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CYTOMEGALOVIRUS AND PREGNANCY: CONTRIBUTION OF VIROLOGY LABORATORY

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ABSTRACT

Cytomegalovirus infection is the most common viral infection reaching the fetus. The infection can be transmitted in utero from maternal primary infection or during reactivation of infection in an HIV-positive mother before pregnancy, which is a situation with high fetal and neonatal risk. The frequency and severity of congenital infection are very different depending on the case and it is therefore essential to make the differential diagnosis between primary infection and reactivation. In this context, there is no gold standard test and the presence of IgM is still too often seen as a test for recent infection. Various techniques have been developed to improve the diagnosis. Among these new approaches, the most used is the measurement of IgGavidity which may exclude a recent infection in many cases. Evidence of fetal infection is provided by the research CMV in amniotic fluid culture and / or PCR; performance of these two techniques in terms of sensitivity and specificity are comparable. However, please keep in mind that if the detection of virus in the amniotic fluid sign congenital infection, it is not possible to assess the severity. Despite this multitude of test there is no legislation in Morocco as well as in developed countries in a systematic search for CMV during pregnancy status.

Key words: Cytomegalovirus; Congenital infection; greed; PCR; legislative.

INTRODUCTION

Infection with cytomegalovirus (CMV) is the most common congenital infection, with an average incidence of 1% [1]. The infection can be transmitted in utero during a maternal primary infection or during reactivation of infection in an HIV-positive mother before pregnancy. The frequency and severity of congenital infection are very different depending on the case and it is therefore essential to make the differential diagnosis between primary infection and reactivation.

VIROLOGICAL CHARACTER: (Figure 1) [2, 3]

The human cytomegalovirus (HCMV or simply CMV current medical language) belongs to the herpesvirus family. It is classified with human herpesvirus 6 and 7 in the subfamily betaherpesvirinae that contains a single type; the kind Cytomegalovirus.

CMV is a 150 to 200 nm diameter and consists of four elements:

➢The genome is a linear double stranded DNA molecule of 230-250 Kbp wound around a core of proteins called core.
➢The icosahedral capsid is about 100 nm in diameter, and 162 capsomers.
➢The casing derives internal cytoplasmic membranes, door viral glycoproteins.
➢The seed coat or matrix, between the capsid and the envelope 7 consists of at least six proteins which are phosphorylated.

EPIDEMIOLOGY:

CMV is a ubiquitous virus endemic. Infection occurs primarily through close contact. Its prevalence is correlated with the socio-economic level. The lower it is, the prevalence is high: 90-100% of young adults have been exposed to CMV in Africa and Asia against 40-50% in Europe (Figure 1) [4] or the United States.

In pregnant woman, the primary infection is associated with viremia, sometimes fleeting, followed by infection of the placenta. This has a protective rô1e since only about 40% of fetuses are infected. The occurrence of primary infection during pregnancy is not uncommon; it is estimated to be between 0.2 and 2%. [5]

CLINICAL

For the mother, less than 10% of its symptomatic primary infection as flu-like symptoms. [4] 90% of fetuses are perfectly asymptomatic when infected. Signs of foetopathy, usually discovered at routine ultrasound examination, are present in 5-15% of cases. [3] The abnormalities are many and varied but the most common are stunting in utero, oligohydramnios or hydropsfetalis, microcephaly, the echogenicity of the bowel loops or hydrocephalus (Figures.2 and 3) signing encephalitis, intrahepatic calcifications (Figure 4) associated with ascites. At birth abnormalities are present in 10% of infected newborns. [5] The disease is widespread cytomegaly exceptional: 1-5 cases / 10,000 births. [3] The time of occurrence of the primary infection influences the severity of fetal damage. Earlier it is the percentage of after-effects is high: 35-40% in the first quarter, 8-25% in the second quarter and 0-7% in the third quarter. However, some infections of the third quarter were also associated with serious complications [6,7].

VIROLOGICAL DIAGNOSIS
Diagnosis of cytomegalovirus infection in pregnant woman.

There is currently no consensus about indication of a systematic monitoring of CMV serology during pregnancy, and for different reasons. [8] One of them is that the serological tests are difficult to interpret and often the diagnosis of maternal primary infection can not be made with certainty.

➢The conventional serology

Routine diagnosis of CMV infection is done by searching for specific IgG and IgM anti-CMV.

