Las serologías fueron todas negativas (*Brucella* spp, toxoplasma, sífilis, hepatitis B y C, VIH, *Coxiella* spp, *Borrelia* spp, *Rickettsia* spp) con positividad IgG para herpes simple, Epstein-Barr y anticuerpos IgG e IgM para parvovirus. La autoinmunidad fue también negativa (ANA, AMA y ENA). Finalmente el diagnóstico del paciente fue probable infección aguda por parvovirus B19 y uveítis anterior bilateral.

Se estima que solo el 20% de las uveítis anteriores son de origen infeccioso, son causadas en su mayoría por virus de la familia Herpesviridae[4]. No obstante, existen pocos casos descritos de infección por parvovirus B19 y uveítis. Los cuatro casos publicados con anterioridad (tabla 1) fueron pacientes menores de 18 años; este el primero de edad adulta[5–8]. Existen dos teorías acerca de la afectación ocular por parvovirus B19: la invasión directa del virus por un lado y la inducción de autoinmunidad por otro[8]. En nuestro caso no se detectaron autoanticuerpos, por lo que presumimos que una invasión directa del virus fue la causa de la uveítis. Así mismo, nuestro paciente tampoco presentó el típico eritema infeccioso. El paciente fue tratado de forma sintomática con paracetamol y antiinflamatorios no esteroides (AINE); mejoró la clínica sistémica. El cuadro de uveítis anterior bilateral respondió al tratamiento corticoideo tópico sin asociar complicaciones, con un buen control posterior.

Presentamos el único caso de uveítis bilateral anterior asociada a probable infección aguda por parvovirus B19 en adultos publicado hasta el momento. El cuadro seudogripal acompañado de artralgias y el desarrollo posterior de uveítis con positivización de IgM para parvovirus B19 condujo al diagnóstico. La uveítis debe ser considerada como una complicación poco frecuente en la segunda fase de infección por parvovirus B19. La comunicación de más casos similares es fundamental para conocer los mecanismos fisiopatológicos de la afectación ocular por dicho virus.

## Bibliografía


1. Jain A, Kant R. Genotypes of erythrovirus B19, their geographical distribution & circulation in cases with various clinical manifestations. Indian J Med Res. 2018 03;147:239–47, http://dx.doi.org/10.4103/ijmr.IJMR_1816_16.
2. Parra D, Mekki Y, Durieu I, Broussolle C, Sève P. [Clinical and biological manifestations in primary parvovirus B19 infection in immunocompetent adult: a retrospective study of 26 cases]. Rev Med Interne. 2014 May;35:289–96, http://dx.doi.org/10.1016/j.revmed.2013.04.015.
3. Kishore J, Kishore D. Clinical impact & pathogenic mechanisms of human parvovirus B19: A multiorgan disease inflictor incognito. Indian J Med Res. 2018 Oct;148:373–84, http://dx.doi.org/10.4103/ijmr.IJMR_533_18.
4. Pleyer U, Chee SP. Current aspects on the management of viral uveitis in immunocompetent individuals. Clin Ophthalmol. 2015;9:1017–28, http://dx.doi.org/10.2147/OPTH.S60394.
5. Corridan PG, Laws DE, Morrell AJ, Murray PI. Tonic pupils and human parvovirus (B19) infection. J Clin Neuroophthalmol. 1991;11:109–10.
6. Maini R, Edelsten C. Uveitis associated with parvovirus infection. Br J Ophthalmol. 1999;83:1403–4, http://dx.doi.org/10.1136/bjo.83.12.1403.
7. Hsu D, Sandborg C, Hahn JS. Frontal lobe seizures and uveitis associated with acute human parvovirus B19 infection. J Child Neurol. 2004;19:304–6, http://dx.doi.org/10.1177/088307380401900413.
8. Ito T, Hoshina T, Mizuki K, Fukuda T, Ishibashi S, Kusuhara K. A pediatric case with parvovirus B19-associated uveitis without autoantibody formation. Nagoya J Med Sci. 2018;80:611–4, http://dx.doi.org/10.18999/nagjms.80.4.611.



