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Brief report

Congenital cytomegalovirus infection in newborns born to HIV-infected mothers

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ABSTRACT

Introduction: Congenital citomegalovirus (CMVc) infection is more common in children exposed to HIV during pregnancy, with reported rates in pre-ART era from 2 to 7%. The use of combined antiretroviral treatment (ARTc) could be a determining factor in reducing this risk of CMV transmission. The aim of this study was to describe the epidemiology of CMVc infection in newborns of HIV-infected mothers at Hospital Universitario 12 de Octubre, Madrid, Spain, from 2000 to 2017.
Material and methods: An observational and retrospective study was carried out. Epidemiological and clinical variables were collected. Statistical analysis was performed with the SPSS 24.0 computer program.
Results: 288 mother-infant pairs were included in the study. We observed a CMVc rate of 2.1% (95% CI 0.9–4.9).
Conclusions: The rate of CMVc in HIV-exposed children observed was lower than that reported in pre-ARTc era but seems higher than those described in general population.

Infección congénita por CMV en recién nacidos hijos de madre con infección por VIH

Palabras clave:
CMV
Infección congénita
VIH
Gestación
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RESUMEN

Introducción: La infección congénita por CMV (CMVc) es más frecuente en hijos expuestos al VIH durante la gestación, con tasas reportadas en la era pre-TAR del 2 al 7%. El control de la carga viral de VIH y la recuperación inmunológica asociada al tratamiento antirretroviral (TAR) podrían ser factores que influyesen en su transmisión. El objetivo de este trabajo fue describir la epidemiología de la infección CMVc en recién nacidos expuestos al VIH en el Hospital Universitario 12 de Octubre entre los años 2000–2017.
Material y métodos: Estudio observacional y retrospectivo. Se recogieron variables epidemiológicas y clínicas a través de la historia clínica de los sujetos incluidos. Se realizó análisis estadístico con el programa informático SPSS 24.0.
Resultados: Se incluyeron 288 pares de madres/hijos. Observamos una tasa de CMVc del 2.1% (IC 95% 0.7–4.9).
Conclusiones: La tasa de CMVc fue menor a la comunicada en la era pre-TAR, aunque aún parece superior a la observada en niños no expuestos al VIH.

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◊ The annex lists the authors who are members of the Working Group on cCMV in children exposed to HIV.

Introduction

Congenital CMV infection (cCMV) is one of the most common causes of sensorineural hearing loss of non-genetic origin and is also a frequent cause of neurological conditions in childhood.[1,2]

According to previous studies, rates of cCMV infection could be higher in children exposed to HIV perinatally (2–7%).[3–6]

Following the widespread use of antiretroviral therapy (ART), some studies have demonstrated that cCMV rates decreased in HIV-exposed uninfected children.[5,7,8] However, the impact of the duration of ART in pregnancy in relation to the rates of cCMV is not yet well understood.[7]

The objective of this study was to describe the epidemiology of cCMV in children exposed to HIV-1 perinatally at the Hospital Universitario 12 de Octubre.

Material and methods

An observational and retrospective study of children exposed to HIV-1 perinatally at the Hospital Universitario 12 de Octubre in Madrid. All cases of pregnant women diagnosed with HIV-1 infection were recorded and variables, both clinical and laboratory, were selected from the data recorded in the Madrid Cohort of mothers with HIV infection and their exposed children. The characteristics of this cohort have been described previously.[9] During the years included in the study, CMV urine culture or PCR was routinely performed at birth in these children. The clinical data of children with cCMV were obtained from a review of the medical records and the database of the Registro Estatal de Infección Congénita por CMV [Congenital CMV Infection State Registry].[10] To evaluate epidemiological changes, two temporal cohorts were defined: Cohort 1 (2000–2008) and Cohort 2 (2009–2017).

Congenital CMV infection was defined as virus detection in urine in the first two weeks of life, or retrospectively by PCR for CMV from filter paper blood used for metabolic screening in newborns (Guthrie card). Prematurity was defined as birth before 37 weeks of gestational age.

Quantitative variables were expressed as medians and ranges, and compared using the Mann–Whitney *U* test Qualitative variables were expressed in absolute frequencies and percentages and compared using Pearson's Chi-square test. Results with a p value <0.05 were considered statistically significant. Statistical analysis was performed with the software program SPSS, version 24.0, IBM, USA.

The study was approved by the Clinical Research Ethics Committee of the Hospital Universitario 12 de Octubre (CREC No. 21/224).

