Early predictors of neurodevelopmental outcome in symptomatic congenital cytomegalovirus infection

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Objective: To determine the ability of neonatal clinical, audiologic, and computed tomography (CT) findings to predict long-term neurodevelopmental outcome in children with symptomatic congenital cytomegalovirus (CMV) infection.

Methods: Longitudinal cohort study of children (n = 41) with symptomatic congenital CMV infection evaluated at birth and followed up with serial age-appropriate neurodevelopmental testing. The performance of birth characteristics as predictors of long-term outcome were determined, and clinical and CT scoring systems were developed and correlated with intellectual outcome.

Results: Microcephaly was the most specific predictor of mental retardation (100%; 95% CI 84.5-100) and major motor disability (92.3%; 95% CI 74.8-99). An abnormality detected by CT was the most sensitive predictor for mental retardation (100%; 95% CI 82.3-100) and motor disability (100%; 95% CI 78.2-100). A highly significant ($P < .001$) positive correlation was found between head size at birth and the intelligence/developmental quotient (IQ/DQ). Approximately 29% of children had an IQ/DQ >90. There was no association between sensorineural hearing loss at birth and cognitive outcome. However, children with sensorineural hearing loss on follow-up (congenital and late-onset) had a lower IQ/DQ ($P = .006$) than those with normal hearing.

Conclusions: The presence of microcephaly at birth was the most specific predictor of poor cognitive outcome in children with symptomatic congenital CMV infection, whereas children with normal findings on head CT and head circumference proportional to weight exhibited a good cognitive outcome. (J Pediatr 2001;138:325-31)

Cytomegalovirus, the most common cause of congenital infection in the United States, affects approximately 1% of all live births, or between 30,000 and 40,000 newborns annually; 85% to 90% will have an asymptomatic or "silent" congenital infection, and 10% to 15% will be symptomatic at birth.[1] Children with symptomatic congenital CMV may have neurologic involvement at birth and experience a poor neurodevelopmental outcome, but prediction of which infants will have developmental disabilities remains controversial.[2,3] Factors that have been associated with a poor neurodevelopmental prognosis include the presence of microcephaly, chorioretinitis, or neurologic abnormalities at birth.[4-7] Intracranial calcifications and other neuroradiologic abnormalities have also been associated with a poor outcome, although they did not always discriminate patients with a good outcome.[8-10]

CMV	Cytomegalovirus
CT	Computed tomography
DQ	Developmental quotient
HC	Head circumference
IUGR	Intrauterine growth retardation
SNHL	Sensorineural hearing loss

