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Hospital Universitario La Paz
Fundación para la Investigación Biomédica
Comunidad de Madrid

Congenital CMV infection: Implementation of a screening program during pregnancy

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EurUS.BRAIN COURSE, Cádiz, 9-10th., May 2019.

European Society for Paediatric Research

UCA Universidad de Cádiz

European Society for Paediatric Research

EurUSbrain Cadiz 9-10th May 2019

Hospital Puerta del Mar, 7th floor. Room: 717

Scanning sessions: Neonatal intensive care unit, 3rd Floor

Local Scientific Committee:

Isabel Benavente Fernández.
Neonatóloga Hospital Puerta del Mar, Cádiz.
Profesora Asociada de Pediatría. Dpto. Materno Infantil y Radiología. Facultad de Medicina. Universidad de Cádiz.

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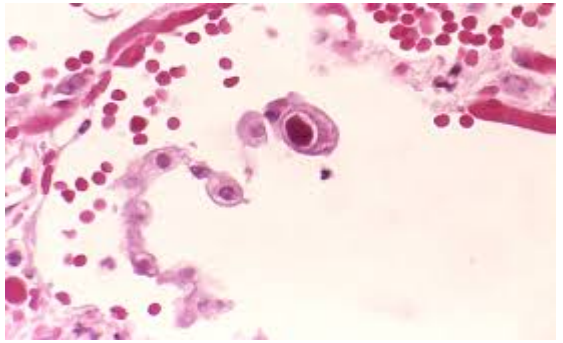
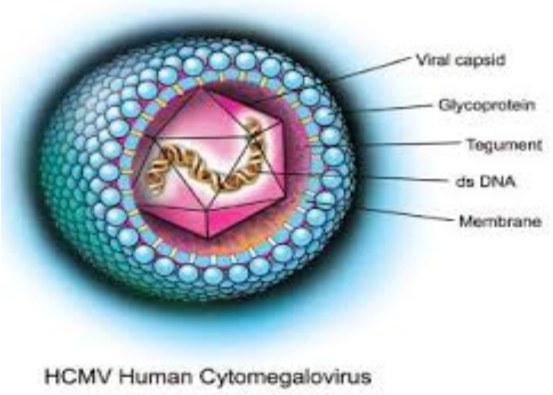
Profesor Asociado de Pediatría. Dpto. Materno Infantil y Radiología. Facultad de Medicina. Universidad de Cádiz.

Alessandro Parodi, Luca Ramenghi, Paul Govaert, Fernando Cabañas

Introduction

- Human CMV is the most prevalent congenital infection in developed countries.*
- Transmission:
  - Maternal primoinfection: 1-4% pregnant woman experiment seroconversion**
  - Recurrent maternal CMV infection





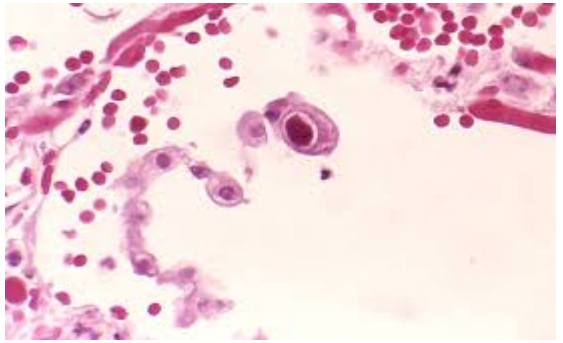
HCMV Human Cytomegalovirus

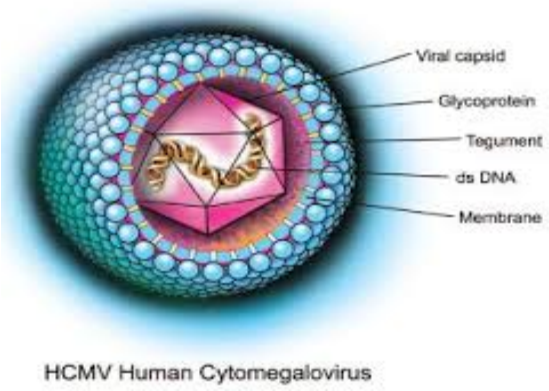
*Engman ML 2008, Foulon I 2008.

