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Case Report

Case report on early treatment with valaciclovir after maternal primary cytomegalovirus infection

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ABSTRACT

Background: Cytomegalovirus (CMV) is the main cause of congenital viral infections. Current guidelines do not include any recommendation about antenatal treatment. Most studies that evaluate the efficacy of valaciclovir aim to treat infected symptomatic fetus but the benefit of anti-CMV therapy remains unclear.
Case presentation: We report the case of cytomegalovirus seroconversion during the second trimester of pregnancy. Early treatment with valaciclovir was introduced, associated with a close monitoring of maternal CMV viremia. The virus was no longer detected in maternal blood soon after the beginning of antiviral therapy. Valaciclovir was stopped at 24 + 5 WG after negative prenatal diagnosis but CMV viremia was still monitored in maternal blood until the end of pregnancy.
Conclusion: The neonate was not infected and remained asymptomatic. It suggests that early treatment with valaciclovir 8 g per day could be effective in quickly reducing maternal viral load and lowering the risk of vertical CMV transmission.

Background

Routine screening for maternal cytomegalovirus (CMV) infection is currently not recommended in France, as in most countries [1]. Seroprevalence is around 50% in France and primary CMV infection will occur in approximately 1% of pregnant women, resulting in a 0.2 to 0.3% incidence of congenital infection following maternal primary infection. No prenatal treatment has yet been fully validated (valaciclovir nor immunoglobulin therapy) and management of pregnant women at risk of transmitting CMV is mainly based on close ultrasound monitoring [2]. The most frequent ultrasound abnormalities related to congenital CMV infection are intrauterine growth restriction, hyperechogenic bowel, hepato-splenomegaly, liver calcifications, microcephaly, hydrocephaly, ventriculomegaly, increased periventricular echogenicity and periventricular pseudocysts [3–5].

Case presentation

Our policy in the obstetrics department of Antoine Béclère Hospital (Clamart, France) is to offer systematic screening for CMV infection to each woman at the first prenatal visit. We report here the case of a 30-year-old pregnant woman not immunized against CMV (IgG negative, IgM negative) at the beginning of pregnancy. At 17 + 5 weeks of gestation (WG) she presented flu-like syndrome. CMV serology was negative (IgG negative, IgM negative). At 18 + 3 WG, CMV-IgM appeared followed by CMV IgG at 19 + 4 WG. At 21 + 3 WG, CMV IgG and CMV-IgM were positive and CMV-IgG avidity was very low, confirming recent primary CMV infection.

Close monitoring of CMV serology and maternal viral load was initiated (Figs. 1 and 2).

The viral load was done in the whole blood, in EDTA tube. The reagent used was

CMV QS-RGQ Artus Qiagen kit. The level of detection was superior to 200 Log_{10}, i.e. copies per mL.

At the time of the seroconversion, the viremia was detectable but below the threshold of 200 Log_{10}.

CMV viral load peaked at 1480 Log_{10} at 19 + 4 WG. After counseling of the patient, informed consent for an experimental treatment was given and oral valaciclovir was introduced at 8 g per day at 19 + 6 WG with stable viremia, based on Leruez-Ville et al.' study [6].

Abbreviations: CMV, cytomegalovirus; WG, weeks of gestation; PCR, polymerase chain reaction; IgG/IgM, immunoglobulin G/M.

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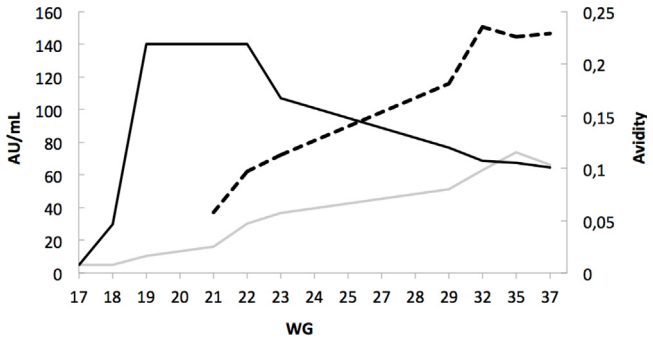

Fig. 1. Maternal serological CMV monitoring.
Plain black line: Anti-CMV IgM; Dashed black line: CMV IgG avidity; Plain gray line: Anti-CMV IgG

We noted a sharp viral load decrease: CMV DNA was no longer detected from 21 + 3 WG until amniocentesis was performed at 24 + 2WG. CMV PCR was negative in the amniotic fluid and valaciclovir treatment was stopped at 24 + 5 WG. Valaciclovir was well tolerated and no side effect was reported. Liver function and platelet count were checked twice a month during the treatment and then monthly until the end of the pregnancy, and were normal. CMV viral load remained undetectable until delivery, except for a small peak at 342 Log_{10} at 27 + 1 WG. Monthly ultrasound monitoring did not reveal any sign of congenital CMV infection. Fetal brain magnetic resonance imaging findings at 34 WG were normal. The patient delivered at 41 + 2 WG an asymptomatic baby girl (birth weight 3615 g [z-score = 0.5], head circumference 36 cm [z-score = 1.0]). CMV PCR assays in urine and saliva were negative at birth.

