AN ATYPICAL CASE OF INTRAUTERINE HSV-1 TRANSMISSION FOLLOWING A PRIMARY MATERNAL INFECTION. A 2-YEARS FOLLOW UP

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Abstract

Keywords:

Background- Herpes Simplex Virus type-1 is commonly associated with oral mucosal infection but, in the last few years, the HSV-1 genital infection has been increasing in prevalence, even more than HSV-2 in several populations. The risk of a maternal-fetal transmission in pregnant women with genital infection is cause of big concerns for neonatologists. Genital herpes is frequently subclinical and could be easily transmitted to the fetus during pregnancy or at birth. Intrauterine HSV infection is very dangerous because it is usually followed by catastrophic consequences (classic triad: cutaneous, ophthalmologic and neurologic involvement). The early diagnosis and treatment are significant in modifying outcomes lifelong.

Case presentation- We report a Caucasian female neonate, born by cesarean section, from a perinatally asymptomatic mother, who presented with skin macular rash on third day of life, followed by an intermittent fever up to 38.4°C. Because of an increased C Reactive Protein (CRP) up to 130 g/l associated with thrombocytopenia (37.000/mcl) and mild hyperexcitability at examination, a lumbar puncture was performed. The Polymerase Chain Reaction (PCR) revealed the presence of HSV type 1 DNA in CSF and Aciclovir iv, at 60 mg/kg per day, was started. Serological investigations revealed HSV1 IgG and IgM positivity in the mother’s blood and IgG positivity in the daughter’s sample. That means that the baby most likely received virus and maternal antibody through placenta in the last period of pregnancy. No history of maternal HSV infection. A clinical follow up at 2 years of age revealed no signs of motor, cognitive or language impairment.

Conclusion- In conclusion, we surely could make several important considerations: neonatal HSV infections are not always associated with a positive maternal clinical history; cesarean section cannot always prevent maternal-fetal transmission; congenital herpes is not necessarily associated with neonatal vesicular lesions and can manifest without the classic triad at birth; finally, early diagnosis and early therapy are associated with an excellent outcome.

Introduction

Case Report
A 37 1/7 week, 2100-gram female infant was born by cesarean section due to fetal tachycardia [1](180 bpm at cardiotocography), to a 35-year-old primigravida caucasian woman. Meconium-stained amniotic fluid was noted intrapartum. Apgar score was 7-8-10 at 1/5/10 minutes respectively and heart rate, 15 minutes after birth, was 189 bpm. The baby, small for gestational age (5th percentile for weight), was transferred to our N.I.C.U. Physical examination was normal at admission.
Over the pregnancy, the woman had smoked 4 cigarettes per day and she had performed obstetric visits and echographic controls once a month. The pregnancy was uncomplicated until 33rd weeks of gestation when a moderate fetal growth restriction was noted. Prenatal serological tests showed negativity for HBsAg, HCV and HIV; furthermore, the woman was not immune for Rubella, Toxoplasma Gondii and Cytomegalovirus (CMV). No clinical history of HSV infection.