** Ory Manchon. Rev Esp Salud Publica 2001

Introduction

- **Most infected infants will be asymptomatic at birth but will develop neurological sequelae during childhood.**
- Serological screening during pregnancy remains controversial.
- Intra-uterus and early postnatal treatment have shown a positive effect on infant's outcome.





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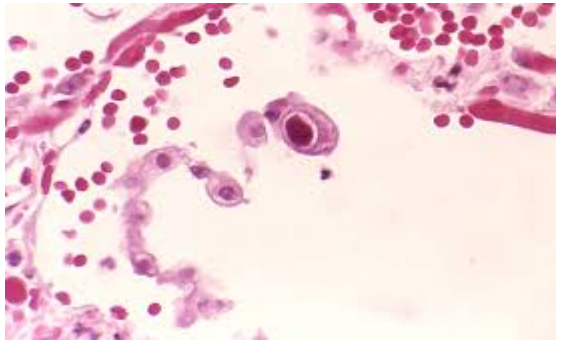

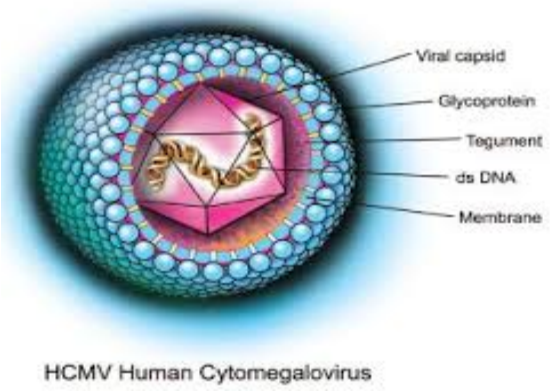

HCMV Human Cytomegalovirus

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Introduction: clinical course

- **Symptomatic**
  - prematurity
  - IUGR
  - Petequiaes
  - Jaundice
  - Hepatosplenomegaly
  - chorioretinitis
  - Neurologic: microcephaly, hypotonia, seizures
  - Blood test:
    - Thrombocytopenia
    - Cholestasis
    - Elevated liver enzimes

- **Asymptomatic**
  - 10% long term neurological sequelaes:
    - Deafness
    - Developmental abnormalities

NEUROIMAGING FINDINGS (US,MRI)*

Eur J Pediatr (2006) 165: 636–645
DOI 10.1007/s00431-006-0160-x

ORIGINAL PAPER

Ana Alarcon · Alfredo Garcia-Alix ·
Fernando Cabañas · Angel Hernanz ·
Dora Pascual-Salcedo · Ana Martin-Ancel ·
Marta Cabrera · Alfredo Tagarro · Jose Quero

Beta$_2$-microglobulin concentrations in cerebrospinal fluid correlate with neuroimaging findings in newborns with symptomatic congenital cytomegalovirus infection

Clinical, Biochemical, and Neuroimaging Findings Predict Long-Term Neurodevelopmental Outcome in Symptomatic Congenital Cytomegalovirus Infection

Ana Alarcon, PhD[1], Miriam Martinez-Biarge, PhD[2], Fernando Cabañas, PhD[2], Angel Hernanz, PhD[3], Jose Quero, PhD[2], and Alfredo Garcia-Alix, PhD[1]

