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Full length article

Asymptomatic CMV infection at birth following maternal primary infection despite valacyclovir treatment and a subsequent negative amniocentesis. Case report

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ABSTRACT

Valacyclovir is currently the only pharmacological intervention demonstrated to reduce the risk of vertical CMV congenital infection within a randomized clinical trial in case of primary infection during pregnancy.

So far, no data are available on the prognosis of children with congenital CMV infection diagnosed at birth after a negative amniocentesis whose mother were treated with valacyclovir during pregnancy, therefore it is essential to carry out a rigorous neurocognitive follow-up in these children in order to investigate the potential clinical consequence.

Background

Congenital cytomegalovirus (cCMV) infection is acknowledged as the most common nongenetic cause of childhood sensorineural hearing loss and cause of an important neurodevelopmental delay affecting 0.2% to 2.5% of all live-born neonates [1–2]. Kenneson and Cannon found rates of vertical transmission of 32% and 1.4% for primary and non-primary infections (exogenous reinfection with a different strain or endogenous viral reactivation), respectively [3].

Until a few years ago, no convincing evidences in favor of pharmacological intervention to prevent intrauterine transmission of CMV in pregnant women with primary CMV infection were available [4–8]. A randomized clinical trial reported a 70% reduction of vertical transmission diagnosed by the time of amniocentesis in pregnant women with primary CMV infection treated with high dose valacyclovir [9]. Similar data were reported from non randomized studies from France and Italy [10–12,19]. Additional evidence also suggest that valacyclovir treatment in women with confirmed mild to moderate fetal CMV disease reduce the rate of symptomatic infection at birth [13].

After a literature review [14], the Italian Society of Infectious and Tropical Diseases (SIMIT), the Italian Clinical Microbiologists Association (AMCLI) and the Italian Society of Perinatal Medicine (SIMP) jointly submitted the request for inclusion of valacyclovir for "prevention of CMV infection and treatment of fetal CMV disease in pregnancy" in the list of law 648/96 [15]. In Italy on December 2020, valacyclovir has been formally introduced in the National Health Service list of reimbursable medicinal products for prevention and treatment of cCMV during pregnancy [16].

We here report a case of a cCMV infected newborn asymptomatic at birth, despite a previous maternal valacyclovir treatment during pregnancy and a negative amniocentesis. We aimed to discuss the possible dynamics of CMV transmission and the potential clinical consequence, highlighting gray areas to be addressed in the future.

Case presentation: A neonate was born at 33 weeks of gestational

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age (GA) from an urgent emergency caesarean section due to placental abruption. Pregnancy was complicated by maternal primary CMV infection in the first trimester: at 9 weeks GA she had an episode of fever, lymphadenopathy and hypertransaminasemia and maternal serology, performed at 10 weeks of gestation, showed CMV IgG 54.4 Au/mL (cut off for positivity > 15), IgM CMIA index 11.60 (cut off for positivity > 1), IgM ELFA positive, IgG avidity 0.05% (low < 0.15). After a counseling of the patient, oral valacyclovir was introduced at 2 g every 6 h (8 g/day) when she was at 11 weeks GA. CMV DNA on blood was initially positive (386 copies/ml) at 10 weeks of gestation, while it was no longer detectable at week 17. CMV- polymerase chain reaction (PCR) in amniotic liquid was negative (amniocentesis performed at 20 weeks + 1 day of gestation). The treatment was discontinued after amniocentesis result, at 21 weeks GA. During pregnancy, valacyclovir was well tolerated and no side effects were reported. At birth the preterm infant weight, head circumference and length were appropriate for gestational age and they were respectively 1,980 Kg, (z-score = 0.06), 32 cm (z score = 0,91) and 45 cm (z score = 0.91); Apgar Score was 7–8 at 5 and 10 min of life. CMV-PCR in saliva, blood and urine, obtained in the first day of life, were positive and respectively 2,825,649 copies/ml, 6,530,141 copies/ml, 5,000 copies/ml. Despite prematurity, the clinical conditions have always been good and the newborn did not show additional symptoms of CMV infection. Considered the prematurity attributable to the infection in progress, the newborn began oral treatment with valgancyclovir (16 mg/kg every 12 h). The treatment was discontinued 2 month later upon completion of investigation including a brain MRI.

Neurodevelopment score of the child at 24 months of correct age estimated with the third edition of Bayley Scales of Infant and Toddler Development (Bayley-III) was in accord with correct age. We planned to perform a follow-up of the child until six years of age for hearing and neurodevelopmental long-term sequelae.

