Brain & Development 38 (2016) 819–826

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Asymptomatic congenital cytomegalovirus infection with neurological sequelae: A retrospective study using umbilical cord

Mitsugu Uematsu [a,*], Kazuhiro Haginoya [b], Atsuo Kikuchi [a], Naomi Hino-Fukuyo [a], Keiko Ishii [c], Takashi Shiihara [d], Mitsuhiro Kato [e], Atsushi Kamei [f], Shigeo Kure [a]

[a] *Department of Pediatrics, Tohoku University School of Medicine, Japan*
[b] *Department of Pediatric Neurology, Takuto Rehabilitation Center for Children, Japan*
[c] *Department of Medical Microbiology, Mycology and Immunology, Tohoku University School of Medicine, Japan*
[d] *Department of Neurology, Gunma Children's Medical Center, Japan*
[e] *Department of Pediatrics, Yamagata University Faculty of Medicine, Japan*
[f] *Department of Pediatrics, Iwate Medical University, Japan*

Received 11 December 2015; received in revised form 8 March 2016; accepted 18 March 2016

Abstract

Background: Congenital cytomegalovirus (CMV) infection causes various neurological sequelae. However, most infected infants are asymptomatic at birth, and retrospective diagnosis is difficult beyond the neonatal period.

Objective: This study aimed to investigate the aspects of neurological sequelae associated with asymptomatic congenital CMV infection.

Methods: We retrospectively analyzed 182 patients who were suspected of having asymptomatic congenital CMV infection with neurological symptoms in Japan. Congenital CMV infection was diagnosed by quantitative polymerase chain reaction amplification of CMV from dried umbilical cord DNA.

Results: Fifty-nine patients (32.4%) who tested positive for CMV were confirmed as having congenital CMV infection. Among 54 congenital CMV patients, major neurological symptoms included intellectual disability ($n = 51$, 94.4%), hearing impairment ($n = 36$, 66.7%) and cerebral palsy ($n = 21$, 38.9%), while microcephaly ($n = 16$, 29.6%) and epilepsy ($n = 14$, 25.9%) were less common. In a brain magnetic resonance imaging (MRI) study, cortical dysplasia was observed in 27 CMV-positive patients (50.0%), and all patients (100%) had cerebral white matter (WM) abnormality. Intracranial calcification was detected by CT in 16 (48.5%) of 33 CMV-positive patients. Cerebral palsy, cortical dysplasia and a WM abnormality with a diffuse pattern were associated with marked intellectual disability.

Conclusions: Brain MRI investigations are important for making a diagnosis and formulating an intellectual prognosis. Analysis of umbilical cord tissue represents a unique and useful way to retrospectively diagnose congenital CMV infection.
© 2016 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.

Keywords: Intellectual disability; White matter abnormality; Magnetic resonance image; Asymptomatic; Congenital CMV infection

1. Introduction

Congenital cytomegalovirus (CMV) infection represents a common cause of intrauterine infection [1–3] and is a major cause of neurological sequelae [4,5].

* Corresponding author at: Department of Pediatrics, Tohoku University School of Medicine, 1-1 Seiryo-cho, Aoba-ku, Sendai 980-8574, Japan. Tel.: +81 22 717 7287; fax: +81 22 717 7290.
E-mail address: uematsu@bk9.so-net.ne.jp (M. Uematsu).

http://dx.doi.org/10.1016/j.braindev.2016.03.006
0387-7604/© 2016 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.

There are two categories of congenital CMV infection—symptomatic and asymptomatic—that are generally based on the presence of clinical findings that suggest congenital infection at birth. Common physical and laboratory findings of symptomatic infants include petechial rash, jaundice, hepatosplenomegaly, microcephaly, elevated aspartate aminotransferase, hyperbilirubinemia and thrombocytopenia [6]. Approximately 90% of infants with congenital CMV infection are asymptomatic [7]. This categorization is clinically useful because infants with symptomatic infection are at a much higher risk for neurological sequelae than asymptomatic infants. Most (60–90%) symptomatic and 10–15% of asymptomatic congenital CMV infection patients develop one or more long-term neurological sequelae, such as intellectual disability [8] and sensorineural hearing loss [2,9]. Several prospective screening studies have shown that symptomatic infants generally show mild symptoms during the neonatal period [5,10]. Therefore, congenital CMV infection could easily be overlooked during the early infantile period.