Borja Arias-Peso[a,*], Alba Navarro-Bielsa[b], María José Vicente Altabas[a] y Nieves Pardiñas Barón[a]

[a] *Servicio de Oftalmología, Hospital Universitario Miguel Servet, Zaragoza, España*
[b] *Servicio de Dermatología, Hospital Universitario Miguel Servet, Zaragoza, España*

* Autor para correspondencia.
*Correo electrónico:* arias_bor@hotmail.com (B. Arias-Peso).


https://doi.org/10.1016/j.eimc.2020.04.002


## Absence of maternal HHV-6-specific T-cell response in the setting of human Herpesvirus-6 chromosomal integration: Potential impact on congenital infection

### *Ausencia de respuesta de células T específicas materna en el contexto de la integración cromosómica del herpesvirus-6 humano: impacto potencial en la infección congénita*

Human herpesvirus 6 (HHV-6) is a ubiquitous pathogen, whose primary infection is often asymptomatic and manifests as exanthema subitum in only 20% of cases.[1]

HHV-6 has the capacity to integrate into the human genome (ciHHV-6). However, the mechanisms involved in HHV-6 integration are still largely unknown.[2–4] HHV-6 Integration into the gametes results in Mendelian transmission to offspring, with 1% of the worldwide human population carrying ci-HHV-6.[5]

It is well established that congenital HHV-6 infection results from the germline passage of ci-HHV-6 and the transplacental passage of maternal HHV-6 infection by either maternal primary infection or maternal virus reactivation.[6] The severity of HHV-6 congenital disease largely depends on the intensity and duration of viral replication, and is related to the maternal anti-HHV6 immune response and the implementation of antiviral treatment. HHV-6 congenital infections are usually asymptomatic[6,7] most likely due to the immune protection provided by maternal immunity. Nevertheless, the impact of the absence of maternal HHV-6-specific immune response in the setting of ci-HHV6 on the development of congenital HHV-6 infections is unknown.[8]

We describe the case of a 35-year-old pregnant woman without a relevant clinical history. Fetal screening sonography at week 12 of the pregnancy showed an isolated severe fetal pleural effusion. Amniocentesis was subsequently performed with a negative result for trisomy 13, 18 and 21. Nevertheless, real-time PCR in amniotic fluid was positive for HHV-6A and negative for other infections (varicella zoster virus, cytomegalovirus, Epstein–Barr virus, toxoplasmosis, herpesvirus 1 and 2 and Parvovirus B19). The patient presented a self-limited abdominal rash at weeks 8 of pregnancy as the only clinical symptom. Given the presence of massive fetal pleural effusion, the patient terminated the pregnancy at 22 weeks. The fetal autopsy showed a prominent pleural effusion, although no other macroscopic alterations were identified. Since HHV-6A had been previously detected in the amniotic fluid, the presence of HHV-6 real-time PCR was investigated in fetal tissues. Hence, all fetal tissues evaluated, including brain and lung tissues, showed the presence of HHV-6A. Four months after the abortion, the patient was referred to the infectious diseases unit of the hospital. HHV-6 viral loads were monitored in the patient by quantitative PCR in plasma (5.083 copies/ml) and whole blood (4.896.701 copies/ml) samples. A HHV-6 antiviral treatment with 900 mg of oral valganciclovir every 12 h was initiated. After four weeks, the HHV-6 PCR remained positive (6.940 copies/ml). Consequently, genotypic antiviral resistance testing for HHV-6 was