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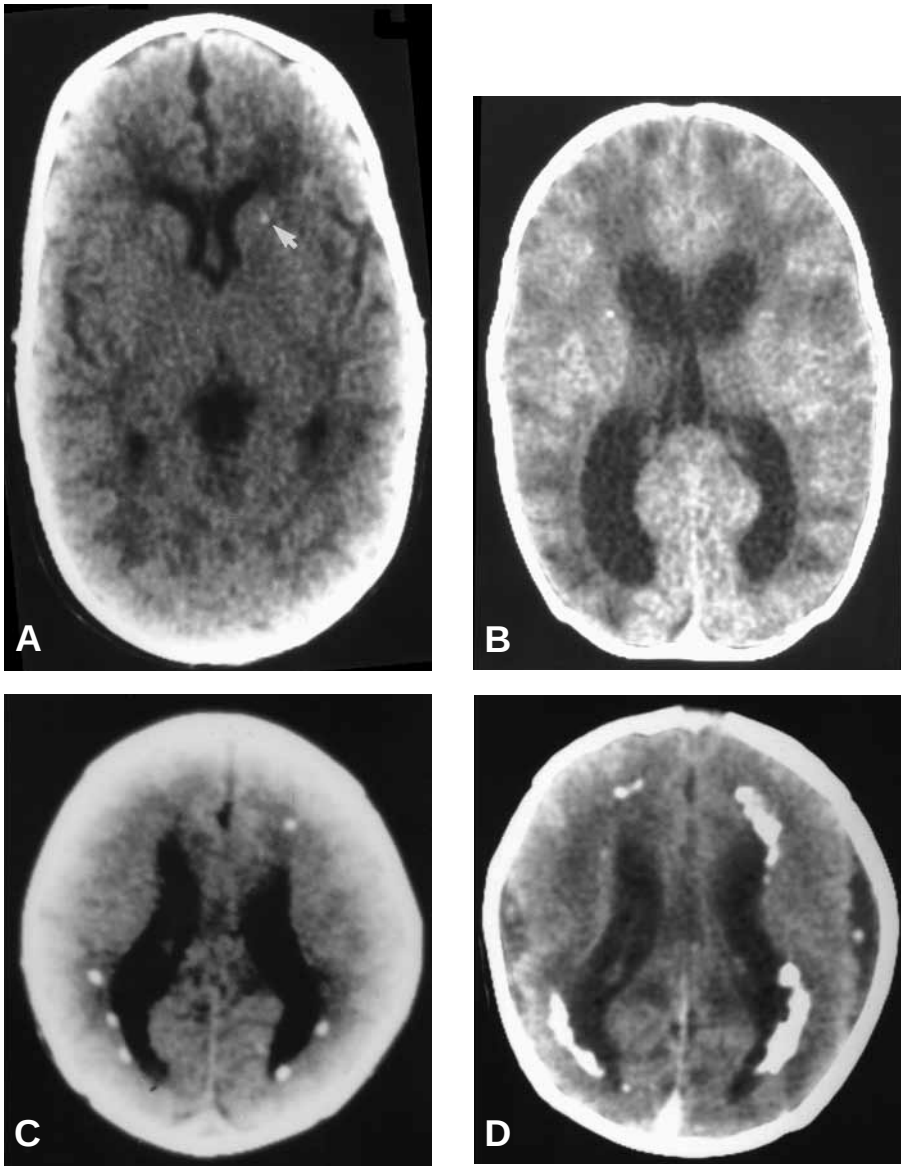

Figure. Head CT scans from children with congenital CMV disease illustrating the CT scan score system. **A,** Single punctate calcification is indicated by *arrow* (CT score = 1). **B,** Ventriculomegaly (CT score = 2). **C,** Multiple discrete periventricular calcifications and ventriculomegaly (CT score = 2). **D,** Extensive periventricular calcifications and brain atrophy (CT score = 3).

Because the predictive value of each of these factors, alone or in combination, as markers for prognosis has not been definitely established, we sought to evaluate carefully and thoroughly the clinical and radiographic findings in the newborn period as predictors of neurodevelopmental outcome in children with symptomatic congenital CMV infection. This information will be useful to parents, health-care workers, educators, and researchers who care for these children.

METHODS

Patient Population

All children with symptomatic congenital CMV infection enrolled in the Houston CMV longitudinal follow-up study, a multidisciplinary study on the long-term effects of CMV infection begun in 1982, were included in this study.[11,12] Patients <6 months of age or those lost to follow-up without neurodevelopmental studies were excluded. A patient was considered to have a confirmed symptomatic congenital CMV infection if CMV was isolated from urine or saliva during the first 3 weeks of life and at least one of the following abnormalities was present at birth: intrauterine growth retardation, hepatomegaly, splenomegaly, petechiae, jaundice, microcephaly, thrombocytopenia (platelet count $<75 \times 10^3/\mu L$), laboratory evidence of hepatitis (alanine aminotransferase level >100 U/L or direct bilirubin level >3 mg/dL), chorioretinitis, or deafness.[1] All patients had a complete physical examination, which included weight, length, and head circumference measurements.

Diagnostic Studies

All patients had unenhanced head CT scan, auditory brainstem responses, and ophthalmologic evaluations performed in the newborn period. Head CT scans were reviewed by at least 2 of the investigators and a pediatric neuroradiologist (P.G.), and findings were classified as normal or abnormal according to a consensus agreement regarding the presence of intracranial calcifications, periventricular radiolucencies, ventricular dilatation, or neuronal migration disorders.[9] Neuronal migration abnormalities consisted of CT evidence of pachygyria, lissencephaly, or cortical dysplasia. Hearing was evaluated at birth by auditory brainstem responses. A hearing threshold >30 dB was considered evidence of sensorineural hearing loss.

