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Fetal CMV Infection: About a Case and Review of the Literature

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Abstract: CMV infection is the main viral fetal infection responsible for congenital neurological and sensory deficit, causing deafness and delayed acquisition. Primary infection during pregnancy is the main cause of sequelae compared to secondary infections. Neonates are asymptomatic in 85% of cases, severe lesions can be seen from birth and can cause neonatal mortality in 30% of cases. Sequelae can be seen in asymptomatic newborns even late after birth. The occurrence of a CMV infection during pregnancy requires specific management to make the diagnosis and establish a prognosis. Diagnostic management of CMV infection during pregnancy relies mainly on ultrasound and fetal brain MRI, which can be supplemented by an invasive gesture and amniocentesis that confirms fetal infection. A fetal blood puncture may also be proposed as part of the prognostic evaluation. A multidisciplinary discussion in prenatal diagnosis is necessary for the study of all cases of CMV infection during pregnancy. We report here the case of congenital CMV infection discovered at 25 WA with continuation of pregnancy until the end of pregnancy and the postnatal care. Our study allows us to analyze the evolution of the case including neonatal ultrasound aspects along the pregnancy in the absence of IMG proposal. We then carry out a review of the epidemiological literature, means of diagnosis and management.
Keywords: CMV, pregnancy, diagnosis, ultrasound, prevention.

INTRODUCTION

Cytomegalovirus (CMV) infection is the most common viral infection transmitted during pregnancy: 1% of children are born with a congenital CMV infection. It is essentially in the course of a CMV primary infection during pregnancy that there is a risk (of around 10%) of multi-organ fetal damage, affecting in particular the central nervous system, the consequences of which are severe (deafness, chorioretinitis, motor deficits, seizures, mental retardation, microcephaly). The frequency and potential severity of the infection justifies antenatal diagnosis of maternofetal infection, but the absence of strict predictive parameters of severity makes it very difficult to manage.

We report the case of a CMV congenital infection discovered at 25 WA with severe brain damage monitored during the pregancy until the delivery. We then carry out a review of the epidemiological literature, means of diagnosis and management.

CLINICAL CASE

We report the case of Mrs. S.J., 30 years old, G1P1, with no particular antecedent, dental secretary, without notion of consanguinity, which was sent by her doctor at 25 WA for a retardation of intrauterine growth and oligo amnios. The beginning of the pregnancy was without particularity with a first ultrasound made at 12 WA + 5d objectifying an evolutionary intra uterine pregnancy without morphological abnormalities visible at this term.

A morphologic ultrasound performed at 24 WA showed early intrauterine growth retardation (IUGR) less than the 3rd percentile with oligoamnios with no other associated morphological abnormality, umbilical and cerebral dopplers were normal and no notch at Doppler uterine arteries.

The patient benefited from an initial biological assessment which showed a blood count without abnormality, a normal vasculo-renal assessment, a positive cytomegalovirus (CMV) serology (positive IgG CMV, IgM doubtful), the other serologies was negative, no anterior CMV serology and no IgG avidity

measurement were done. The CMV serology control at 15 days found negative IgM and stable IgG, amniocentesis was not done.

Ultrasonographic follow-up at 26 WA + 2 days showed cerebral abnormalities with dilatation of the 3rd ventricle, presence of intracerebral calcifications [Fig 1] and irregular appearance of the ventricular walls. Biometrics showed an IUGR below the 3rd percentile predominant at the cephalic pole level without break in the growth curve or other associated extra brain malformation. Umbilical, cerebral and venous doppler were without particularity.

An ultrasound of control made at 28 WA objectified the aggravation of the cerebral ultrasound signs with appearance of destructive, clastic lesions, abnormalities of the gyration and a widening of the peri-cerebral spaces [Fig 2,3]. The severity of the cerebral lesions was confirmed by fetal brain MRI that induced distension and diffuse, bilateral and severe destructive lesions [image 4]. Monitoring was scheduled every 15 days including clinical examination, fetal heart rate, and fetal ultrasound that showed progressive worsening of brain lesions

The patient gave birth at 38 WA and 3 days by vaginal delivery to a newborn male, Apgar 5-8-9, birth weight 2000g with good adaptation to extra uterine life. The examination at birth finds a microcephaly with significant hypertonia. No chorioretinitis on ophthalmic examination.