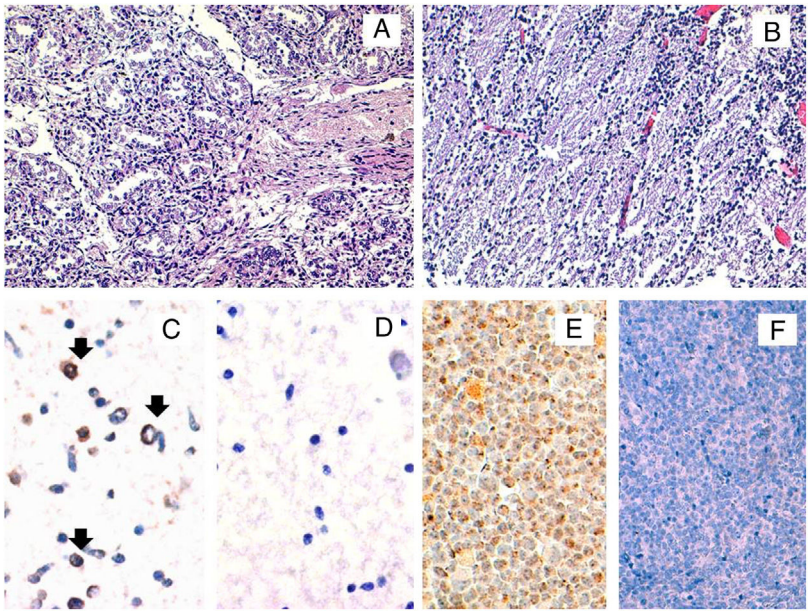


**Fig. 1.** Histopathological and HHV-6A immunohistochemical studies in fetal tissues. The microscopic study by conventional hematoxylin and eosin stainings of the fetal lung (A) and brain (B) tissues did not reveal any histopathological finding. The immunohistochemical study for the HHV-6 late antigen gp116/64/54 showed positive cells in the brain (black arrows) (C). Representative image of HHV-6 negative brain control tissue incubated with protease negative control reagent (D) HSB2 cells infected with HHV-6A were used as a positive control (E). HHV-6 negative tonsil tissue was used as a negative control (F). Original magnifications: A and B: 200×; C, D and E: 400×.

performed in plasma samples. This study did not reveal mutations associated with ganciclovir resistance.

We studied the HHV-6 serostatus in all family members (including her parents and three of her father's cousins who did not present any complications during the pregnancies). All members were found to be HHV-6-seropositive. In addition, we performed a ci-HHV-6 study from hair follicles. The study revealed that the patient (and the patient's father) were ciHHV-6A, while the patient's mother had undetectable HHV-6 DNA levels. In addition, the ci-HHV-6 analysis showed that only one cousin, named cousin 2, was also ciHHV-6A. Both, the patient's father and cousin 2 had HHV-6 positive viral load in plasma (260 copies/ml and 395 copies/ml respectively).

Since fetal tissues were positive for HHV-6 by real-time PCR in a mother with ci-HHV-6, we tested for the presence of ci-HHV-6 in the fetus by FISH. As expected, HHV-6 signals were observed in most (95%) of the evaluated cells in both brain and lung fetal tissues.

In order to confirm the expression of viral proteins, immunohistochemical staining for the late antigen gp116/64/54 was performed. Positivity was observed in the brain, thus suggesting an active infection but not in the lung (Fig. 1). All female family members showed HHV-6-specific response for at least one cytokine in at least either CD4+ or CD8+ cells, except the patient. When we compared the cytokine production between both ciHHV-6A female family members, we observed that cousin 2 produced IFN-γ and TNF-α, while the patient did not show any cytokine production.

We studied if the patient's lack of response to HHV-6 antigens also occurred against another viral antigen such as CMVpp65, which is a highly immunodominant protein for T-cell responses. We observed that her CMV-specific response was restricted to the production of TNF-α.

In conclusion, we present a case of HHV-6 congenital infection in the setting of ci-HHV-6 with an absence of maternal HHV-6-specific T-cell response, which suggests the possible role of maternal HHV-6 immunity on the development of congenital infection. Further studies are necessary to confirm our observations.

## Funding

This work was supported by Plan Nacional I+D+I 2013-2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Economía y Competitividad, Spanish Network for Research in Infectious Diseases (REIPI RD12/0015 and RD16/0016) co-financed by European Development Regional Fund ERDF "A way to achieve Europe", Operative program Intelligent Growth 2014–2020.