Different situations can be encountered:
• specific IgG undetectable, the woman is considered negative. Serological monitoring (including the ideal pace yet to be determined ...) can be made to highlight a possible seroconversion;

• In the presence of IgG and IgM undetectable, the CMV is considered old. No special monitoring during pregnancy is recommended unless sonographic findings suggestive of CMV infection in utero;

• The most complex situation is where, on a first serology during pregnancy in a woman whose history is unknown serological, IgG and IgM are detected simultaneously. Indeed the presence of IgM is still widely seen as a test for recent infection. However, IgM may persist for months after primary infection and reappear during reactivation (favored by pregnancy) or during intercurrent infections [9]. The only clear evidence of primary infection is the observation of seroconversion. The presence of IgM on a one-time serum can in no way be interpreted as a marker of recent infection.

There is no gold standard test, for the diagnosis of primary CMV infection. Various techniques have been developed in recent years to improve the differential diagnosis between primary infection and reactivation of CMV infection: research neutralizing antibodies [10], Western blotting [11], the measurement of specific IgG avidity [12] and more recently, research directed against the CMV gB glycoprotein antibody [13-14]. Among these approaches, the currently most widely used is the measurement of the avidity of IgG.

➢**The IgG avidity**

It has been shown in different models that measuring IgG avidity allows differentiate recent infection (IgG low avidity) and old infection (IgG high avidity). [3] In the model of CMV, the measurement of IgG avidity is important during supervision of pregnancy. Techniques *in house* were first developed by different teams. [12] Currently, measurement of IgG avidity anti-CMV is marketed by several firms as a kit (Biomerieux, Dade Behring, DiaSorin). According to the technique used criteria interpretations are very different and must avoid comparing avidity index calculated by different techniques. In all cases avidity mesurement should be used as a criterion for exclusion of a recent infection and not as confirmation, if high avidity exclude a primary infection during previous three months, low avidity does not allow it to conclude. Indeed, the kinetics of maturation of IgG avidity is highly variable from one patient to another, some keep a low avidity more than 6 months after seroconversion. Finally, a high avidity index should not be interpreted as reassuring if the gestational age at the time of serology is ≤ 12 weeks.

➢The antibodies anti gB of CMV

An enzyme-linked immunosorbent assay based on direct research of the CMV gB glycoprotein antibodies has recently been developed [13]. The gB protein (or gpUL55) has an important role in viral entry into the cell; it is the target of neutralizing antibodies that limit the spread of the virus. The humoral immune response directed against this protein is late and the first detectable antibodies appear only 2 to 3 months after infection. The anti-gB presence exclude a recent primary infection. It has been reported that the combination of IgG avidity measurement and research of anti-gB antibodies allowed to reassure a larger number of patients. Indeed some patients which maintaining low avidity long after seroconversion develop anti-gB antibody and vice versa, some patients develop late anti-gB antibody properly mature their greed [14]

Diagnosis of congenital infection in utero

This method requires a taking of amniotic fluid during amniocentesis

• virus culture

1 Technical Reference but the fragility of the virus sometimes makes it difficult

2 Request for one to three weeks

3 very specific (100%) but average sensitivity (50%)

4 The technique known as rapid culture increases the sensitivity

• **Determination of pp65 antigenemia**
by immunoperoxidase or specially by immunofluorescence, using specific monoclonal antibodies, it is simple and fast (2-3h)
• **Polymerase chain reaction or PCR virus**

Reference method for the diagnosis of fetal damage virus

Two approaches can be used: search of virus after culture [3] or search the viral genome by PCR. The sensitivity of these techniques is very similar, highly dependent on conditions of taking. For maximum sensitivity, two factors are critical. The most important is the time between seroconversion and amniocentesis, the ideal time limit is 6 to 8 weeks. The age of pregnancy (ideally> 21 weeks) at the time of amniocentesis may also influence the sensitivity of detection. Depending on the conditions of sampling sensitivity of culture and PCR varies between 30% and> 95% [15].

In negative cultured amniotic fluids, small amounts of DNA have sometimes been found[16]. The risk of congenital infection was estimated at 33% when amniotic fluid is positive in PCR and negative in culture. This means that if PCR is a little more sensitive than culture, it is also less specific. In quantitative PCR, it was suggested that beyond $\mathbf{10^3}$ copies / ml of amniotic fluid, congenital infection was certain.