Discussion and conclusions

Our findings suggest that early treatment with valaciclovir 8 g per day could be effective in quickly reducing maternal viral load and lowering the risk of vertical CMV transmission. The patient was treated for five weeks and viral load was undetectable very soon after the start of antiviral therapy. We noted a slight peak when valaciclovir was stopped, but viral load remained undetectable throughout the third trimester of pregnancy. The baby was not infected at birth (CMV PCR assay negative in urine and saliva) and was clinically asymptomatic. Transfontanellar ultrasound showed no sign of CMV-related fetal brain lesions.

In 1999, a randomized trial showed that prophylactic treatment with high doses (8 g/day) of valaciclovir was a safe and effective way to prevent CMV disease after renal transplantation [7]. Valaciclovir reduced the incidence or delayed the onset of CMV disease in both seronegative and seropositive patients with a kidney transplant from a CMV seropositive donor. At a lower dose, a randomized controlled trial showed that CMV infection of infants born to HIV-seropositive pregnant women did not differ whether mothers received 1 g valaciclovir per day or not [8]. Ten years ago, an observational study showed that in the case of confirmed fetal CMV infection after primary maternal infection, administration of valaciclovir 8 g per day to the pregnant women significantly decreased CMV viral load in fetal blood after 1 to 12 weeks of treatment [9]. More recently, a multicenter open-label phase II study evaluated maternal antiviral therapy with valaciclovir 8 g/day in pregnant women presenting with symptomatic fetuses (measurable extracerebral or mild cerebral ultrasound symptoms). In this study, valaciclovir was well tolerated and seemed to increase significantly the rate of asymptomatic neonates. CMV viral load in either neonatal cord blood or neonatal urine did not differ significantly in symptomatic or asymptomatic neonates, but neonatal platelet count was significantly lower in symptomatic infants [6,10].

In terms of teratogenicity, the Aciclovir and Vlaciclovir Registry has no reports of developmental abnormalities or birth defects in more than 600 embryos and fetuses exposed across all trimesters of pregnancy [11,6].

With regard for high doses of aciclovir, except for decreased body weight gain in neonatal rats treated at 80 mg/kg/day, aciclovir did not produce adverse effects on mammalian development when tested in a variety of preclinical toxicology studies [12].

Most studies focusing on prenatal treatment of congenital infection with valaciclovir were designed to treat women once congenital infection was confirmed (CMV PCR positive in amniotic fluid) and the results still need to be confirmed in larger studies [13]. Our aim was different as we introduced valaciclovir immediately after maternal seroconversion in order to prevent vertical transmission to the fetus. Even if our patient delivered an uninfected neonate,

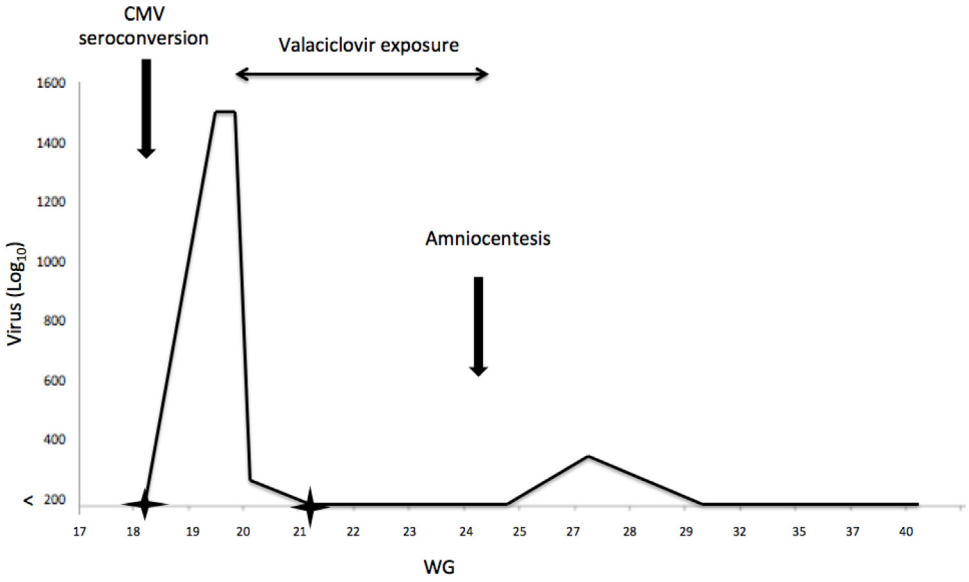

Fig. 2. Maternal CMV viral load monitoring.
Cross mark: the viremia is detectable but below the threshold of 200 Log_{10} (level of detection).

whether or not the treatment has avoided fetal infection is impossible to confirm as vertical transmission occurs in around 40% of cases of maternal primary infection in the second trimester of pregnancy. However, our observation tends to show that early treatment after primary infection leads to a sharp decrease in maternal CMV viral load. Moreover, the absence of CMV in the blood suggests that continuation of treatment until delivery was not necessary to prevent vertical transmission. We chose not to reintroduce valaciclovir after the small peak interpreted as a rebound effect. We noted no side effect of the treatment in this case.

There is currently no publication regarding the use of valaciclovir during pregnancy to prevent vertical transmission after CMV seroconversion. However, an ongoing phase II, double-blinded clinical trial is evaluating the efficacy of valaciclovir in preventing congenital CMV infection after maternal primary infection during pregnancy (NCT02351102).

Consent for publication

Informed consent to publish this information was obtained from the patient.

Authors' contributions

All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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