A post natal transfontanellary ultrasound was performed showing the same abnormalities detected prenatally: Multiple brain lesions with ventricular dilatation with homogeneous hypoechoic content and thickening of the ventricular wall (image 5)

In post natal, the CMV serology of the newborn was positive at 9000 copies and the newborn was put under GANCICLOVIR for 1 month allowing the negativation of the viral load. Control after 1 year finds a significant psychomotor delay.

FIGURES

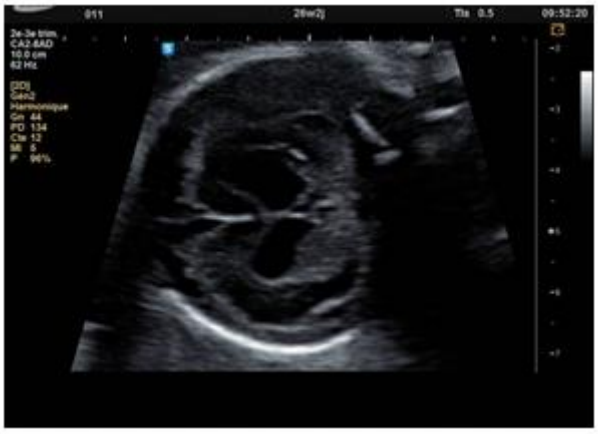

Fig-1: Coronal sections showing an irregular aspect of the wall of the hyperechoic lateral ventricles with multiple calcifications and moderate ventricular dilatation

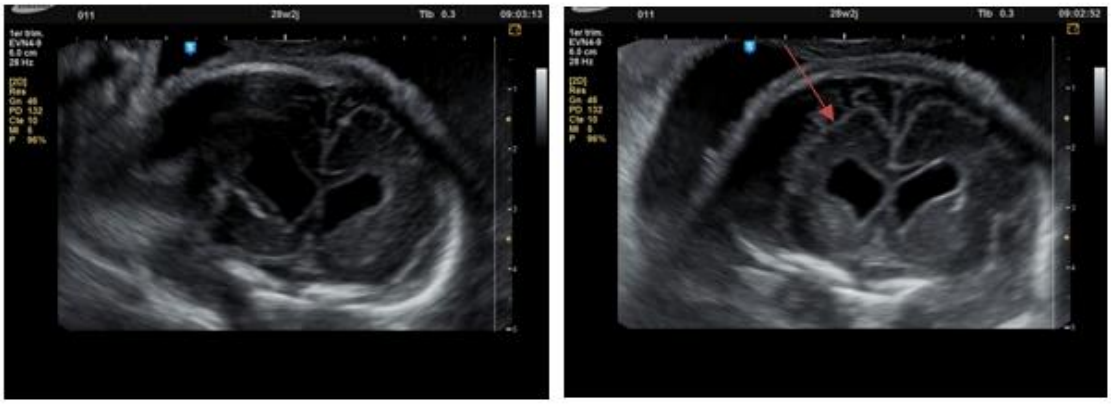

Fig-2: Coronal sections showing the widening of the cerebral spaces with anomaly of gyration (red arrow)

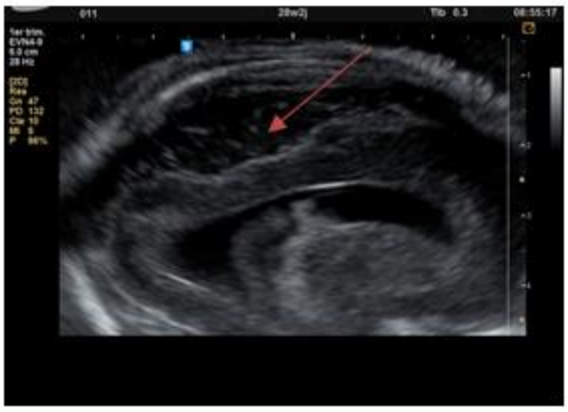

Fig-3 : Para-sagittal section showing destructive lesions in the cerebral cortex (red arrow)

