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Original article

Role of cerebral ultrasound and magnetic resonance imaging in newborns with congenital cytomegalovirus infection

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Abstract

Purpose: To assess the diagnostic and prognostic value of cerebral magnetic resonance imaging (cMRI) in comparison with that of cerebral ultrasound (cUS) in predicting neurodevelopmental outcome in newborns with congenital cytomegalovirus (CMV) infection. *Methods:* Forty CMV-congenitally infected newborns underwent cUS and cMRI within the first month of life. Clinical course, laboratory findings, visual/hearing function and neurodevelopmental outcome were documented. *Results:* Thirty newborns showed normal cMRI, cUS and hearing/visual function in the first month of life; none showed CMV-related abnormalities at follow-up. Six newborns showed pathological cMRI and cUS findings (pseudocystis, ventriculomegaly, calcifications, cerebellar hypoplasia) but cMRI provided additional information (white matter abnormalities in three cases, lissencephaly/polymicrogyria in one and a cyst of the temporal lobe in another one); cerebral calcifications were detected in 3/6 infants by cUS but only in 2/6 by cMRI. Four of these 6 infants showed severe neurodevelopmental impairment and five showed deafness during follow-up. Three newborns had a normal cUS, but cMRI documented white matter abnormalities and in one case also cerebellar hypoplasia; all showed neurodevelopmental impairment and two were deaf at follow-up. One more newborn showed normal cUS and cMRI, but brainstem auditory evoked responses were abnormal; psychomotor development was normal at follow-up. *Conclusions:* Compared with cUS, cMRI disclosed additional pathological findings in CMV-congenitally infected newborns. cUS is a readily available screening tool useful in the identification of infected newborns with major cerebral involvement. Further studies with a larger sample size are needed to

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BAERs, brainstem auditory evoked responses; BW, birth weight; CI, confidence interval; CMV, cytomegalovirus; CNS, central nervous system; CT, computed tomography; cMRI, cerebral magnetic resonance imaging; cUS, cerebral ultrasound; DQ, developmental quotient; GA, gestational age; IUGR, intrauterine growth retardation; LSV, lenticulostriate vasculopaty; PCR, polymerase chain reaction; SNHL, sensorineural hearing loss; WM, white matter

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determine the prognostic role of MRI, particularly regarding isolated white matter lesions.

Keywords: Cytomegalovirus; Neurodevelopment; Hearing loss; Ultrasound; Cerebral MRI

1. Introduction

Congenital cytomegalovirus (CMV) infection is a major health problem in developed countries as it is a leading cause of hearing loss and neurodevelopmental impairment in children. CMV is a neurotropic virus, mostly involving the central nervous system (CNS) [1]. Almost all CNS cell types are susceptible to infection, with varying abilities to support a complete viral replication cycle. Fetal brain damage is the combined result of viral infection, inflammatory infiltration and hypoxia due to severe placentitis [1]. Congenital CMV infection can lead to a wide spectrum of brain abnormalities, including microcephaly, intraparenchymal calcifications, ventriculomegaly, intraventricular adhesions, periventricular pseudocystis, sulcation and gyral abnormalities, hypoplastic corpus callosum, cerebellar abnormalities, white matter injury [2–4].

Computed tomography (CT) has been widely used in CMV congenitally infected newborns to detect brain lesions, establish a prognosis [5] and identify newborns who could benefit from ganciclovir treatment to reduce hearing and neurodevelopmental impairment [6,7].

However, there is great concern about the radiation exposure, especially in children, that are particularly at risk for adverse effects from overexposure to radiation because of several factors, including increased tissue sensitivity and longer life expectancy [8–10].

In recent years cerebral ultrasound (cUS) and cerebral magnetic resonance imaging (cMRI) have been advocated to evaluate brain injury in infants with CMV disease [11–14].

A previous study reported a good correlation between pathological cUS and the prediction of outcomes in newborns congenitally infected with CMV [11], but insufficient data precluded any conclusion for asymptomatic infants. The study lacked a full CNS evaluation because all enrolled infants underwent cUS examination but cMRI was performed only in those with pathologic cUS findings.

The aim of this prospective observational study was to investigate further the feasibility, diagnostic and prognostic ability of cMRI compared with cUS to select CMV-congenitally infected newborns with cerebral involvement and to predict their neurodevelopmental outcome.

2. Patients and methods

2.1. Study population

A prospective longitudinal observational study was carried out. All consecutive newborns born from January 2003 to January 2010 with congenital CMV infection diagnosed within the first two weeks of life were eligible for the study. Our study protocol is routinely applied to all infants with congenital CMV infection, as it overlaps with our care protocol. Before enrolment written informed consent was obtained from each infant's parents.

2.2. Methods

2.2.1. Virological tests

Active CMV infection was documented in urine, saliva, or blood of pregnant women by culture and/or Real Time polymerase chain reaction (PCR). Serological results were documented by a commercially available enzyme immunoassay (EIA) (Enzygnost A-CMV-IgG and A-CMV-IgM Siemens Healthcare Diagnostics, Deerfield IL, USA). Anti-CMV IgG avidity was determined using a commercial kit (Cytomegalovirus IgG avidity EIA WELL; RADIM, Rome, Italy). Women who had anti-CMV IgM and low avidity index of anti-CMV IgG or who seroconverted to CMV IgG positivity were classified as undergoing primary infection. Women who were found to be CMV-seropositive (for both IgG and IgM) and with a high avidity index of anti-CMV IgG before 16–18 weeks gestation were defined as non-primary CMV infection [15].

The shell vial procedure was used for virus isolation on infant urine. The inoculated cells were fixed 24–48 h after inoculation and were stained by an indirect immunofluorescence assay with a monoclonal antibody reacting with the CMV IE1 and EA gene product (E13 + 2A2; Argene, Varilhes, France) [15].

2.2.2. Auditory tests

Hearing function was evaluated by brainstem auditory evoked responses (BAERs) test until 24 months of life and then by audiometric test, adding BAERs test if necessary. Tympanometry was routinely performed to exclude middle ear disorders. The BAERs threshold was defined as the lowest intensity level at which wave