Antibiotic therapy (Ampicilin-Sulbactam) was initiated at birth as prophylaxis for meconium-stained amniotic fluid. On the second and third day of life a transient macular rash appeared on her face (fig. 1), quickly progressing to the upper and lower limbs and disappearing in few hours. There weren’t blistering, target lesions or skin swelling. The day after, the C Reactive Protein (CRP) was 17 mg/l (n.v. <5), thus blood culture was obtained and Netilmincina i.v. was started as well. Two days later, an intermittent fever appeared for the first time (T max 38.4°C). On the sixth day, laboratory data revealed a white blood cell count (WBC) of 30,700/ml (neutrophilis 80%), platelets count of 52,000/ml and increased CRP up to 92 mg/l (T max 38.3°C). For this reason, Ceftazidime iv was added to the previous therapy. On day 7, pyrexia was persistent and a further increasing of CRP to 130 mg/l associated with a worsening thrombocytopenia (37,000/ml) were found, whereby Ampicilin-Sulbactam and Netilmicin were replaced by Teicoplanine iv. Furthermore, clinical examination showed mild hyperexcitability. Thus, for suspicion of encephalitis, a lumbar puncture was done in order to perform cerebrospinal fluid (CSF) biochemical, cytological and culture examination. A blood culture was obtained again. Twenty-four hours later, Polymerase Chain Reaction (PCR) revealed the presence of HSV type 1 DNA in CSF and diagnosis of HSV1-encephalitis was made. Biochemical examination showed the CSF to have 5 cells/µl (0-10), increased protein level of 0.62 g/l (laboratory normal value <0.40), glucose of 2.1 mmol/l (2.2-4.4). Aciclovir iv, at 60 mg/kg per day, was initiated and a mother’s blood sample was collected for viral investigations.
Cerebral ultrasound showed a “slight increase in volume of the lateral ventricles, front to back (3 mm); ventricular system within the limits”. The Cerebral Function Monitor (CFM), applied for 72 hours, revealed no anomalies, but the EEG exam showed “fronto temporal epileptiform abnormalities on the right”. For this reason, Phenobarbital iv was administered until the normalization of EEG trace. Between day 8 and 10 of life, the skin rash appeared again, on her face and limbs, such as an erythematous slightly scaly macule (fig.2). Subsequently her clinical general status improved with resolution of the skin lesions and the disappearance of the fever. CRP value gradually decreased up to normalization within a few days from the beginning of treatment.

Two weeks after, lumbar puncture was performed again and CFS resulted negative. Cerebral MRI, on the 35th day of life, did not reveal any abnormality.

During the hospitalization, renal and liver function and blood glucose level were always normal. Urine culture, central epicutaneous catheter tip and blood cultures were all negative. Fundus oculi was normal. The infant’s urine resulted negative for CMV infection.

Serological investigations revealed HSV1 IgG and IgM positivity in the mother’s blood and IgG positivity in the daughter’s sample.

The chest X-ray was normal and she didn’t need oxygen supplementation or ventilatory support. Recently, at 2 years of age, the little child performed a psychological test for detecting any consequences about her congenital infection. The Bayley Scales of Infant Development (BSID) performed by our follow up team resulted negative. Aciclovir treatment was interrupted after 21 days, as suggested by the AAP recommendation [2]] and recently confirmed by Harris and Holmes[3]].

Discussion
Herpes simplex viruses (HSV)-1 and -2 are enveloped virions that belong to alphaherpesviridae with a linear double-stranded DNA core. [4] Primary infection in immunocompetent individuals may cause gingivostomatitis, pharyngitis, or ulcerative genital lesions, but infection is frequently subclinical [5]. HSV-1 is commonly associated with oral mucosal infection while HSV-2 is commonly associated with genital infection. In the last few years HSV-1 genital infection has been increasing in prevalence, with recent studies suggesting it surpassed HSV-2 as a cause of genital infection in several different populations [6]. Overall, since genital herpes is frequently subclinical, it is one of the most prevalent sexually transmitted diseases worldwide [7]. One of the most dangerous risks is the maternal-fetal transmission in pregnant women with the genital herpes, as it happened in the case we described. The most common form of genital HSV infection during gestation is the recurrent genital herpes. However, it is the woman with primary infection who is at highest risk of transmitting the virus to her baby [4], more and more those with
HSV1 genital infection [8]. In our case, we discovered maternal HSV-1 IgG and IgM positivity associated with no clinical history, as sign of primary infection.

The stated incidence of neonatal herpes infection per 100 000 live births varies widely from 8 to 60 in the USA, to 4.6 in mainland Europe. In the United States, HSV-2 is responsible for 75% of genital and neonatal infections, while HSV-1 causes the rest [9][10]. In our experience, a tertiary centre with about 3,000 deliveries per year, it is confirmed as very rare. In fact, this is the first documented case of HSV 1 encephalitis by congenital infection in the last 10 years.

Both HSV-1 and HSV-2 establish latency in sacral nerve ganglia after primary genital tract infection and then they reactivate from this latent state and travel by anterograde transport to a genital tract mucocutaneous surface [11]. Thus, the fetus may be infected through retrograde spread through rupture of membrane or even apparently intact membrane or transplacently through the chorionic villi. Therefore, HSV disease of the newborn is acquired during one of three distinct time intervals: intrauterine, peripartum, and postpartum. The time of transmission for the overwhelming majority (85%) of infected neonates is in the peripartum period. An additional 10% of infected neonates acquire the virus postnatally, and the final 5% are infected with HSV in utero [4]. The woman in our case, did not have any genital lesions, so she probably transmitted the infection over intrauterine life, through the chorionic villi.