Finally, two cases were recently described with demonstration of CMV in amniotic fluid culture and PCR and newborns not infected. This observation may suggest the possibility of infections in utero self-limited and transient. [15] If the detection of CMV in amniotic fluid means in the majority of cases, there has fetal infection, it does not, however, predict the severity of the infection. It was suggested that the detected amount of virus in the amniotic fluid may be a reflection of the severity of the infection; a result $\geq$ $\mathbf{10^5}$ copies / ml would predict symptomatic infection [16]. This observation needs to be confirmed; other factors influence indeed significantly the amount of detected viruses, especially the time between seroconversion and amniocentesis.

Diagnosis of congenital infection in the newborn

The gold standard to confirm congenital infection is the search for CMV in the urine of newborns. These urine should be collected as soon as possible. A positive result on the urine collected over 2 weeks after birth, does not confirm to congenital infection; it can be in this case, infection at or shortly after birth.

If a retrospective diagnosis is desired in a child older than 2 weeks, it is then possible to perform PCR on the map of Guthrie [17, 18].

CONCLUSION

CMV infection is the most common congenital infection, with an average incidence of 1%. However, there is no consensus on the indication of a systematic monitoring of CMV serology during pregnancy, for different reasons. One of them is that the serological tests, despite the new approaches developed recently (measurement of IgG avidity, for anti-gB antibodies, etc.) are difficult to interpret and diagnosis of maternal primary infection can not always be made with certainty. Serological uncertainties are not the only ones. It is known that among children infected in utero, 80% will have no ill effects. However, in most cases, prenatal monitoring does not assess the severity of fetal thrombocytopenia. Finally, currently no effective therapeutic measures can be proposed. If fetal infection is confirmed and given the impossibility of reliably predict the consequences, indicating a termination of pregnancy should be discussed

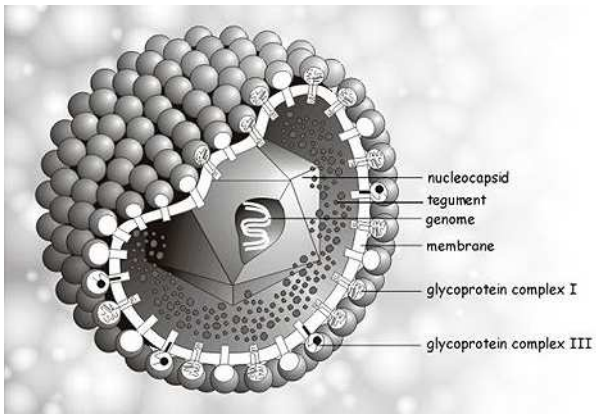

FIGURE 1: Diagram representing a CMV [2]

