Brain imaging on development delay of children with cytomegalovirus infection

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Abstract

Background: A frequent sequel to cytomegalovirus (CMV) infection is developmental delay (DD). Computed tomography (CT) scan can be performed for early diagnosis.

Objectives: To describe imaging findings in children with CMV infection and to assess their association with DD.

Method: A descriptive cross-sectional study was conducted in Dr. Soetomo Hospital, Surabaya, Indonesia from January 2011 to June 2016 on data collected from 176 patients with CMV infection of whom 114 had DD. Statistical analysis was performed using Cochran's test.

Results: Out of 114 subjects included, CT scan imaging showed atrophy of hippocampus (AH) in 26 (22.8%), intracranial calcifications (ICC) in 20 (17.5%), hypoplasia of corpus callosum (HCC) in 17 (14.9%), ventriculomegaly in 12 (10.5%), cerebral atrophy (CA) in 10 (8.7%), schizencephaly in 8 (7.4%), subdural hygroma (SH) in 7 (6.1%), temporal cyst (TC) in 7 (6.1%), asymmetric bulbus oculi (ABO) in 5 (6.1%) and intracranial haemorrhage (ICH) in 2 (1.7%). According to Cochran's test results (df=3; a=0.05), HCC (0.972), ICC (0.820) and CA (0.963) were significantly associated with global DD in CMV infection.

Conclusions*:* In this study hypoplasia of corpus callosum, intracranial calcifications and cerebral atrophy were significantly associated with global DD in children with CMV infection.

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Introduction

Most infants with congenital cytomegalovirus (CMV) infection are asymptomatic at birth but approximately 10 percent have symptoms[1]. A study conducted at the Dr. Soetomo General Academic Hospital found that 64.4% of congenital CMV infection occurred in the 0-3 month age group[2]. CMV belongs to the herpes virus family which includes human herpes virus (HHV), simple herpes virus and the Epstein-Barr virus. The viruses share structural features such as a dual-beam linear deoxyribonucleic acid (DNA) genome, an icosahedral symmetry capsid virus and a viral envelope[3,4]. In newborns, CMV infection is diagnosed by isolating the virus from urine, finding immunoglobulin M (IgM) in blood, detecting CMV antigen in blood, and recognizing CMV-DNA using polymerase chain reaction (PCR)[5,6].

Developmental disorders affect approximately 5–10% of preschool children[7]. Early detection is important to avoid delays in diagnosis and intervention that can impact children's speech and language skills in the long-term[8]. Neuroimaging, in particular, computed tomography (CT) and brain magnetic resonance imaging (MRI), are essential approaches for evaluating children with developmental delay (DD) as they provide good information on brain tissue architecture and abnormality[4,9,10]. In investigations performed using CT scan, extensive encephalopathy, white-matter alterations, polymicrogyria, cysts and structural abnormalities were found[10,11]. A multitude of neuropsychiatric illnesses have been related to modest cognitive shortcomings to pervasive developmental disturbances[12-15].

Objectives

The objectives of this study were to describe imaging findings in children with CMV infection and to assess their association with DD.

Method

A descriptive cross-sectional study was conducted in Dr. Soetomo Hospital, Surabaya, Indonesia, a tertiary care hospital, from January 2011 to June

2016 on demographic data, admission data and diagnosis data collected from the patients. Due to the scarcity of cases, all paediatric patients who had CMV infection from hospital medical records were taken as secondary data.

Subject inclusion criteria were children aged <10 years with CMV infection as evidenced by standardized test results, while patients who had other comorbidities that could affect children's development, such as hearing loss, were excluded from this study.

The sampling technique used was non-probability purposive sampling and data were obtained for 176 patients with CMV infection. There were 114 children infected with CMV with DD and 62 patients without DD. Most children were diagnosed with CMV infection using blood serology and central nervous system (CNS) images.