The factors that influence the transmission of HSV infection in the peripartum period include maternal HSV antibody status, duration of rupture of membrane, integrity of cutaneous barrier, mode of delivery, type of HSV infection and type of maternal infection, subdivided into first episode or primary infection (57% of cases) and first episode nonprimary infection (25%) [12]. Intrauterine HSV infection is rare and has been reported seldom rarely in scientific literature. In fact, it occurs in approximately 1 in 100,000 deliveries [13]. Despite this low incidence, intrauterine HSV infection is very dangerous because it is usually followed by catastrophic consequences. Infants acquiring HSV in utero typically have a triad of clinical findings consisting of cutaneous manifestations (scarring, active lesions, hypo- and hyperpigmentation, aplasia cutis, and/or an erythematous macular exanthem), ophthalmologic findings (microophthalmia, retinal dysplasia, optic atrophy, and/or chorioretinitis), and neurologic involvement (microcephaly, encephalomalacia, hydranencephaly, and/or intracranial calcification) [4]. Actually, not all the HSV intrauterine infections follow the characteristic triad, as stated by Lucila Marquez et coll. [13]. Our case, for instance, has had a cutaneous manifestation represented by an erythematous macular exanthena but the ophthalmologic assessment was normal. Furthermore, the neurologic involvement has been only transient with a good long term outcome. Therefore, the atypical presentation of our case confirms the not specific nature of this disease. It’s important to underline that generally HSV infection symptoms appear 10-12 days after birth. In our case first signs of HSV infection appeared on second day of life with skin macular lesions, confirming powering the hypothesis of maternal-fetal transmission. In a study looking at the clinical features and risks of death, Batra et al. [14] revealed, according their experience, a statistically significant value (p=0.003) for risk of death in patients with CNS involvement in congenital HSV infections. However, as Kimberlin [15] states, high doses of Aciclovir (60 mg/kg/day for 3 weeks) reduces 1 year mortality to 4%. This suggests that the combination of early recognition and effective treatment significantly modifies outcomes. That’s why our case, now 2 years old, does not present any sort of consequences of the HSV1 encephalitis.

Lucila Marquez et coll. [13] in their review stated that “there are deficiencies in published reports of intrauterine HSV; single case reports or small case series are limited by inconsistent definitions of intrauterine disease and misclassification of intrapartum cases as intrauterine”. Conversely, our case represents a real intrauterine HSV-1 infection for at least three reasons. First, mother’s clinical history was negative for HSV infection before pregnancy and it means that she had a primary infection of HSV. As Kimberlin D. reported [4], primary genital HSV disease is at highest risk of transmitting the virus to the baby. Second, we could exclude a peripartum (perinatal) infection because of the cesarean delivery that prevents neonate contact with maternal genital skin and mucosa, even if no lesions were found at examination. Third, because of the positivity at serological investigations. In fact, while blood examination in the mother showed IgG and IgM positivity for HSV1, serological tests of her baby, performed 10 days after birth, were positive for IgG (24.2 with pos>1.1) and negative IgM (<0.5 with neg<0.9). That means that the baby most likely received virus and maternal antibody through placenta in the last period of pregnancy, probably
in last few 3 months because type specific antibodies to HSV generally develop within the first 12 weeks after an infection and persist indefinitely [12]. Our case is consistent with the reports where 60% to 80% of mothers with infants who develop neonatal HSV disease have no symptoms at the time of delivery nor a history of genital herpes [13].

The atypical presentation of our case confirms the not specific nature of this disease. Considering the recent increasing of worldwide HSV prevalence and the possibility of silent maternal-fetal transmission, this case suggests that Neonatologists must closely monitor neonates for signs and symptoms of HSV infection, not only when they are born to mothers with a history or clinical evidence of HSV infection, but every time a newborn is suspected for sepsis. In fact, combination of early recognition and effective treatment may significantly modify outcomes, as our case clearly shows.

References