Definition of Microcephaly

IUGR was defined as birth weight <2 SDs from the mean for gestational age according to newborn growth curves.[13] Because HC has been shown to correlate more closely with weight than with gestational age,[14-16] particularly in patients with IUGR, HC was adjusted for degree of weight deficit before determining the presence of microcephaly by calculating a modified HC z score. The z scores for HC and weight were calculated by using means and SDs of each variable (HC and

weight) according to the gestational age[13] with the following formula:

$$z \text{ Score} = \frac{\text{Patient's measurement of variable} - \text{Mean of tested variable for gestational age}}{\text{SD of tested variable}}$$

The modified HC z score was then calculated by subtracting the weight z score from the HC z score. The modified HC z score indicated the number of SDs by which the HC differed from the mean in excess of the weight deficit. Infants with HC proportional to weight would have a modified HC z score of zero, whereas those with small heads relative to weight would have a negative modified HC z score. In this study, a modified HC z score less than –2 was considered microcephaly and represented HC smaller than 2 SDs from the mean, after adjustment for weight deficit.

CT Scoring System

The CT score was considered to be zero when CT showed no abnormalites or showed abnormalities deemed not related to CMV (such as cephalohematoma or isolated cyst); scores of 1 through 3 were assigned according to the degree of abnormalities as shown in the Figure.

Outcome Measures

Follow-up evaluation of patients included age-appropriate neurodevelopmental assessments performed by a developmental pediatrician and intellectual evaluations performed by a clinical psychologist. Instruments used according to developmental stage included the Bayley Scales of Infant Development,[17] Kaufman Assessment Battery for Children,[18] and Wechsler Intelligence Scale for Children-Revised.[19] For purposes of this study, the IQ/developmental quotient obtained at the latest evaluation was used. Outcome variables were normal intelligence (IQ/DQ ≥90), mental retardation (IQ/DQ <70), severe mental retardation (IQ/DQ <50), and the presence of major motor deficits. A major motor deficit was defined as the presence of motor abnormalities, such as hypertonia and spasticity, that impaired the ability of the patient to perform tasks of daily living.

Table I. Clinical, audiologic, and CT findings at birth in children with symptomatic congenital CMV infection

Birth characteristic	No. (%)
Sex	
Male	21 (51.2)
Female	20 (48.8)
Birth weight (g)	
Mean	2456
Range	1134-4224
Gestational age (wk)	
Mean	37.4
Range	33 - 41
Symptoms at birth	
Non-neurologic	
Anemia	3 (7.3)
Pneumonitis	3 (7.3)
IUGR	11 (26.8)
Jaundice	17 (41.5)
Hepatomegaly	23 (56.1)
Splenomegaly	23 (56.1)
Thrombocytopenia	28 (68.3)
Petechiae	31 (75.6)
Neurologic	
Seizures	3 (7.3)
Chorioretinitis	7 (17.1)
Microcephaly	8 (19.5)
Other neurologic abnormality*	15 (36.6)
Hearing loss	17 (41.5)
Intracranial calcifications	24 (58.5)
Abnormal CT scan†	32 (78)

IUGR, Intrauterine growth retardation; *CT,* computed tomography.
*Includes hypotonia, jitteriness, split sutures, immature primitive reflexes, and feeding difficulties.
†Includes white matter lucencies, ventriculomegaly, intracranial calcifications, destructive encephalopathy, brain atrophy, and neuronal migration disorders.

Validation of Results

To validate our results, we compared the predictive values of abnormalities detected by CT of our study population with that calculated from another cohort of children with virologicaly confirmed congenital CMV infection reported by Boppana et al.[10] In that study 56 children had head CT scans and were followed up prospectively to evaluate their intellectual function. Outcome measures correlated to CT scan findings included IQ <50, IQ <70 (reported for 36 subjects), and the presence of cerebral palsy (reported for 47 subjects).