More than two-thirds of patients with symptomatic congenital CMV infection exhibit various neuroimaging abnormalities, such as intracranial (especially periventricular) calcifications, cortical dysplasia, periventricular cysts (especially anterior temporal) and a parietal dominant white matter (WM) abnormality [11]. However, few previous studies have assessed brain imaging abnormalities in asymptomatic cases with neurological sequelae because retrospective diagnosis is difficult beyond the neonatal period.

A recent study reported that intellectual disability in 5 of 20 patients was caused by congenital CMV infections, which were retrospectively diagnosed using umbilical cords [12]. To determine the clinical characteristics of asymptomatic congenital CMV infection associated with neurological sequelae, we performed retrospective diagnoses of congenital CMV infections using preserved dried umbilical cord tissues and investigated the associated clinical and neuroimaging findings.

2. Subjects and methods

2.1. Data collection

This study was performed retrospectively between January 2005 and December 2013. Samples and data were collected from patients from all regions of Japan with possible congenital CMV infection who showed neurological symptoms such as intellectual disability, hearing impairment, cerebral palsy, microcephaly, and epilepsy. The lead author (MU) announced the enrollment of patients through the website of The Japanese Society of Child Neurology and the mailing list of the Annual Zao Conference on Pediatric Neurology, which includes >500 pediatric neurologists from throughout Japan. Clinical information and neuroimaging data of potential patients were sent to the lead author by each attending physician. Most patients had undergone a brain imaging study, such as computed tomography (CT) and/or magnetic resonance image (MRI). Patients with another significant disease of the central nervous system were excluded by each attending physician.

2.2. Study design

The Ethical Committee of Tohoku University Hospital approved this study, and informed consent was obtained from all enrolled patients or their parents. Patient's intelligence quotient (IQ) was evaluated using the Wechsler Intelligence Scale for Children (Third Edition) or standard Japanese methods for young children, i.e., the Enjoji developmental test [13]. The level of intellectual disability was classified into 3 categories: severe, DQ/IQ of <50; mild, DQ/IQ of 50–69; and normal, DQ/IQ of >70. Hearing impairment was evaluated based on otoacoustic emissions, auditory brainstem responses and/or audiometer tests. The degree of hearing loss was confirmed by an otolaryngologist. Cerebral palsy was defined as motor impairment that limited activity and could be attributed to nonprogressive disturbances during brain development in fetuses or infants [14]. Microcephaly was defined as a small head circumference (less than the norm by more than two standard deviations) beyond the neonatal period. Epilepsy was defined as the occurrence of at least two unprovoked epileptic seizures. Brain MRI findings were classified into the following three categories: cortical dysplasia and diffuse or parietal-dominant deep WM abnormalities. A WM abnormality was assessed via high intensity areas on T2-weighted spin-echo images. A parietal-dominant pattern was defined as a high-intensity area that was predominantly located in the parietal deep WM, especially around the parietal posterior horns [15]. A diffuse pattern was defined as diffuse distribution of a high-intensity area in the WM. The review of clinical data and neuroimaging findings of enrolled patients was performed by two authors who were experienced child neurologists (MU and KH).

2.3. Laboratory investigation

The diagnosis of congenital CMV infection was confirmed based on a retrospective analysis of dried umbilical cord tissues [12,16]. The preservation of dried umbilical cord tissue, which has been stored clean in a box, is customary in Japan. Each umbilical cord sample ($\sim$0.3 cm^3) was cut using a clean blade. To avoid cross-contamination, blades were changed for each sample. DNA was extracted using the DNeasy Blood and Tissue Kit (QIAGEN, Hilden, Germany). About 0.2 μg extracted DNA (the ratio of absorbance at

Download English Version:

https://daneshyari.com/en/article/3036425

Download Persian Version:

https://daneshyari.com/article/3036425

Daneshyari.com