Objective To evaluate clinical, biochemical, and neuroimaging findings as predictors of neurodevelopmental outcome in patients with symptomatic congenital cytomegalovirus (CMV).
Study design The study cohort comprised 26 patients with symptomatic congenital CMV born between 1993 and 2009 in a single center. Absolute and weight deficit–adjusted head circumference were considered. Cerebrospinal fluid (CSF) investigations included standard cytochemical analysis, determination of beta$_2$-microglobulin (β_2-m), neuron-specific enolase, and CMV DNA detection. Neuroimaging was classified according to a validated scoring system comprising calcifications, ventriculomegaly, and atrophy, with findings graded from 0 to 3. Systematic long-term neurodevelopmental assessment included motor function, cognition, behavior, hearing, vision, and epilepsy. Sequelae were graded as mild/absent, moderate, or severe; adverse outcome was defined as death or moderate to severe disability.
Results Three children died. The mean age at follow-up of the survivors was 8.7 $\pm$ 5.3 years (range, 19 months to 18.0 years). Neonatal findings showing a significant association with adverse outcome were relative microcephaly, CSF β_2-m concentrations, and grade 2-3 neuroimaging abnormalities ($P < .05$). Receiver operator characteristic curve analysis indicated that the most accurate single factor for predicting unfavorable outcome was CSF β_2-m >7.9 mg/L (area under the curve, 0.84 $\pm$ 0.08; sensitivity, 69%; specificity, 100%). The combination of CSF β_2-m >7.9 mg/L and moderate-severe neuroimaging alterations improved predictive ability (area under the curve, 0.92 $\pm$ 0.06; sensitivity, 87%; specificity, 100%).
Conclusion Adjusted head circumference, CSF β_2-m level, and neuroimaging studies have prognostic significance for neurodevelopmental outcome in newborns with congenital CMV. A combination of early findings improves the predictive value. *(J Pediatr 2013;163:828-34)*.

NEUROIMAGING FINDINGS (US,MRI)*

We are graded the neuroimaging finfings in order to evaluate he predictive vaues of prognostic for poor outcome

Neuroimaging Studies

Neonatal neuroimaging studies included cranial ultrasonography (US), computed tomography (CT), and/or magnetic resonance imaging (MRI). Findings were systematically evaluated by a blinded investigator (F.C.), who graded them as follows: (0) no abnormalities or abnormalities not related to CMV; (1) single punctate periventricular (PV) calcification and/or lenticulostriate vasculopathy; (2) multiple discrete PV calcifications and/or moderate to severe ventriculomegaly; or (3) extensive PV calcifications and/or brain atrophy.[5,21]

- Alarcón A, Martinez- Biarge M, Cabañas F. J Pediatr 2013; 163:828-34

Table IV. Predictive values of prognostic factors for poor outcome in infants with symptomatic congenital CMV infection

Finding	AUC	Sensitivity, %	Specificity, %	PPV, %	NPV, %	OR (95% CI)
Adjusted microcephaly	0.72 ± 0.09	44	100	100	44	1.80 (1.19-2.72)
CSF β_2-m >7.9 mg/L	0.84 ± 0.08	69	100	100	63	3.25 (1.43-7.34)
Neuroimaging score 2-3	0.80 ± 0.08	61	100	100	53	2.57 (1.44-4.58)
β_2-m >7.9 mg/L or adjusted microcephaly	0.91 ± 0.06	82	100	100	70	5.66 (2.02-15.82)
Adjusted microcephaly or neuroimaging score 2-3	0.83 ± 0.07	66	100	100	57	3.00 (1.56-5.76)
β_2-m >7.9 mg/L or neuroimaging score 2-3	0.92 ± 0.06	87	100	100	77	8.00 (2.18-29.24)

AUC, area under the curve; *NPV*, negative predictive value; *PPV*, positive predictive value.

Neonatology

Original Paper

Neonatology 2016;110:277–285
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A Prognostic Neonatal Neuroimaging Scale for Symptomatic Congenital Cytomegalovirus Infection

Ana Alarcon[a, c] Miriam Martinez-Biarge[b, d] Fernando Cabañas[d] Jose Quero[d]
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Key Words

Congenital · Cytomegalovirus · Developmental disabilities · Lenticulostriate vasculopathy · Magnetic resonance imaging · Malformations of cortical development · Neuroimaging · Prognosis · Ultrasonography · White matter disease

