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Original Article

Congenital Cytomegalovirus Infection and Brain Clefting

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ABSTRACT

BACKGROUND: Human cytomegalovirus, a major cause of permanent neurodevelopmental disability in children, frequently produces intracranial abnormalities, including calcifications and polymicrogyria, in infants with congenital cytomegalovirus infections. This report describes the features of cerebral cortical clefting, including schizencephaly, in children with congenital cytomegalovirus infection. **METHODS:** This is a retrospective review of the medical records of infants and children with congenital cytomegalovirus infection evaluated at Primary Children's Medical Center, Salt Lake City, Utah, between 1999 and 2008. **FINDINGS:** Twenty-five children with congenital cytomegalovirus infection were identified during this 10-year period; 23 (92%) had computed tomography and 17 (68%) had magnetic resonance imaging. Imaging was obtained at a median age of 6 months (mode 1 month or less). Of 15 children with confirmed congenital infections, 10 (66%) had polymicrogyria or abnormal gyral patterns, five (33%) had cleft cortical dysplasia, and two (13%) had schizencephaly. Of 10 children with suspected congenital cytomegalovirus infection, eight (80%) had polymicrogyria, two (20%) had cleft cortical dysplasia, and one (10%) had bilateral schizencephaly with calcifications. Seventeen of the 25 infants (68%) had intracranial calcifications. **INTERPRETATION:** These results indicate that clefting, either as cleft cortical dysplasia or schizencephaly, is an important feature of congenital cytomegalovirus infection.

Keywords: cytomegalovirus, congenital infection, cortical dysplasia, schizencephaly

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Introduction

Congenital infection with human cytomegalovirus (CMV) remains the most common congenital viral infection in many regions of the world. In the United States, 0.3% to 1% of live-born infants shed CMV at birth,[1] and 5% to 10% of these are symptomatically infected.[2] Symptomatic infants have high rates of neurodevelopmental sequelae because of sensorineural hearing loss,[3] chorioretinitis, and virus-induced damage in the developing brain.[4] Postnatal therapy with ganciclovir may reduce the risk of sensorineural hearing loss[5] and may also have modest effects on other neurodevelopmental outcomes.[6] However, current therapies do not affect the CMV-induced brain abnormalities that develop in utero.

Intracranial calcifications, often considered a hallmark of congenital infection with CMV, occur in approximately 50% of the symptomatic CMV-infected infants and are strongly associated with adverse neurodevelopmental and hearing outcomes.[7,8] However, several other abnormalities of the brain, including lissencephaly and polymicrogyria, can result from congenital CMV infections. Schizencephaly has been described in occasional infants.[9,10] Direct infection of the brain is presumed to be the triggering event for these abnormalities, a conclusion supported by observations in an animal model.[11]

To understand more completely the nature of the CMV-induced brain abnormalities, we reviewed the imaging features of infants and children evaluated for congenital CMV infection at the University of Utah and Primary Children's Hospital, Salt Lake City, Utah. Our primary objective was to

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describe the clefting anomalies, including schizencephaly and cleft cortical dysplasia, that can be associated with congenital CMV infection.

Methods

Setting and study population

Approval for this study was obtained from the institutional review board of the University of Utah and Primary Children's Hospital. Primary Children's Hospital, operated by Intermountain Healthcare, and the University of Utah Health Care, both located in Salt Lake City, serve as the tertiary care centers for children living in the intermountain region, a large geographical area that includes Utah and portions of Colorado, Idaho, Wyoming, Montana, and Nevada. Approximately 2 million children 18 years of age and younger live within the region served by the Division of Pediatric Neurology, University of Utah Health Care.

Selection criteria

The University of Utah Health Care billing records were used to identify children who met the following inclusion criteria: (1) evaluation by a University of Utah pediatric neurologist between January 1, 1999, and April 1, 2008; (2) diagnosis of cytomegalovirus infection (International Classification of Diseases-9 codes 777.1 or 078.5); and (3) computed tomography (CT) or magnetic resonance imaging (MRI) studies available for review.

Microbiological studies

CMV infection was assessed using centrifugation-enhanced culture of urine (shell vial assay), detection of CMV-specific immunoglobulin M and immunoglobulin G by enzyme-linked immunosorbent assay, or detection of CMV in a body fluid using the polymerase chain reaction. CMV studies were performed by the Intermountain Healthcare microbiology laboratory or ARUP Laboratory, Inc., Salt Lake City, UT. Congenital infection was considered *confirmed* when CMV studies were positive in the first 4 weeks of life and *suspected* when CMV studies were positive after this period and no alternative explanation for the infant's condition was identified.