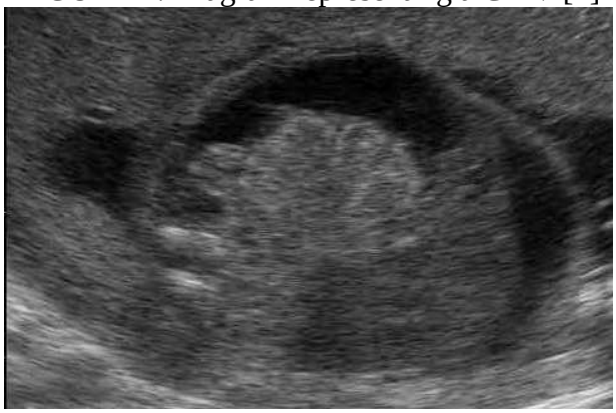

FIGURE 2: echogenicity of bowel and handles ascites

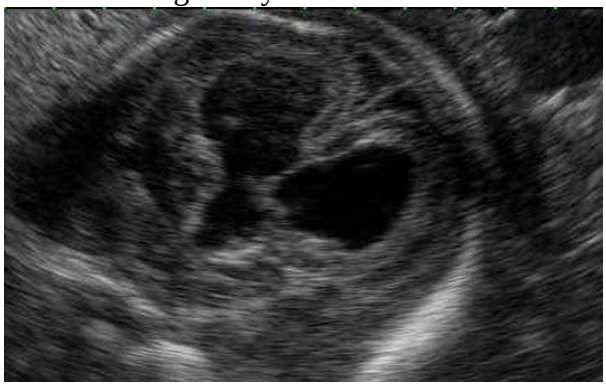

FIGURE 3: fetal hydrocephalus

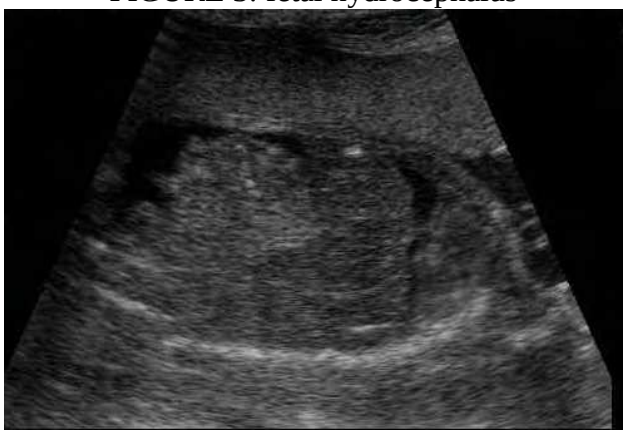

Figure 4: hepatic calcifications

REFERENCES

[1]. Peckham CS. Cytomegalovirus infection: congenital and neonatal disease. Scand J Infect Dis **1991**; 78 : 82–7.

[2]. www.spectrosciences.com*:*M. Reschke. Représentation du cytomégalovirushumain

[3]. Huraux J. M, nicolas J. C, Agut. H, Peigue-Lafeuille. H: traité de virologiemédicale. Edition Estemédition **2003** : 195 – 211

[4]. Gouarina. S, : diagnostic des infections maternofoetales àcytomegalovirus (HCMV) Revue Française des Laboratoires **2003** ; 353 : 45-53

[5]. Berrebi. A, Duclusaud. A, Kessler. S, Ayoubi. J.M: Infection CMV etgrossesse. Médecine et maladies infectieuses **2005** ; 35 : 22-25

[6]. Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. Theoutcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med **1992**;326:663–7.

[7]. Steinlin MI, Nadal D, Eich GF, Martin E, Boltshauer EJ. Late intrauterine cytomegalovirus infection: clinical and neuro-imaging findings. PediatrNeurol **1996**;15:249–53.

[8]. Hagay ZJ, Biran G, OrnoyA, Reece EA. Congenital cytomegalovirus infection: a long-standing problem seeking a solution. Am J ObstetGynecol **1996**;174:241–5.

[9]. MiendjeDeyi Y, Goubau P, Bodéus M. False-positive IgM antibody for cytomegalovirus in patients with acute Epstein-Barr virus Infection. Eur J ClinMicrobiol Infect Dis **2000**;19:557–60.

[10]. Eggers M, Bader U, Enders G. Combination of microneutralization and avidity assays: improved diagnosis of recent primary human cytomegalovirus infection in single serum sample of second trimester pregnancy. J Med Virol **2000**;60:324–30.

[11]. Lazzarotto T, Brojanac S, Maine GT, Landini MP. Search for cytomegalovirus-specific immunoglobulin M: comparison between a new Western blot, conventional Western blot, and 9 commercially available assays. ClinDiagn Lab Immunol **1997**;4:483–6.

[12]. Bodéus M, Feyder S, Goubau P. Avidity of IgG antibodies distinguishes primary from non-primary cytomegalovirus infection in pregnant women. ClinDiagVirol **1998**;9:9–16.

[13]. Eggers M, Radsak K, Enders G, Reschke M. Use of recombinant glycoprotein antigens gB and gH for diagnosis of primary human cytomegalovirus infection during pregnancy. J Med Virol **2001**;63: 135–42.

[14]. Sipewa MJ, Goubau P, Bodéus M. Evaluation of a cytomegalovirus glycoprotein B recombinant enzyme immunoassay to discriminate between a recent and a past infection. J ClinMicrobiol **2002**;40:3689–93.

[15]. Bodéus M, Hubinont C, Bernard P, Bouckaert A, Thomas K, Goubau P. Prenatal diagnosis of human cytomegalovirus by culture and polymerase chain reaction: 98 pregnancies leading to congenital infection. PrenatDiagn **1999**;19:314–7.

[16]. Lipitz S, Achiron R, ZalelY, Mendelson E, Tepperberg M, Gamzu R. Outcome of pregnancies with vertical transmission of primary cytomegalovirus infection. ObstetGynecol **2002**;100:428–33.

[17]. Barbi M, Binda S, Caroppo S, Ambrosetti U, Corbetta C, Sergi P. A wider role for congenital infection in sensoneural hearing loss. Pediatr Infect Dis J **2003**;22:39–42.

[18]. Haginoya K, Ohura T, Kon K, et al. Abnormal white matter lesions with sensoneural hearing loss caused by congenital cytomegalovirus infection: retrospective diagnosis by PCR using Guthrie cards. Brain Dev **2002**;24:710–4.