Discussion and conclusions

The diagnosis of cCMV at birth after a negative amniocentesis is already reported in literature regardless of maternal treatment with valacyclovir. This can be due to both false negative amniocentesis or later transplacental transmission. Before the use of valacyclovir during pregnancy, the prevalence of cCMV among neonates born from mother with primary CMV infection after a negative amniocentesis was 8% [17,18]. Results from the clinical trial by Shahar-Nissan et al. showed that the prevalence of cCMV at birth in neonates with a previous negative amniocentesis, were 10% (4 of 40) and 6% (2 of 33) in the group of children born from mothers who received valacyclovir and those born from not-treated mothers respectively [9]. In the observational study carried out by De Santis et al. enrolling women treated with valacyclovir until amniocentesis the prevalence of cCMV at birth after a negative amniocentesis was 30% (3 out of 10) [10]. In a multi-centre study collecting data on valacyclovir use during pregnancy, among 103 children born from mother treated with valacyclovir and negative amniocentesis, diagnosis at birth after a negative amniocentesis was encountered in 16 of 103 neonates (15.5% of cases), while in the historical untreated control group the prevalence of cCMV at birth after negative amniocentesis was 6.7% (6 of 89) [19].

In a similar multicentre study carried out in France, among 44 neonates borne after a negative amniocentesis form mother with primary CMV infection treated with valacyclovir, only one was affected by cCMV at birth (2%), compared to 6% (2 of 33) of untreated controls. However, in this study it is not clear for how long mothers was treated with valacyclovir since continuation of valacyclovir until birth was offered in some cases [12].

These data may rise the question on increased probability of diagnosis of cCMV at birth after a maternal treatment with valacyclovir, despite a negative amniocentesis.

The main hypothesis explaining the phenomenon of cCMV diagnosis at birth after negative amniocentesis is an efficient control of viral replication and prevention of vertical transmission during the antiviral treatment, with subsequent resurgence of viral replication after treatment discontinuation and mother to child transmission after the amniocentesis [10,20]. A recent report, described a woman with recurrent fetal cytomegalovirus infections in two consecutive pregnancies which was treated with valacyclovir during the first pregnancy. The authors hypothesized that valacyclovir treatment, although unsuccessful in preventing fetal infection during the first pregnancy, had delayed the adaptive maternal immune response and might have contributed to fetal infection during the sequential pregnancy [21]. The higher rate of cCMV at birth after negative amniocentesis observed in some studies describing women treated with valacyclovir could be in accordance with this hypothesis.

Available data from studies carried out before valacyclovir was used show that the prognosis of neonates diagnosed with cCMV at birth after a negative amniocentesis is usually good. Among 46 children with this features the rate of symptomatic cCMV at birth was low (4.3%) and no long term sequelae were diagnosed [22]. A recent *meta*-analysis showed lack of fetal insult and long-term sequelae in children with cCMV diagnosed at birth after a negative amniocentesis, [17]. So far, no data in the long term period are available on the prognosis of children with cCMV diagnosed at birth after a negative amniocentesis whose mother was treated with valacyclovir, thus a strict and long term follow-up is recommended.

In conclusion, valacyclovir is currently the only pharmacological intervention proved to be effective in a randomized clinical trial in reducing the risk of CMV mother to child transmission in case of primary infection during pregnancy. Currently it is available in Italy for infection acquired within 24 weeks of gestation and also suggested by certain guidelines in case of documented primary CMV infection in the first trimester [23].

However additional studies are needed to better understand the frequency of cCMV diagnosis at birth after negative amniocentesis in case of prenatal valacyclovir treatment and its clinical relevance.

Consent for publication

The family has agreed to the publication of the case.

Competing interests

The authors declare no conflict of interest for this work. Outside of this research work, Prof. Alessandro Bartoloni reports institutional grants from MSD and ViiV and personal honoraria from GSK and Gilead. Prof. Lorenzo Zammarchi has received funding for travel and speaker honoraria from Biotest. M.S.T., R.B., I.C.,B.B., M.T., L.G, L.P.. declare that they have no competing interests.

Authors' contributions

M.S.T. and L.Z. drafted the initial manuscript. It was reviewed and partially modified by the other authors (I.C., B.B., R.B., L.G., M.T.). All authors critically revised, read, and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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