Primary data such as types of DD and CT scans of the brain were collected from examination of the patient. To avoid bias, primary and secondary data were collected using the blind method. Evaluation data for child developmental delays were classified based on test results using the Denver II screening test (DDST) instrument and the Clinical Adaptive Test / Clinical Linguistic / Auditive Milestone Measure (CAT/CLAMS). This test assesses developmental delays and/or other disabilities, nonverbal intelligence and developmental intelligence (IQ/DQ), depending on the areas of adaptive fine motor skills, gross motor skills, and personal social and language. Brain scan examination using a Philips CT scan type MRC 880, number: 145782 and Siemens type M-CT-172, number 625351576, were examined to show the results of the CT scan of the brain. The results have been categorized by type and location of the anomaly.

Ethical issues: This study was approved by Ethic and Medico-legal Committee of Soetomo Hospital and Universitas Airlangga, Surabaya, Indonesia. Consent waiver was obtained from the Ethic and Medico-legal Committee Soetomo Hospital for the evaluation of the medical record data and parental written informed consent was obtained prior to data collection.

Statistical analysis: Data distributions were reported by medians with ranges (for continuous data) and frequencies of percentages (for categorical data). Statistics Package of Social Sciences (SPSS) version 20 has been utilized for analysing data. The Cochran test was used to evaluate statistical associations with the fourth aspect of DD (fine motor adaptive ability, gross motor skills, personal social, speech and social) with a probability (alpha) of 0.05 in CT imaging of the cytomegalovirus infection child.

Results

Of the 114 outpatients, with CMV infection and DD, 47 (41.2%) were boys and 67 (58.8%) were girls. The mean age of the 114 patients was 3 ± 05 years. The brain abnormalities consisted of 26 (22.8%) with atrophy of hippocampus (AH), 20 (17.5%) with hypoplasia of corpus callosum (HCC), 17 (14.9%) with intracranial calcification (ICC), 12 (10.5%) with ventriculomegaly (VM), 10 (8.7%) with cerebral atrophy (CA), 8 (7.4%) with subdural hygroma (SH), 7 (6.1%) with schizencephaly (SE), 7 (6.1%) with temporal cyst (TC), 5 (6.1%) with asymmetric bulbus oculi (ABO), and 2 (1.7%) with intracranial haemorrhagic (ICH). (Figure.1).

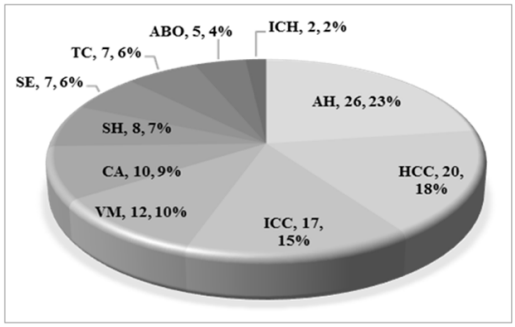

Figure 1: ***Brain abnormalities on computed tomography scan in children with cytomegalovirus infection***
AH: atrophy of hippocampus, HCC: hypoplasia of corpus callosum, ICC: intracranial calcifications, VM: ventriculomegaly, CA: cerebral atrophy, SH: subdural hygroma, SE: schizencephaly, TC: temporal cyst, ABO: asymmetric bulbus oculi, ICH: intracranial haemorrhagic

In 17 (68%) of the 26 children with AH, the type of DD was fine motor (Table 1).

The characteristic data of brain abnormalities in CT scan finding with type of developmental delay was analysed using Cochran's Q-test for the association (Table 2).

Table 1: ***CT scan imaging related to type of developmental delay in children with CMV infection***

CT scan imaging	Without developmental delay	Developmental delay			
		Fine motor delay (%)	Language delay (%)	Gross motor delay (%)	Personal social delay (%)
AH	18/44	17/26 (68)	14/26 (56)	13/26 (50)	7/26 (26)
HCC	6/26	12/20 (60)	11/20 (55)	12/20 (60)	11/20 (55)
ICC	2/19	11/17 (64)	11/17 (64)	13/17 (76)	13/17 (76)
VM	10/22	7/12 (58)	2/12 (16)	5/12 (41)	1/12 (08)
CA	2/12	9/10 (90)	9/10 (90)	9/10 (90)	7/10 (70)
SH	7/15	4/8 (50)	3/8 (38)	0/8 (0)	0/8 (0)
SE	5/12	6/7 (85)	5/7 (71)	0/7 (0)	0/7 (0)
TC	6/13	2/7 (28)	4/7 (57)	1/7 (14)	0/7 (0)
ABO	4/9	4/5 (80)	4/5 (80)	5/5 (100)	5/5 (100)
ICH	2/4	2/2 (100)	2/2 (100)	0/0 (0)	0/0 (0)