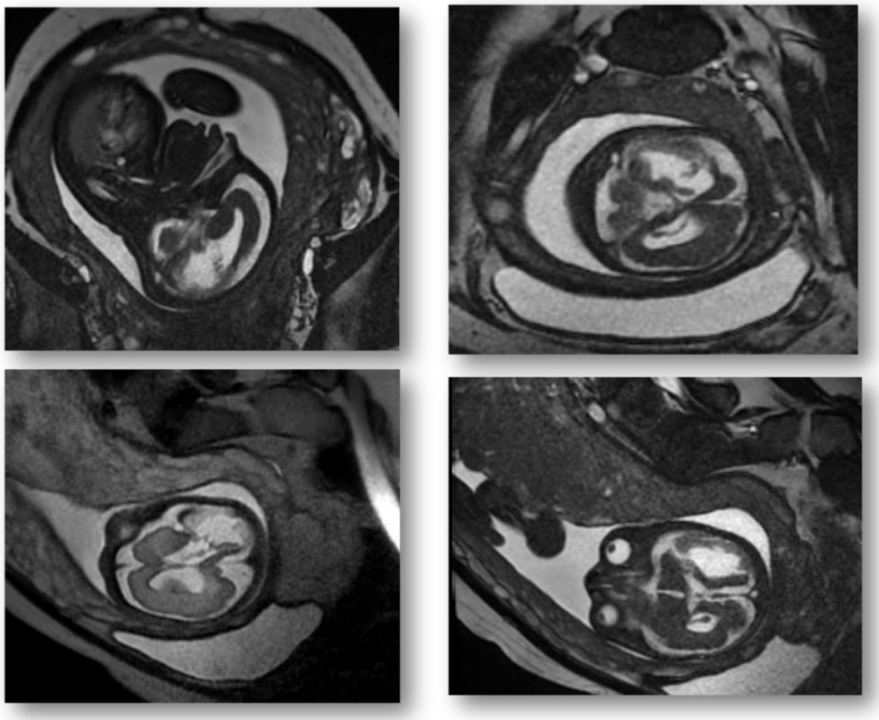

Fig-4: Fetal MRI shows moderate ventriculomegaly with bilateral destructive lesions and abnormal gyration

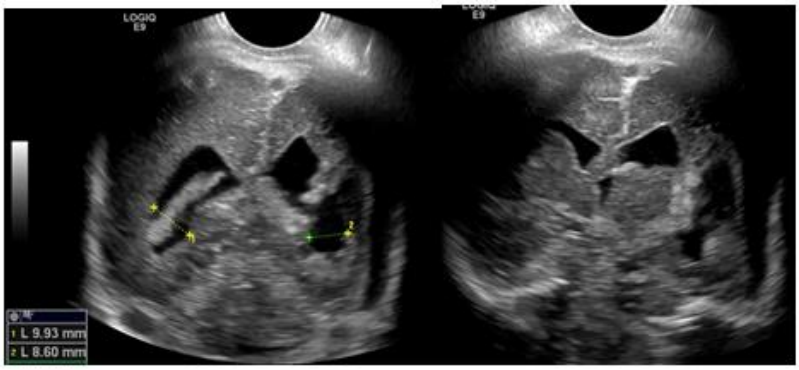

Fig-5: Coronal sections showing destructive lesions affecting both cerebral hemispheres

DISCUSSION

Cytomegalovirus is the most common cause of intrauterine infection, occurring in 0.2% to 2.2% of all live births, and is a common cause of perceptual deafness and mental retardation [1,2].

Maternal contamination occurs through contact with infected secretions (saliva, urine, genital and nasal secretions, blood). The incubation time is 2 to 4 weeks. Primary infection is asymptomatic in 90% of cases; it can lead to a flu-like illness. After primary infection, CMV persists in the quiescent state and may be responsible for secondary infections by reactivation of the endogenous genome. Even in case of normal immunity, reinfections with a new strain are possible but rare because the antibodies do not provide absolute protection. It is estimated that 10 to 15% of children with CMV congenitally are symptomatic at birth (hypotrophy, microcephaly, hepatosplenomegaly, hepatic cytolysis, thrombocytopenia, chorioretinitis). Mortality would reach 10 to 30% in this group. The majority of survivors develop severe sequelae that are both developmental and neurosensory. Unlike this so-called "symptomatic" group, most infected children (85-90%) have no symptoms at birth. It is estimated, however, that 5 to 15% of them will develop sequelae such as hearing loss, developmental delay or visual disturbances [3]. Hearing impairment may occur only in a delayed manner (sometimes several years later) and is very variable in severity (uni or bilateral, slight or deep) [4].

Maternal serological screening is not recommended in routine during pregnancy. The main indications of a CMV serology are therefore the discovery of ultrasound signs suggestive of infection, as part of the etiological assessment of intrauterine growth retardation (IUGR) especially if it is severe, early and/or predominant on the cephalic pole, or in front of intestinal hyperechogenicity [5].