Statistical Analysis

Statistical analysis was performed by using SPSS for Windows, version 7.0 (SPSS Inc, Chicago, Ill). Sensitivity, specificity, and positive and negative predictive values were calculated from 2 by 2 contingency tables with IQ/DQ

Table II. The ability of neonatal findings to predict neurodevelopmental outcome in children with symptomatic congenital CMV infection

			Predictive value	
	Sensitivity	Specificity	Positive	Negative
Major motor deficit				
Microcephaly	40*	92.3	75	72.7
Chorioretinitis	33.3	92.3	71.4	70.5
SNHL	40	57.7	35.2	62.5
Abnormal CT scan	100	34.6	46.8	100
IQ <70				
Microcephaly	42	100	100	66.6
Chorioretinitis	31.5	95.5	85.7	61.7
SNHL	42.1	59.1	47	54.1
Abnormal CT scan	100	40.9	59.3	100
IQ <50				
Microcephaly	46.7	96.2	87.5	75.7
Chorioretinitis	33.3	92.3	71.4	70.5
SNHL	46.7	61.5	41.1	66.6
Abnormal CT scan	100	34.6	46.8	100
IQ >90†				
Microcephaly	100	27.6	36.3	100
Chorioretinitis	100	24.1	35.2	100
SNHL	58.3	41.4	29.1	70.5
Abnormal CT scan	41.6	86.2	55.5	78.1

SNHL, Sensorineural hearing loss; *CT,* computed tomography.
*The 95% CIs were wide and ranged from 14.2 to 71.7.
†Ability of normal test or absence of physical findings to predict IQ >90.

at last follow-up as the reference standard. Patient characteristics and outcome data were analyzed by a 2-tailed Fisher exact test or χ^2 test as appropriate. Continuous variables were analyzed by the independent sample *t* test. A *P* value <.05 was considered significant.

RESULTS

Patient Follow-up

Children with symptomatic congenital CMV infection (n = 54) had been enrolled in the longitudinal study; 7 were <6 months of age at their last recorded visit; one died at 2½ months of age, and 5 were lost to follow-up. The remaining 41 children had neonatal and follow-up evaluations available for analysis and constitute the study population. The median age at last follow-up was 5.7 years (range, 11 months-13 years). Symptoms at birth of the study subjects were similar to those previously reported in children with symptomatic congenital CMV (Table I).[20,21]

Neurodevelopmental Outcome

Of the 41 children, 12 (29.2%) had an IQ/DQ of ≥90, 10 (24.3%) had an IQ/DQ of 70 to 89, 4 (9.7%) had an IQ/DQ of 50 to 69, 15 (36.5%) had an IQ/DQ of <50, and 15 (36.5%) had a major motor disorder on follow-up. All children with a major motor disorder had an IQ/DQ <70. Microcephaly at birth, present in 8 children, had the highest specificity (100%; 95% CI 84.5-100), whereas an abnormality detected by head CT had the highest sensitivity (100%; 95% CI 82.3-100) for the prediction of mental retardation (IQ/DQ <70) and/or major motor deficits (Table II). The absence of microcephaly had a high sensitivity (100%; 95% CI 73.5-100) but low specificity (27.6%; 95% CI 12.7-47.2) for the prediction of an IQ/DQ >90. Normal findings on CT scan had 86.2% specificity to predict such an outcome, but the sensitivity was only 41.6%. The predictive values of an abnormality detected by head CT were compared with those derived from another cohort of children with congenital CMV infection (Table III). All children with microcephaly had abnormalities detected by head CT and had a poor prognosis (mean IQ/DQ of 50.2 and a major motor deficit in 75%). Among children without microcephaly, those with normal findings on head CT had a good prognosis (mean IQ/DQ of 93.6 and a major motor deficit in 0%), whereas those with an abnormality detected by CT had an intermediate outcome (mean IQ/DQ of 72.3 and a major motor deficit in 37.5%).

Abnormalities were detected by head CT in 32 (78%) of the children, including white matter abnormalities (9), ventriculomegaly (15), intracranial calcifications (24), neuronal migration disorder defects (4), brain atrophy (4), and destructive encephalopathy (2). The presence of lucent white matter and a single punctate calcification was not associated with a greater likelihood of an IQ/DQ <70, whereas the presence of multiple, extensive periventricular calcifications, or parenchymal calcifications had a statistically significant association with an IQ/DQ <70 ($P < .02$). Cognitive, motor, and audiologic outcomes according to the CT score are shown in Table IV.