Abstract

Background: Congenital cytomegalovirus (cCMV) can cause brain inflammation/destruction and teratogenic effects. The only validated neuroimaging prognostic categorization for symptomatic cCMV available is based on destructive lesions seen on computed tomography (CT). ***Objective:*** The aim of this study was to establish the predictive ability of a comprehensive neonatal neuroimaging scale in symptomatic cCMV. ***Methods:*** Twenty-six infants were studied by neonatal cranial ultrasound scans (US; n = 25), CT (n = 11) and magnetic resonance imaging (MRI; n = 9). A previously validated neuroimaging scale comprising calcifications, ventriculomegaly and atrophy was compared to a newly proposed system adding cerebral dysgenesis and white matter disease. The findings were graded from 0 to 3. Neurodevelopmental assessment included motor and cognitive functions, epilepsy, vision, hearing and behavioral disorders. ***Results:*** Both scales showed a significant association with outcome ($p < 0.005$). Our scale was more accurate in predicting death or moderate-severe disability (area under the curve for scores ≥2, 0.88 ± 0.06 vs. 0.80 ± 0.08). All 5 infants with normal neuroimaging survived with intact neurological function. While our scale was highly associated with outcome in patients studied by MRI, it was unable to predict unfavorable outcomes in 2 patients with mildly abnormal US and/or CT. ***Conclusions:*** A comprehensive scale based on US and MRI predicts neurodevelopment in symptomatic cCMV. Significant destructive lesions are associated with a poor prognosis. While a strictly normal cranial US predicts a favorable outcome, in case of subtle US abnormalities, MRI is crucial for prognostication.

Introduction

Brain involvement is the most serious manifestation of symptomatic congenital cytomegalovirus (cCMV). CMV infection of the fetal central nervous system (CNS) can cause inflammatory and destructive lesions. In addition, when occurring during the first 2 trimesters, it can result in cerebral dysgenesis [1].

Table 1. Classification of neuroimaging findings in newborns with symptomatic cCMV infection

Score	Classic scoring system	New scoring system
0	None of the following abnormalities	None of the following abnormalities
1	Single punctate periventricular calcification and/or lenticulostriate vasculopathy	Single punctate periventricular calcification, lenticulostriate vasculopathy, caudothalamic germinolysis, ventriculomegaly (excluding severe)[1] and/or focal/multifocal white matter signal abnormality on MRI
2	Multiple discrete periventricular calcifications and/or severe ventriculomegaly[1]	Multiple discrete periventricular calcifications, paraventricular germinolytic cysts, severe ventriculomegaly[1], diffuse white matter signal abnormality and/or temporal lobe involvement
3	Extensive periventricular calcifications and/or brain atrophy	Extensive calcifications, brain atrophy, abnormal gyration, cortical malformation, dysgenesis of the corpus callosum and/or cerebellar hypoplasia

[1] Ventriculomegaly was defined as a ventricular index exceeding the 97th centile for gestational age and considered severe when the ventricular index surpassed the 97th centile plus 4 mm [12].

AlarcónA, , Martinez- Biarge M, Cabañas et al Neonatology 2016; 110:277-285

Objectives:

- Identify:
  - Prospective study in order to produce evidence that helps deciding whether to treat or not newborns with congenital CMV infection and mild signs of CNS involvement.
  - Each participating Centre must have the possibility to scan patients with MRI (and to send the images for centralized analysis) and of course to perform high quality

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Objetives

- 1) Assessment of **Minor findings**
- Germinolysis/pseudocysts is NOT a problem as we are planning to centralize MRI scan assessment in Genoa / Lenticulostriate vasculopathy

- 2) Definition of "Abnormal white matter" is NOT difficult if we use a double reader and blinded QUALITATIVE assessment of white matter signal intensity, followed by agreement by the two blinded readers (again, centralizing MRI images allows to avoid one bias);

- 3) However, as we aim to produce a high-quality evidence (high quality methods & imaging), we would like to use a QUANTITATIVE assessment of white matter involvement. Therefore, we are trying to calculate the normal values of ADC in different ROIs of white matter among normal