*Other researchers participating in the study*: Julián Torre-Cisneros, Manuel Causse (Hospital Reina Sofia, Córdoba), Anna Cervilla, Marta Marginet, Antonio Martinez (Clinic Hospital, Barcelona).

## Conflict of interests

All authors report no conflicts of interest relevant to this article.

## Acknowledgements

We are grateful to the patient and all family members.

## Bibliografía

1. Yamanishi K, Okuno T, Shiraki K, Takahashi M, Kondo T, Asano Y, et al. Identification of human herpesvirus-6 as a causal agent for exanthem subitum. Lancet. 1988;1:1065–7, http://dx.doi.org/10.1016/s0140-6736(88)91893-4.
2. Luppi M, Marasca R, Barozzi P, Ferrari S, Ceccherini-Nelli L, Batoni G, et al. Three cases of human herpesvirus-6 latent infection: integration of viral genome in peripheral blood mononuclear cell DNA. J Med Virol. 1993;40:44–52, http://dx.doi.org/10.1002/jmv.1890400110.
3. Arbuckle JH, Medveczky MM, Luka J, Hadley SH, Luegmayr A, Ablashi D, et al. The latent human herpesvirus-6A genome specifically integrates in telomeres of human chromosomes in vivo and in vitro. Proc Natl Acad Sci USA. 2010;107:5563–8, http://dx.doi.org/10.1073/pnas.0913586107.
4. Tweedy J, Spyrou MA, Pearson M, Lassner D, Kuhl U, Gompels UA. Complete genome sequence of germline chromosomally integrated human herpesvirus 6A and analyses integration sites define a new human endogenous virus with potential to reactivate as an emerging infection. Viruses. 2016:8, http://dx.doi.org/10.3390/v8010019.
5. Clark DA, Ward KN. Importance of chromosomally integrated HHV-6A and -6B in the diagnosis of active HHV-6 infection. Herpes. 2008;15:28–32.

6. Hall CB, Caserta MT, Schnabel KC, Shelley LM, Carnahan JA, Marino AS, et al. Transplacental congenital human herpesvirus 6 infection caused by maternal chromosomally integrated virus. J Infect Dis. 2010;201:505–7, http://dx.doi.org/10.1086/650495.
7. Hall CB, Caserta MT, Schnabel KC, Boettrich C, McDermott MP, Lofthus GK, et al. Congenital infections with human herpesvirus 6 (HHV6) and human herpesvirus 7 (HHV7). J Pediatr. 2004;145:472–7, http://dx.doi.org/10.1016/j.jpeds.2004.06.017.
8. Lanari M, Papa I, Venturi V, Lazzarotto T, Faldella G, Gabrielli L, et al. Congenital infection with human herpesvirus 6 variant B associated with neonatal seizures and poor neurological outcome. J Med Virol. 2003;70:628–32, http://dx.doi.org/10.1002/jmv.10441.

Isabel Machuca[a,b,1], Rocío Aguado[a,b,1], Luis Veloza[c], M. Ángeles Marcos[d,*]

[a] *Clinical Unit of Infectious Diseases, Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Reina Sofía University Hospital/University of Cordoba, Cordoba, Spain*
[b] *Spanish Network for Research in Infectious Diseases (REIPI RD12/0015 and RD16/0016), Instituto de Salud Carlos III, Madrid, Spain*
[c] *Department of Pathology, Clínic Hospital, Barcelona, Spain*
[d] *Microbiology Unit, Clínic Hospital, University of Barcelona, ISGLOBAL Institute for Global Health, Barcelona, Spain*

* Corresponding author.
*E-mail address:* mmarcos@clinic.ub.es (M.Á. Marcos).
[1] R.A. and I.M. both have contributed equally to this work.

https://doi.org/10.1016/j.eimc.2020.04.003


## No decrease in CD4/CD8 ratio after 36 months therapy in patients switched to dual regimens containing rilpivirine

### *Estabilidad del cociente CD4/CD8 a los 36 meses de tratamiento en pacientes que cambiaron a doble terapia con regimenes que incluyen rilpivirina*