To determine whether there was a quantitative relationship between HC and IQ/DQ score, linear regression analysis between a modified HC *z* score and IQ/DQ score was performed. We found a highly significant positive correlation between these 2 variables ($R = 0.62$, $P < .001$) with a slope of 11.55. That is, for every increase in modified HC *z* score of 1 (1 SD), there was an increase of IQ score of 11.55, with at least 39% of this vari-

Table III. Value of abnormal CT scan in predicting poor neurodevelopmental outcome in children born with symptomatic congenital CMV disease from two longitudinal studies conducted in Houston and Birmingham[10]

			Predictive value	
	Sensitivity	Specificity	Positive	Negative
Cerebral palsy				
Present study (n = 41)	100 (78.2-100)	34.6 (17.2-55.6)	46.8 (29-65.2)	100 (66.3-100)
Boppana et al[10] (n = 47)	91.3 (71.9-98.9)	62.5 (40.5-81.2)	70 (50.6-85.2)	88.2 (63.5-98.5)
Two studies combined (n = 88)	94.7 (82.2-99.3)	48 (43.2-70.2)	58 (44.8-70.4)	92.3 (74.8-99)
IQ <70				
Present study (n = 41)	100 (82.3-100)	40.9 (20.7-63.6)	59.3 (40.6-76.3)	100 (66.3-100)
Boppana et al[10] (n = 36)	94.1 (71.3-99.8)	42.1 (20.2-66.5)	59.2 (38.8-77.6)	88.8 (51.7-99.7)
Two studies combined (n = 77)	97.2 (85.4-99.9)	41.4 (26.3-57.8)	59.3 (45.7-71.9)	94.4 (72.7-99.8)
IQ <50				
Present study (n = 41)	100 (78.2-100)	34.6 (17.2-55.6)	46.8 (29-65.2)	100 (66.3-100)
Boppana et al[10] (n = 36)	100 (75.2-100)	39.1 (19.7-61.4)	48.1 (28.6-68)	100 (66.3-100)
Two studies combined (n = 77)	100 (87.6-100)	36.7 (23.4-51.7)	47.4 (34.3-60.8)	100 (81.4-100)

Numbers in parentheses are 95% CIs.

ability attributed to difference in HC. This significant association persisted after multivariate linear regression analysis—including the presence of abnormalities detected by head CT, chorioretinitis, and neurologic abnormalities—was performed (P = .001).

Hearing Loss and Outcome

The presence of SNHL at birth had no predictive ability for neurodevelopmental outcome on follow-up, since the likelihood of a good intellectual outcome and/or major motor disorder was virtually identical in children with and without hearing loss detected at birth. However, hearing evaluations were also performed during follow-up of all children, and 11 children had late-onset SNHL detected for the first time after the newborn period. When children with SNHL detected at any time (17 congenital, 11 late-onset) were compared with the 13 children with normal hearing, significant differences in cognitive and motor functions were noted. The mean IQ/DQ score for children with SNHL was 65.3 compared with 88.7 for those without hearing deficits (P = .006), and 14 of those with SNHL (50%) had motor disabilities compared with one (7.7%) of those with normal hearing (P = .01). Children with SNHL were also more likely to have an abnormality detected by head CT (89.3%) than children with normal hearing (53.8%; P = .03) and had a higher mean CT score (2.1) than those with normal hearing (0.77; P < .001).

Table IV. Cognitive, motor, and audiologic outcome in children with symptomatic congenital CMV infection according to head CT scan score

	Mean IQ (range)	Major motor disorder (%)	SNHL (%)
CT scan score 0 or 1 (n = 16)	92 (71-114)	0	6 (37.5)
CT scan score 2 (n = 12)	77 (49-110)	3 (25)	9 (75)
CT scan score 3 (n =13)	45 (21-69)	12 (92.3)	13 (100)

SNHL, Sensorineural hearing loss; *CT,* computed tomography.

DISCUSSION

It is generally presumed by many health-care professionals that symptomatic congenital CMV infection carries a universally grave prognosis for developmental outcome. However, in one study, 59% of children born with symptomatic CMV infection had a normal IQ,[4] and preliminary results from our cohort of patients corroborated this finding, with 54% of children attaining an IQ of >70 and 29% attaining an IQ of >90.[5] Therefore the chances for a good neurodevelopmental outcome in these children may be more favorable than previously appreciated. The ability to accurately predict long-term outcome in the newborn period has advantages, including opportunities for appropriate counseling of parents and early intervention to maximize performance in children at high risk for disabilities. Identifying reliable predictors for children with good prognosis may diminish parental anxiety. Furthermore, stratification of patients at risk for different outcomes may help in the evaluation of interventions, such as antiviral therapy, aimed at improving outcome.