Results

288 pairs of mothers and children were included in the study, with 209 corresponding to Cohort 1.

Epidemiological characteristics are shown in Table 1. The mothers were mainly of Caucasian ethnicity, with a significant increase in the immigrant population in Cohort 2. We observed a significant decrease in the acquisition of HIV infection associated with intravenous drug use and a lower prevalence of HCV and HBV co-infection in Cohort 2.

In the second period, a higher percentage of women received antiretroviral therapy (ART) during pregnancy and for a longer time, although this difference was not significant. However, we observed a significantly higher percentage of women with undetectable HIV viral load close to delivery in Cohort 2. The vertical HIV transmission rate was 1.4% (95% CI 0.4–3.6).

A cCMV study was performed on a total of 236 (82%) children. The number of children screened was lower in Cohort 1 (77%) compared to Cohort 2 (95%). We observed a cCMV rate of 2.1% (95% CI 0.7–4.9), which corresponded to four cases (2.5%) in Cohort 1, and one case (1.3%) in Cohort 2.

Four cases of congenital CMV were detected at birth. In case five, the diagnosis was made retrospectively by means of PCR using the newborn metabolic screening Guthrie card. Table 2 shows the main characteristics of the cCMV cases.

It is worth noting that cases four and five had a head circumference less than or equal to the third percentile at birth. In cases two and four, mild and moderate intrauterine growth restriction was detected, respectively, during pregnancy. No hearing loss or neurodevelopmental abnormalities were detected in these patients during follow-up. Case three was diagnosed at birth with bilateral sensorineural hearing loss in the brainstem auditory evoked response test, which was more pronounced in the right ear (30 dB), and received treatment with valganciclovir for six months. None of the other cases received valganciclovir.

Discussion

This study describes the epidemiological changes of cCMV infection in children exposed to HIV perinatally over almost two decades at Hospital 12 de Octubre. We observed a rate of cCMV of 2.1% (95% CI 0.7–4.9).

The most notable results from the cohort show a percentage increase in immigrant women in the second period, which is also accompanied by a decrease in HIV infections related to parenteral drug use and HBV and HCV co-infections. Similarly, we observed better control of viral load associated with ART. The vertical transmission rate of HIV remains below 2% in the cohort. The epidemiological changes observed show the changing profile of these women over time, as well as the improvements in the measures implemented to prevent vertical transmission of HIV.[11]

In the pre-ART era, cCMV rates in perinatally HIV-exposed uninfected newborns were estimated to be between 2% and 7%.[3–5] These results were justified by a greater probability of viral reactivation of CMV during pregnancy due to the state of immunosuppression inherent to the infection.[1] Based on this, the introduction of ART could be a determining factor in reducing transmission. In the French Cohort, a reduction in cCMV transmission rates to 1.2% in the ART era, compared to 3.5% in the pre-ART era, was observed.[5] However, this decrease was not observed in a cohort of HIV-exposed children in the United States, despite the use of ART.[7]

In the previous study at the Hospital 12 de Octubre, involving patients from the pre-ART era and the first few years of ART, which included a total of 257 children, the cCMV rate was 4.6% (95% CI, 2.5–7.8). In the first stage of this study, from 1987 to 1997, which corresponds to the era prior to combination ART in pregnant women, the cCMV rate was 9.2% (95% CI, 4.7–15.8).[12] Thus, over time, from the pre-ART era to the present, we observed a progressive decrease in cCMV rates at Hospital 12 de Octubre which, like that observed in other cohorts, suggests that the introduction of ART and secondary immune reconstitution could be a decisive factor in CMV transmission.

Although the cCMV rates obtained in our study could represent low rates, we must be cautious when comparing them directly with the general population. In a recent prospective study in the general population (PICCSA study), which included more than 3000 neonates, carried out at Hospital Universitario 12 de Octubre in 2017, a prevalence of cCMV infection of 0.47% was observed.[2] Based on the results of our study and compared with the results of the PICCSA study, the rate of cCMV transmission in perinatally HIV-exposed uninfected children continues to be higher than that of the general population.

Table 1
Characteristics of pregnant women with HIV infection and exposed children.