Dual therapy (DT) for maintenance is nowadays a very interesting option. Several regimens have been tested, among those rilpivirine containing regimens avoid drawbacks and toxicities due to the nucleosidic backbone, while maintaining the efficacy and convenience of robust ART. Rilpivirine (RPV) in combination with dolutegravir (DTG) or darunavir (DRV) have shown to be effective, safe and well tolerated.[1–4] The SWORD-1 and SWORD-2[1] studies had provided relevant evidence on the DTG/RPV regimen however the DRVb/RPV combination has been less investigated. DRVb/RPV combine both a high efficacy and genetic barrier with a lower pill burden, especially when DRV is used coformulated with cobicistat. Safety and effectiveness among those receiving DRV/r with those receiving DRV/c[4] seems to be similar. Cobicistat, generally considered to be an equipotent inhibitor of CYP3A4, was approved to address limitations of ritonavir such as co-formulation difficulties and drug interactions secondary to its broad effects on CYP isoenzymes and drug transporters.

However, although DT has been proved effective, there is concern about whether it may be associated with a worse immune control that leads to a progressive CD4/CD8 ratio decrease. Low CD4/CD8 ratio is known to be a predictor of non-AIDS related events, non-AIDS-defining cancers and mortality in HIV-patients.

Some studies have explored the effect of DT on CD4/CD8 ratio[5–8] but nowadays just few data with mixed results are available. In the case of rilpivirine in combination with dolutegravir or darunavir information is scarce and in all cases for a follow-up period no longer than 48 weeks.[2,9,10]

In this context, we aimed to evaluate the changes in the CD4/CD8 ratio, after 36 months of treatment, in a group of patients who changed to DT with rilpivirine containing regimens.

We conducted a retrospective, descriptive, study including all the patients from an HIV Clinic at the Arnau de Vilanova Hospital in Valencia, Spain who switched to RPV (25 mg daily) and DRV cobicistat (800/150 mg daily) or RPV (25 mg daily) and DTG (50 mg daily) between January 2014 and December 2016. Patients were previously on triple therapy and should have VL < 50 copies/mL for at least 6 months before switch. The last registers before switch of CD4, CD8 cell count and CD4/CD8 ratio and after 12, 24, 36 months of DT were recorded. Mean and CI 95%, were calculated for quantitative variables and frequencies for qualitative variables. The *t*-test for repeated measures was applied. The variables were retrieved from the medical records and analyzed with the GNU. PSPP Statistical Analysis Software. Release 1.0.1-g 818227.

The study had the approval of the ethic committee, patient's anonymity was carefully protected and all the guidelines required by the institution were strictly followed.

From a total of 61 patients on DT, 7 were excluded because VL was not <50 copies/mL before switch. Finally, 54 patients entered the analysis, 31 of them were on RPV/DTG and 23 were on RPV/DRVc. The mean age was 51 (CI 95%: 49–53) years and 50% were men. Patients had suppressed VL for a mean of 6 (CI 95%: 5–8) years before switch and the mean of CD4 cells at switch was 740 (CI 95%: 646–834) cell/mm$^3$. Mean time on DT was 33 months. No differences were observed among baseline characteristics between groups. During the follow-up period just one patient, in the DRVc/RPV group, had VL > 50 copies/mL in 2 consecutive determinations after one year of treatment, and it was due to poor adherence, finally he was lost to follow-up. No significant variations for the CD4, CD8 cell count and the CD4/CD8 ratio after 12, 24 and 36 months of treatment are found in Table 1. The results did not change after stratified analysis for type of therapy (RPV/DTG or RPV/DRVc).

Previous studies showed diverse results such as that of Mussini et al.[6] which showed that patients who remained on triple regimen had a higher mean CD4/CD8 ratio increased when compared to those who switched to DT or monotherapy. In others studies, such as TivEdo study, Capetti et al.[10] observed no decrease in the CD4/CD8 ratio at 48 weeks after treatment simplification with DTG/RPV. Pasquau et al.[3] also reported a slight increase in the