5 (6)	15 (15)	
Previous Pregnancies			
0	40 (51)	40 (40)	NS
1	20 (26)	40 (40)	
2	18 (23)	20 (20)	

Table 2

Clinical findings in the newborns with symptomatic congenital CMV infection identified based on virologic screening (screened) or clinical suspicion (referred)

	Screened (N = 78)	Referred (N = 100)	P-value
No (%)			
Jaundice	31 (40)	59 (59)	0.009
Petechiae	43 (55)	74 (74)	0.006
Hepatosplenomegaly	13 (17)	57 (57)	<0.001
Purpura	2 (3)	17 (17)	0.002
Microcephaly	27 (35)	53 (53)	0.01
Seizures	1 (1)	7 (7)	NS
Small for Gestational Age *	21 (27)	48 (48)	0.004
Single Clinical Finding	33 (42)	8 (8)	<0.001
2 or more Clinical Findings	45 (58)	91 (91)	<0.001

* Weight less than 10th percentile for gestational age.

Table 3

Laboratory and imaging abnormalities in infants with symptomatic congenital CMV infection identified based on newborn screening (screened) or clinical suspicion (referred)

	Screened (N=78)	Referred (N=100)	P-value
Positive/Total Examined (%)			
Elevated Aspartate Aminotransferase (>80 IU/mL)	17/31 (55)	50/67 (75)	0.05
Thrombocytopenia (<100,000/mm ³)	22/58 (38)	64/89 (72)	<0.001
Direct Hyperbilirubinemia (>2mg/dL)	22/48 (46)	44/75 (59)	NS
Head CT Abnormalities	15/21 (71)	39/53 (74)	NS
Calcifications	10/21 (48)	31/53 (58)	NS

Table 4

Sequela in children with symptomatic congenital CMV infection identified based on newborn screening (screened) or clinical suspicion (referred)

	Screened (N=78)	Referred (N=100)	P-value
Positive/ Total Examined (%)			
Sensorineural Hearing Loss	28/78 (36)	52/93 (56)	0.009
Progressive	15/28 (54)	28/52 (54)	NS
Delayed	10/28 (36)	13/52 (25)	NS
Bilateral	14/28 (50)	39/52 (75)	0.02
IQ<70	10/40 (25)	28/60 (47)	0.03
Motor Abnormalities	11/70 (16)	27/99 (27)	NS
Chorioretinitis	7/77 (9)	16/89 (18)	NS
Seizures	9/78 (11)	23/98 (23)	0.04
No Sequelae	36/71 (51)	24/86 (28)	0.003
One Sequelae	19/71 (27)	26/86 (30)	NS
Two Or More Sequelae	16/71 (21)	36/86 (42)	0.01