	Total	Cohort 1	Cohort 2	p
Maternal age [median, IQR]; (n = 268)	32 (16–44)	33 (17–41)	32 (16–44)	0.510
Ethnicity [n, %]; (n = 265)				<0.0001
White	168 63.4%	147 73.1%	21 32.8%	
Latin American	47 17.7%	27 13.4%	20 31.3%	
Sub-Saharan African	43 16.2%	24 11.9%	19 29.7%	
North African	4 1.5%	3 1.5%	1 1.6%	
Eastern European	3 1.1%	0 0.0%	3 4.7%	
Risk factors for acquiring HIV [n, %]; (n = 262)				0.031
Vertical	7 2.7%	3 1.5%	4 6.7%	
Heterosexual	180 68.7%	136 67.3%	44 73.3%	
Intravenous drug use	75 28.6%	63 31.2%	12 20.0%	
Maternal diagnosis of AIDS? [n, %]; (n = 264)				0.522
Yes	34 12.9%	27 13.6%	7 10.6%	
No	230 87.1%	171 86.4%	59 89.4%	
Maternal HCV co-infection? [n, %]; (n = 252)				<0.0001
Yes	77 30.6%	70 37.6%	7 10.6%	
No	175 69.4%	116 62.4%	59 89.4%	
Maternal HBV co-infection? [n, %]; (n = 249)				0.080
Yes	24 9.6%	21 11.7%	3 4.3%	
No	225 90.4%	159 88.3%	66 95.7%	
Maternal percentage of CD4 lymphocytes at 1st pregnancy visit [n, %]; (n = 175)				0.328
<15%	18 10.3%	15 11.6%	3 6.5%	
≥15%	157 89.7%	114 88.4%	43 93.5%	
Maternal CD4 lymphocytes at 1st pregnancy visit [n, %]; (n = 192)				0.129
<200/mm^3	18 9.4%	16 11.3%	2 4.0%	
≥200/mm^3	174 90.6%	126 88.7%	48 96.0%	
Maternal viral load at 1st pregnancy visit [n, %]; (n = 188)				<0.0001
≤50 copies/ml	69 36.7%	36 25.2%	33 73.3%	
>50 copies/ml	119 63.3%	107 74.8%	12 26.7%	
Maternal percentage of CD4 lymphocytes at last pregnancy visit [n, %]; (n = 188)				0.048
<15%	15 8.0%	14 10.6%	1 1.8%	
≥15%	173 92.0%	118 89.4%	55 98.2%	
Maternal CD4 lymphocytes at last pregnancy visit [n, %]; (n = 208)				0.715
<200/mm^3	15 7.2%	10 6.7%	5 8.5%	
≥200/mm^3	193 92.8%	139 93.3%	54 91.5%	
Maternal viral load at last pregnancy visit [n, %]; (n = 263)				0.002
≤50 copies	170 64.6%	115 59.2%	55 79.7%	
>50 copies	93 35.4%	79 40.8%	14 20.3%	
Antiretroviral therapy during pregnancy [n, %]; (n = 267)				0.172
Yes	245 91.8%	179 90.4%	66 95.7%	
No	22 8.2%	19 9.6%	3 4.3%	
Duration of antiretroviral therapy [n, %]; (n = 229)				0.141
≤12 weeks' duration	26 11.4%	22 13.3%	4 6.3%	
>12 weeks' duration	203 88.6%	144 86.7%	59 93.7%	
Type of ART [n, %]; (n = 251)				0.080
HAART with PI	203 80.9%	144 78.3%	59 88.1%	
HAART without PI	48 19.1%	40 21.7%	8 11.9%	
Monitored pregnancy? [n, %]; (n = 269)				0.008
Yes	245 91.1%	174 88.3%	71 98.6%	
No	24 8.9%	23 11.7%	1 1.4%	
Delivery method [n, %]; (n = 279)				0.032
Elective caesarean	92 33.0%	75 37.3%	17 21.8%	
Unplanned caesarean	58 20.8%	42 20.9%	16 20.5%	
Unassisted vaginal	124 44.4%	82 40.8%	42 53.8%	
Instrumental vaginal	5 1.8%	2 1.0%	3 3.8%	
Premature newborn; (n = 278)				0.086
Yes	68 24.5%	55 27.3%	13 16.9%	
No	210 75.5%	146 72.7%	64 83.1%	
Newborn with confirmed HIV infection? [n, %]; (n = 288)				0.296
Yes	4 1.4%	2 1.0%	2 2.5%	
No	284 98.6%	207 99.0%	77 97.3%	
Congenital CMV infection? [n, %]; (n = 236)				0.810
Yes	5 2.1%	4 2.5%	1 1.3%	
No	231 97.9%	157 97.5%	74 98.7%	

ART: antiretroviral therapy; CMV: cytomegalovirus; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IQR: interquartile range; PI: protease inhibitor.