AH: Atrophy of hippocampus, HCC: Hypoplasia of corpus callosum, ICC: Intracranial calcifications, VM: Ventriculomegaly, CA: Cerebral atrophy, SH: Subdural hygroma, SE: Schizencephaly, TC: Temporal cyst, ABO: Asymmetric bulbus oculi, ICH: Intracranial hemorrhagic

Table 2: ***CT scan imaging associated with global developmental delay in children with CMV infection (with df = 3, a = 0.05)***

CT scan imaging	Q test	Asymptotic significance
Atrophy of hippocampus (AH)	1.636	0.651
Hypoplasia of corpus callosum (HCC)	0.231	0.972
Intracranial calcifications (ICC)	0.923	0.820
Ventriculomegaly (VM)	7.378	0.067
Cerebral atrophy (CA)	2.571	0.963
Subdural hygroma (SH)	7.286	0.063
Schizencephaly (SE)	14.760	0.002
Temporal cyst (TC)	8.077	0.044
Asymmetric bulbus oculi (ABO)	12.000	0.007
Intracranial hemorrhagic (ICH)	6.000	0.112

After analysing the data, the results (df=3; a = 0.05) indicated that HCC (0.972), ICC (0.820) and CA (0.963) were significantly associated with global DD in CMV infection.

Discussion

All patients in this study with brain abnormalities on CT scan had DD. The major types of DD were fine motor and language delay. The major brain abnormality in our study was AH (22.8%). From 1991 to 1997, WHO conducted a study in France of 224 children with DD and noted 109 (48.6%) cases with positive brain imaging findings of which 55 had structural brain abnormalities[16,17]. A study from 1991 to 1993 of 26 (76.5%) children with global developmental delay (GDD) in Korea found significant abnormal brain imaging results[18]. In one trial of symptomatic CMV, 90% of children who had an abnormal CT scan had sequelae compared to 29% of those who had a normal scan[19,20]. Brain imaging is a good predictor of adverse neurodevelopmental outcomes[21].

A variety of disorders, many of them associated with abnormalities of brain CT or MRI, are key factors for DD. HCC was most common brain abnormality among 3,4 million live births in the 1st year of life in a study conducted in California from 1983 to 2003[22]. Retrospective and cross-sectional cohort studies have shown that 30% to 40% of cases have identifiable causes; however, up to 75% of HCC cases do not have a known cause[23,24]. HCC is a type of corpus callosum abnormality (CCA) that has been described as a completely formed, decreased thickness corpus callosum[25,26]. The aetiology remains unclear and the pathogenesis remains controversial. Although agenesis / hypoplasia of the corpus callosum is a rare congenital disorder[27-30], HCC is among the common brain malformations in children with DD[31,32].

Most children (90%) have developed at least one sequel of an abnormal CT scan, compared to 29% of those who have a normal CT scan. There was only one child with an IQ <70 for normal CT scans, compared with 59% for abnormal CT scans. Moreover, over half of children with CT scan abnormalities had an IQ <50 compared to none who had a normal CT scan[33]. ICC was similarly

associated with global development delay in our patients on CT image analysis. Of patients with cerebral calcification 78% had abnormal CT results[34]. University of Alabama Department of Paediatrics has reported abnormal CT scans in 70% of children with intracerebral calcification[4].

Our study also revealed that cerebral atrophy was associated with global DD. Noyola DE, *et.al*[19] stated that cerebral atrophy occurred in 27% cases of CMV infection. CA consists of a morphological depiction of parenchymal brain volume loss, which is common in cross-sectional imaging. The CA finding predicts delays in development, cognitive, and sound reasoning in later life and predicts a poor neurodevelopmental forecast[34,35].

Conclusions

In this study hypoplasia of corpus callosum, intracranial calcifications and cerebral atrophy were significantly associated with global developmental delay in children with CMV infection.

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