Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Apr 18; 10(C):133-136.
https://doi.org/10.3889/oamjms.2022.8869
eISSN: 1857-9655
Category: *C - Case Reports*
Section: *Case Report in Gynecology and Obstetrics*

Isolated Ventriculomegaly and Cytomegalovirus Infection during Pregnancy: A Case Report and Diagnostic Challenges

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Edited by: Ksenija Bogoeva-Kostovska
Citation: Kovachev E, Anzhel S, Slavov S, Ingilizova G, Dimova S, Zhekov Z. Isolated Ventriculomegaly and Cytomegalovirus Infection during Pregnancy: Case Report and Diagnostic Challenges. Open Access Maced J Med Sci. 2022 Apr 18; 10(C):133-136. https://doi.org/10.3889/oamjms.2022.8869
Keywords: Cytomegalovirus; Ppregnancy; Ventriculomegaly; IgG avidity; Nneurological disorders
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Received: 22-Feb-2022
Revised: 07-Apr-2022
Accepted: 08-Apr-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

INTRODUCTION: Cytomegalovirus (CMV) is the most frequent cause of congenital viral infection, associated with developmental delay, sensorineural hearing loss, and fetal death. The primary infection during first trimester is associated with poor prognosis and a higher risk for neurological damage such as mental retardation, cerebral palsy, or behavior spectrum disorders. Short interval between infection and ultrasound manifestations is a poor prognostic marker.

CASE PRESENTATION: The authors present a case of an acute CMV infection with isolated ventriculomegaly, diagnosed at 16 gestational weeks. A review of the literature about screening and diagnostic challenges for CMV infection during pregnancy was done, emphasizing the bad prognosis in cases with the early primary infection and the need for regular screening programs and prevention.

CONCLUSION: Screening for anti CMV IgM/IgG and IgG avidity in all pregnant women could be recommended to identify risk groups and improve diagnostic capabilities.

Introduction

Cytomegalovirus (CMV), known as human herpesvirus-5, is the most frequent cause of congenital viral infection, with a prevalence of 0.2% to 2.5% of all live births [1]. It is associated with neurodevelopmental delay and is the leading infectious cause of hearing impairment in children. It is estimated that congenital CMV infection can manifest with neurological disabilities such as autism spectrum disorders and decline in the intelligence quotient in schizophrenia patients [2].

The exact risk for congenital CMV infection is up to 15% after primary and 2% after secondary infection with more severe neurological damage if infection occurs during the first half of pregnancy [3]. Maternal-fetal infection can occur in several ways: Directly from infected placental tissue, ascending cervical CMV infection, direct contact during delivery with the infected cervical mucus, or during breastfeeding.

The diagnosis of CMV infection during pregnancy can be difficult, as ultrasound (US) features may not be evident until many weeks after fetal infection. Prenatal US findings in CMV infected fetuses include fetal growth restriction, cerebral abnormalities such as ventriculomegaly, occipital horn calcifications, microcephaly, and non-cerebral multi-organ abnormalities such as echogenic bowel, ascites, hepatomegaly, and cardiomegaly [4]. However, the absence of fetal abnormalities does not exclude fetal damage, and fetal death may also occur in those cases with normal US examination [3]. Maternal seroconversion based on the detection of IgG antibodies to CMV in the serum is nearly 100% sensitive and specific marker for detection of acute infection [5].

Case Report

It is a case of s 26-years-old secundigravida with a history of miscarriage at 9 gestational weeks 2 years ago. The current pregnancy has normal early fetal morphology scan and a negative free fetal DNA

result for trisomies 21,13,18, and sexual aneuploidies. On a regular woman consultation at 16 weeks, an isolated hydrocephaly was detected on transventricular plane of the head on transabdominal ultrasonography (Figure 1). Woman has a history of flu-like symptoms around 10 g.w., in which she has not reported at that time to the attending gynecologist.