Several authors have raised the importance not only of ART, but also of the time of starting ART and the associated immune recovery, as determining factors in CMV transmission, so that women who have started ART prior to pregnancy, and with adequate immune recovery, would be those with the lowest risk of transmission. In our study, in two of the cases of cCMV infection, the women started ART during pregnancy. In the other three cases, the women received ART from before conception with adequate immune recovery.

With all this, we would like to stress the importance of CMV screening in all newborns exposed to HIV infection during preg-

Table 2
Characteristics of newborns with cCMV infection.

Case no.	Case 1	Case 2	Case 3	Case 4	Case 5
Maternal diagnosis of HIV	Prior to pregnancy	Prior to pregnancy	During pregnancy	Prior to pregnancy	During pregnancy
Monitored pregnancy?	Yes	Yes	Yes	Yes	Yes
Year of birth	2001	2003	2005	2005	2010
GA at birth	36 + 6	35 + 1	38 + 5	37 + 5	40 + 5
Sex of the newborn	Male	Male	Male	Female	Female
ART before the pregnancy	Yes	Yes	No	Yes	No
ART during the pregnancy	Yes	Yes	Yes	Yes	Yes
Weeks of treatment during pregnancy	>12	≤12	>12	>12	>12
Maternal number of CD4/mm^3 at 1st pregnancy visit	759	520	301	802	140
Viral load at last visit during pregnancy (copies/ml)	<50	<50	<50	74	<50
Confirmed HIV infection in the newborn	No	No	No	No	No
Type of delivery	Singleton	Twin	Singleton	Singleton	Singleton
Delivery method	Unassisted vaginal	Emergency caesarean section due to non-progression	Unassisted vaginal	Unassisted vaginal	Unassisted vaginal
Breast-feeding mother	No	No	No	No	No
Birth weight [g] (percentile)	3310 (p50)	1750 (p5)	3600 (p80)	2010 (p1)	2990 (p18)
Length at birth [cm] (percentile)	49 (p50)	41 (<p1)	49 (p31)	45 (p4)	48 (p11)
Head circumference at birth [cm] (percentile)	32 (p10)	31 (p10)	35 (p31)	32 (p3)	33 (p3)
Hearing loss at birth (BAER)	No	No	Yes	No	No
Neurodevelopmental abnormality	No	No	No	No	No

HIV: human immunodeficiency virus; GA: gestational age; ART: antiretroviral therapy; BAER: brainstem auditory evoked response.

nancy. This recommendation is included as part of the national consensus documents and represents an important opportunity to start antiviral treatment that, in symptomatic patients, can prevent the progression of the disease.[13]

This study had some limitations. This was a retrospective study, where there may have been bias in the collection of variables. However, as it is a large series, it is presumable that the results adequately represent the changes produced at the Hospital Universitario 12 de Octubre over these years. In addition, we observed a different distribution of cases between the two cohorts when dividing them according to a temporal criterion. Although this may lead to difficulties in the analysis, on the other hand it allows us to observe epidemiological differences and differences in care practices over time. Lastly, during part of the first stage of our study, the performance of urine culture or PCR for CMV at birth in children of mothers with HIV infection was not included as a recommendation in the clinical guidelines, so the prevalence of cCMV in the first cohort could have been underestimated because a diagnostic test was not performed in a percentage of cases.

In conclusion, in this ART-era cohort, we observed a cCMV rate of 2.1% (95% CI 0.7–4.9) in children exposed to HIV perinatally, which, although lower than that reported in the era prior to ART, is higher than that observed in children of mothers without HIV infection in our setting. Additional studies, including large cohorts, will be necessary to elucidate the effect of ART and immune recovery on mother-to-child transmission of CMV in HIV-infected pregnant women.

Author contribution

Dr Prieto, Dr Rubio Mancha and Dr Torres Pastor performed the literature review, developed the project, performed the analysis, and drafted the initial manuscript. Dr Prieto, Dr Blázquez Gamero, Dr Torres Fernández, Dr Manzanares, Dr Muñoz, Dr Moraleda, Dr Fernández Cooke, Dr Epalza Ibarrondo, Dr Villaverde, Dr Rojo and Dr Ramos Amador recorded all the data during the study period.

Dr Mazariegos and Dr Prieto participated in the analysis. All authors critically reviewed the manuscript prior to acceptance.

All authors approved the final manuscript as is.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Authors who are members of the Working Group on cCMV in children exposed to HIV

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