Although microcephaly has been associated with poor outcome in children with congenital CMV disease,[2,3,7] others have not found such an association.[6,22] A possible source of discrepancy is failure to adjust the head size to the weight of the infant when defining microcephaly. When we adjusted the HC according to the degree of weight deficit to define microcephaly, we found that the presence of microcephaly at birth had a 100% specificity and positive predictive values for the development of mental retardation and 92% specificity for prediction of major motor deficits. The presence of chorioretinitis had a lower, although adequate, specificity for the prediction of poor outcomes but had poor sensitivity. Conversely, abnormalities detected by head CT examinations demonstrated a very high sensitivity and negative predictive value for poor outcome, whereas the specificity and positive predictive values were low. That is, not all children with an abnormality detected by CT will have mental retardation. However, because of the small number of patients studied, the CIs obtained for our calculations were wide. The validity of our observations is supported by the almost identical predictive values derived from a previous report of CT abnormalities in children with congenital CMV disease.[10] Although abnormalities on CT were found in 78% of the patients, not all abnormalities were associated with an IQ of <70. Subtle abnormalities, such as white matter abnormalities and single punctate calcifications, were not associated with poor outcome. Similar abnormalities have been observed on CT scans of asymptomatic congenitally infected children and have been associated with SNHL, but not with adverse neurodevelopmental outcomes.[12] Thus categorizing abnormalities detected by CT helps to determine the prognosis of children with symptomatic congenital CMV. Likewise, categorizing patients according to the presence of microcephaly and abnormalities detected by head CT can be used to create groups with different levels of risk for disabilities.

We also found a highly significant correlation between birth modified HC *z* score and IQ/DQ score on follow-up, reinforcing the value of a carefully performed physical examination that includes anthropometric measurements. Correlation between the degree of microcephaly and IQ has been reported both in newborns with microcephaly of mixed etiology and older children with microcephaly.[23,24] However, because of wide variations in outcome, a particular head size did not allow accurate prediction of the precise IQ/DQ score for each child in our study. Patients with congenital CMV infection can occasionally have significant hydrocephalus with an HC proportional to their weight or larger than that expected for weight, an instance in which HC may not be predictive of long-term outcome. Thus although the modified HC *z* score provides useful prognostic information, a full clinical assessment of the patient provides the most accurate information.

Although microcephaly and abnormalities detected by head CT predicted the presence of mental retardation (IQ/DQ <70), the ability to predict an IQ/DQ score >90 was more difficult. The absence of microcephaly was a sensitive marker for normal cognitive function; however, the positive predictive value was only 36.3%, implying that 63.7% of children without microcephaly had an IQ/DQ <90. A normal head CT had 86.2% specificity for predicting an IQ/DQ score >90, but the positive predictive value was only 55.5%, implying that 44.5% of those with normal CT findings had an IQ/DQ <90. No other neonatal characteristic had a higher positive predictive value for this outcome.

The presence of SNHL at birth did not correlate with long-term cognitive outcome. However, 11 (27%) children had SNHL that was first detected after the neonatal period, and when all children with SNHL were compared with those without hearing loss, there was a significant difference in cognitive and motor outcome noted. Children with SNHL were more likely to have an abnormality detected by head CT, as well as a greater mean CT scan score. Boppana et al[10] and Williamson et al[12] also reported a significant association between abnormalities detected by head CT and the presence of hearing loss in children with symptomatic and asymptomatic congenital CMV infection. These findings support the notion that invasion to the inner ear is associated with central nervous system invasion during intrauterine dissemination of CMV.

In summary, almost one third of children with symptomatic congenital CMV infection had a normal cognitive outcome. The presence of microcephaly at birth, when carefully assessed by adjusting for gestational age and weight, was the most specific predictor of poor cognitive outcome in children with symptomatic congenital CMV infection. The combination of normal findings on head CT scan and normal HC proportional to weight carried an almost universal prognosis for an IQ/DQ >70. Further efforts to identify predictive factors should be targeted at infants who have abnormalities detected by head CT and normal HCs, because these infants had variable cognitive prognoses. These findings should assist pediatricians, neonatologists, neurologists, developmentalists, and infectious disease specialists in counseling families about the prognosis of newborns with symptomatic congenital CMV infection.

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