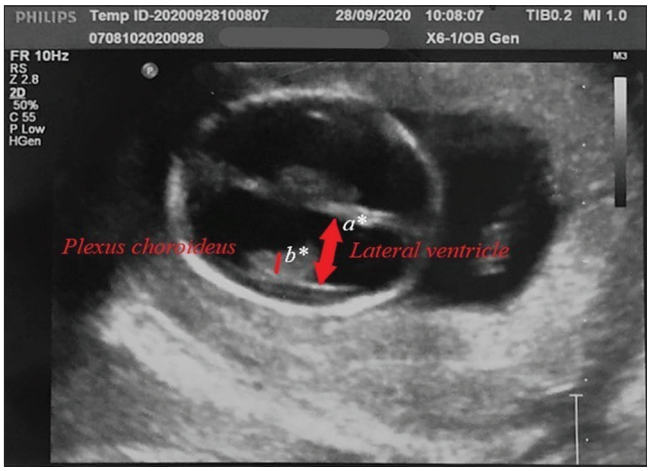

Figure 1: 2D visualization of the enlarged lateral ventricle – 16 mm (a) and compressed plexus choroideus – 4 mm (b*) measured by placing the calipers on the inner and outer edges of the ventricles and plexus on transventricular view of the head*

The patient was examined with TORCH screening test and anti-CMV IgM positive immune response was detected with low avidity IgG antibodies. Her immune status was unknown in the beginning of the pregnancy. This suggests a primary infection, reactivation of chronic infection, and/or reinfection with a new virus strain. CMV infection was suspected to be the reason for the detected anomaly. The pregnancy was terminated, as the risk for vertical transmission and neurological defects is higher when an acute infection occurs in the first half of pregnancy with the early US manifestation.

Discussion

Fetal cerebral ventriculomegaly is defined as an atrial diameter of lateral ventricle of >10 mm on prenatal US. The correct measurement should be obtained in the transventricular (axial) plane at the level demonstrating the frontal horns and cavum septi pellucidi, in which the cerebral hemispheres are symmetric in appearance. The calipers should be positioned on the internal margin of the lateral walls of the atria, at the level of the parietal-occipital groove and glomus of the choroid plexus, on an axis perpendicular to the long axis of the lateral ventricle.

Ventriculomegaly can be a result of different causative processes which include abnormal turnover of cerebrospinal fluid, chromosomal abnormalities, neuronal and migration disorders, and infection. In 5% of cases, it is a manifestation of trisomy 21, inherited X-linked or, in rare cases, autosomal recessive diseases. Intrauterine infections such as Toxoplasma gondii, rubella, CMV, and herpes simplex virus infections are found in 10%–20% of those with severe isolated ventriculomegaly [6]. The most common structural causes of fetal ventriculomegaly include aqueductal stenosis, Chiari malformation type II, dysgenesis of the corpus callosum, and abnormalities of the posterior fossa [7], [8]. In our case, a prenatal cell-free DNA was done with negative result for trisomy 13, 18, 21, and normal sex chromosomes. No other structural abnormalities were detected on fetal US evaluation of the brain at the time of the diagnosis of isolated ventriculomegaly. Hence, the less expensive and non-invasive method before karyotyping was serology for congenital infections. If serology was negative, fetal karyotyping should be the next step to exclude other rare causes for ventriculomegaly.

The frequency of congenital CMV infection, determined most often by DNA viral testing in European countries ranges between 0.18 and 0.48% [9]. Approximately 40,000 babies in United were born with congenital CMV infection, with 400 deaths reported each year and about 8,000 children with disorders such as hearing and vision loss or intellectual disability [10].

The gold standard for identifying primary infection in a pregnant woman is anti-CMV IgG avidity with a blood sample drawn from a vein. It is both a sensitive and specific method for diagnosis of acute infection and also detects pregnancies at increased risk for vertical CMV transmission [11]. Antibody avidity, measured by ELISA, is an indirect measure of the tightness of antibody binding to its target antigen. Low avidity anti-IgG antibodies to CMV persist for up to 20 weeks after a primary infection and is an accurate indicator for primary infection within the preceding 3 months. At present, the combination of the presence of anti-CMV IgM antibodies and low avidity anti-CMV IgG antibodies along with maternal or fetal symptoms is used for the diagnosis of a primary maternal infection [12].