The positive diagnosis of fetal infection is best done by collecting amniotic fluid for virus screening by culture or PCR, after checking the negativity of maternal viremia and at least 4 to 6 weeks after maternal infection (seroconversion or clinical signs) [6, 7]. There are currently no recommendations for the routine practice of amniocentesis documented in case of maternal CMV infection. On the other hand, the discovery of an ultrasound sign that can be explained by fetal CMV infection should lead to a search for this infection in the fetus as part of the etiological assessment [8].

Footal blood sampling has no interest in the diagnosis of fetal infection. The search for IgM has a very low sensitivity because some fetuses produce IgM later [6,8].

Ultrasound allows a morphological study of signs suggestive of CMV infection and allows surveillance if the infection is suspected or proven. The sonographic semiology described by the various authors includes the following signs:

- Overall intrauterine growth retardation, nonspecific, particularly in growth of skull [9]
- Abnormalities in the amount of amniotic fluid, often oligamnios (25% of cases reported in the literature) [10]
- Have also been described thick placenta, subcutaneous edema [11], hydramnios [9], serous effusions: ascites [9,12], hydrothorax and transient anasarca
- Hepatosplenomegaly, difficult to objectify in utero, which may be associated with changes in hepatic echogenicity and ascites [11]
- Splenomegaly [11,10]
- Renal hyperechogenicity [13]
- Digestive abnormalities: The hyperechogenicity of the small intestine is most often the transient expression of viral enteropathy occurring in the initial stage of infection and disappearing secondarily without leaving any sequelae [9]. More serious intestinal lesions may result in meconium peritonitis by perforation, responsible for ascites, of hyperechoic pelvic mass, or of peritoneal calcifications [14, 9, 10]
- brain abnormalities:
- relatively late-onset images showing severe and irreversible lesions: microcephaly, porencephaly, ventriculomegaly, cerebellar hypoplasia, lissencephaly-pachygyria, hydranencephaly, major cerebral destruction, o calcifications essentially periventricular or under cortical
- candelabra images due to radial hyperechogenicities sitting in thalami and lymph nodes and drawing the thalamo-striated vessels, witnesses of a vasculitis [9], and aspects of "germinolysis" under ependymal, cystic lesions multi-partitionned located at the germinal zones, few different from those observed during subependymal hemorrhages [9,14].
- A potential specific sign not found in other fetal pathologies is an anechoic cavity at the end of the occipital and/or temporal horn; A better understanding of these signs suggestive of CMV could increase the sensitivity of ultrasound and clarify the pathophysiology of congenital infection [15].

MRI can be a very useful adjunct to ultrasound both for specifying suspicious ultrasound images or for finding lesions difficult to demonstrate in ultrasound.

Early infection (before 18 WA) occurs during the early stages of neuronal migration and may lead to lissencephaly [16]. Diagnosis may be suggested by ultrasound (microcephaly, ventricular dilatation, lack of

trapping of Sylvian valleys). With a good knowledge of the chronology of development of the peri-cerebral furrows, the MRI will allow their visualization and the diagnosis of lissencephaly [17].

Between 18 and 24 weeks, during the phase of neuronal organization, a CMV infection may be responsible for cortical dysplasia, delayed myelination and/or micropolygyria, the detection of focal lesions of the white matter, periventricular leucomalacia and porencephalias [18], screening for subependymal lesions, regions particularly sensitive to ischemia, where necrotic lesions and secondary calcifications can be observed. Necrosis can also result in the presence of subependymal cysts ("subependymal germinolysis"). Ultrasound does not differentiate a cystic lesion in relation to germinolysis from the evolution of an ependymal haemorrhage [18].

Despite breakthroughs in the diagnosis of CMV fetal infection, no effective treatment is available. With regard to postnatal treatment, some studies have shown some improvement in hearing and less deterioration of hearing in neonates treated with Ganciclovir.

The implementation of preventive measures for women in contact with young children either for work or in their family is effective in reducing the risk of maternal infection during pregnancy. It is recommended that all women and their spouses wash their hands frequently, especially after changing diapers and blowing children. It forbids kissing children on the mouth, sharing cutlery and using children's bath linens. These measures are easy to implement and applicable to all patients and their spouses [8].

CONCLUSION

CMV infection is the most common congenital infection in the world (1% births) and is the leading infectious cause of mental retardation and sensory deafness. This is most often a reinfection or reactivation.

Once the diagnosis of primary maternal CMV infection is established, the presence of fetal infection can be accurately determined by amniocentesis. In cases of fetal infection with severe lesions on ultrasound, termination of pregnancy should be discussed as one of the possible options for management. routine serological screening of all pregnant women is not recommended.

Currently no treatment has been formally proven effective in term of primary or secondary prevention.

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