Neuroimaging studies

CT was performed on either a Toshiba (Toshiba American Medical Systems, Tustin, CA, USA) 16-slice or 64-slice multidetector scanner using automated exposure control or weight-based protocol to reduce radiation dose. No intravenous contrast or sedation was required. MRI examinations were performed on either a General Electric (GE Healthcare, Milwaukee, WI, USA) 1.5 Tesla or 3.0 Tesla MR imaging system. Sedation for MRI was managed by a nurse practitioner. The CT and MRI examinations were reviewed by a board-certified pediatric neuroradiologist (G.L.H.).

Statistical analysis

The Mann-Whitney test was used to analyze the ages of the patients, and the Fisher's exact test was used to compare clinical and imaging manifestations between patients with confirmed and suspected infections.

Results

Study population

Twenty-five infants or children were identified for inclusion in this study. Fifteen had confirmed CMV infections, and 10 were considered to have suspected infections. The ages of the study patients ranged from 6 months to 16 years, 7 months, at the time of imaging analysis (median: 70 months; mean: 72.5 months). The patients in the confirmed group were significantly younger at the time of imaging than those in the suspected group (mean of 54.9 ± 45.6 months versus 99.0 ± 45.6 months; $P = 0.019$).

TABLE 1.
Systemic Manifestations of Congenital CMV Infection

Manifestation	Confirmed	Suspected	Total
Jaundice	10/15 (67%)	0/10	10/25 (40%)
Hepatomegaly	3/15 (20%)	0/10	3/25 (12%)
Splenomegaly	4/15 (27%)	0/10	4/25 (16%)
Sensorineural hearing loss	7/15 (47%)	5/10 (50%)	12/25 (48%)
Chorioretinitis	2/15 (13%)	0/10	2/25 (8%)
Thrombocytopenia	12/15 (80%)	0/10	12/25 (48%)
Elevated transaminases	5/15 (33%)	0/10	5/25 (20%)

Diagnosis of CMV infection and systemic manifestations

CMV infection was identified by detection of virus by culture in 13 patients, detection of viral DNA by polymerase chain reaction of urine, blood, cerebrospinal fluid, or amniotic fluid in eight, and detection of CMV-specific immunoglobulin G or immunoglobulin M serologies in five. Some infants had more than one microbiological study. One child included in the confirmed group, a former 36-week gestation infant with jaundice, rash and a birth weight of 2.0 kg, had CMV testing at an unknown date in the newborn period. In a child with schizencephaly and intracranial calcifications, the diagnosis of suspected congenital CMV infection was made clinically by the examining neurologist, but the results of microbiological studies were not available.

The spectrum of the systemic manifestations of congenital CMV is summarized in Table 1. Infants with confirmed infections were more likely ($P < 0.001$) to have jaundice or thrombocytopenia, features that led clinicians to suspect CMV infection and obtain confirmatory microbiological tests. However, the prevalence of sensorineural hearing loss, a major feature of congenital CMV infection, was similar in both groups. Sensorineural hearing loss was often the clinical feature that led treating child neurologists to suspect CMV infection. In one patient, CMV was detected in the maternal amniotic fluid and in the infant's urine. This child's CT and hearing testing were normal, and the child was later considered to have asymptomatic congenital CMV infection.

Imaging studies

Twenty-three patients (92%) underwent cranial CT at a median age of 6 months, and 17 patients (68%) underwent

TABLE 2.
Imaging Features of Congenital CMV Infection

Feature	Confirmed	Suspected	Total
Polymicrogyria/abnormal gyri	10/15 (66%)	8/10 (80%)	18/25 (72%)
Calcification(s)	12/15 (80%)	5/10 (50%)	17/25 (68%)
Abnormal white matter	8/15 (53%)	6/10 (60%)	14/25 (56%)
Cleft dysplasia	5/15 (33%)	2/10 (20%)	7/25 (28%)
Schizencephaly	2/15 (13%)	1/10 (10%)	3/25 (12%)
Cerebellar hypoplasia	3/15 (20%)	0/10 (—)	3/25 (12%)