The detection of IgM antibodies in maternal blood can be helpful but has problems; although IgM antibodies to CMV occur in all primary infections, they may also occur after reactivations or reinfections and has a high false positive rate. IgM usually peaks 3 to 6 months after a primary infection but may remain present in serum for over 12 months [11].

To detect the virus itself, in patients who are symptomatic, the sample may be blood, urine, amniotic fluid, cerebrospinal fluid, duodenal fluid, other body tissues, or saliva in newborns, where polymerase chain reaction (PCR) is used to detect viral DNA. Some samples, such as amniotic fluid, cerebrospinal fluid, or body tissue (biopsy), may require a special procedure to collect [4], [10], [12].

A normal prenatal cerebral assessment by MRI and US in women diagnosed with CMV infection should be considered as a good prognostic factor. MRI seems to be mainly indicated in cases with isolated extra cerebral features. If the fetal US is normal in an infected fetus, MRI may not find brain anomalies [13].

In our case, an acute infection was detected with low avidity Ig G antibodies and an US manifestation with ventriculomegaly at 16 weeks, which were poor prognostic factors for the developing fetus and a decision for termination of the pregnancy was taken.

Four-fifths of fetuses with severe ventriculomegaly survive and, of these, just over two-fifths show normal neurodevelopment. The overall survivors without disability account for more than one-third of the total. The possibility to follow-up, prolong the pregnancy till term and have a child with normal development can be taken as a missed opportunity in this case [14].

Amniotic fluid testing can be helpful in maternal diagnosis but cannot replace maternal serologic testing, because amniotic fluid may contain CMV even if the mother was immune to CMV before conception [15]. Prenatal diagnosis of congenital CMV infection, when based on amniocentesis, should be made at least 7 weeks after the presumed time of maternal infection and after 21 weeks of pregnancy, according to literature data. This interval is important, according to the authors, because after fetal infection and subsequent replication of the virus in the kidneys, it takes 5–7 weeks for the detectable amount of viral DNA to accumulate in the amniotic fluid [16].

In a survey of 300 pregnant women who tested positive for CMV antibodies (IgM) and were classified, as high-risk for congenital injection was demonstrated that fetal abnormalities detected by US and positive PCR results from cervical samples were the two most effective ways to predict congenital infection before birth. This is the first report to demonstrate that uterine cervical secretion can be used to predict congenital CMV infection. Both US and PCR tests are non-invasive procedures, and using them can offer a safer method to test high-risk pregnant women and predict the occurrence of congenital infection. Accurately identifying the affected infants enable a possibility to start antiviral treatment early and could improve the neurological prognosis of infants infected by CMV [17].

Only few countries routinely screen pregnant women for CMV by serology (Israel, France, Belgium, Spain, Italy, Germany, Austria, Portugal, and the Netherlands) [18]. Serologic testing for CMV may be considered for women who develop influenza-like symptoms during pregnancy or following detection of sonographic findings suggestive of CMV infection.

Screening for CMV infection of pregnant women in Bulgaria is not a routine practice. Demireva recommended screening for anti CMV IgM/IgG and IgG avidity in all pregnant women to identify risk groups and improve diagnostic capabilities [19].

A possible algorithm for limited CMV screening during pregnancy could be to define CMV serostatus as early as possible during pregnancy. For seronegative women at a high-risk group (household exposure to a child <3 years of age), hygienic interventions and monthly serologic testing are proposed until 20 weeks and if seroconversion is detected consider amniocentesis and preventive hyperimmune globulin application. For low-risk seronegative women, interventions if abnormal US findings at 20–22 weeks scan [20].

Conclusion

In the absence of routine serological screening for CMV infection in pregnancy, US remains the best tool to detect signs of fetal CMV infection. The prevention is critical, especially for those pregnancies exposed to contact with young children. Women at a higher risk should be counseled about the importance of careful hand hygiene practices, which decrease the risk of primary CMV infection and subsequent fetal transmission. An acute infection during the first trimester is associated with poor prognosis for the developing fetus with higher rate for neurological damage and elective termination of pregnancy could be better option for those cases.

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