

CYTOMEGALOVIRUS INFECTION IN PREGNANCY AND THE FETUS: A CASE PRESENTATION

The objective of this case study was to study possible clinical manifestations of Human Cytomegalovirus (HCMV) which demonstrate the vertical transmission of HCMV from mother to her children. The patient, an HCMV infected woman with chronic socioeconomic problems and depression, was observed between 2003 and 2011. During that time, five pregnancies were clinically monitored with use of immunograms, PCR, and general blood and urine analyses. This case showed that HCMV infection of pregnant mother caused death of newborns due to HCMV-associated complications. Due to combinatory therapy the fifth pregnancy was successful with delivery of a HCMV asymptomatic newborn. With the deficit of knowledge on HCMV and its effect on pregnant women in Uzbekistan, such research for the clinical manifestation of the virus is vital to deter the transmission of the virus and improve the wellbeing of both mother and child.

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Introduction

Cytomegalovirus (CMV) is one infection that is capable of “vertical” transmission from mother to infant, before, during or after birth. CMV may persist in a latent state, but under unfavorable conditions, is capable of causing a variety of pathological processes. Cytomegalovirus transmission also occurs “horizontally” by direct person-to-person contact with virus-containing bodily secretions and by transfusions of blood, leukocytes and platelets from infected donors (Pickering et al., 2009).

Cytomegalovirus localizes favorably in the salivary glands where it develops in the epithelial cells, and in the kidneys. Affected cells enlarge and develop large nuclear inclusions, which may acquire an “owl’s eye” appearance. The virus may remain in this state for a long time, secreted in urine and saliva. However, CMV can affect any cells of the body, thereby resulting in a polymorphic clinical picture.

Once infected, the human may never be rid of CMV, although if the immune status is satisfactory viral replication may be suppressed, leading to a latent state. In this sense, the manifestations of CMV infection vary with the effectiveness of the immune response.

This clinical case demonstrates clearly the insidious and aggressive nature of Cytomegalovirus (CMV) infection in the context of personal and social conditions similar to those described above.

Case report

In 2003 a 24-year-old primigravida was referred to our clinical department with a twin pregnancy of 28 weeks gestation. Her initial visit to the referring gynecologist was late due to unfavorable social conditions and a complicated relationship with the husband’s family. A routine TORCH screen was performed, which revealed IgG antibodies to CMV and Herpes Simplex (HSV) Types 1 and 2.

Blood Analysis: Hb - 85 g/L; RBC - $2.3 \times 10^{12}/L$; Platelets - $110 \times 10^9/L$;

WBC - $2.3 \times 10^9/L$; Monos - 1%; Bands - 1%; Segs - 1%; Eos - 0%;
Lymphs - 91%; ESR - 32mm/h

Urine Analysis: Yellow, turbid; Specific Gravity - 1.020;

WBCs - 17-18 per field; Epithelial Cells - 8-9 per field; Oxalates present;

Casts - none

A qualitative analysis for the CMV genome in blood plasma by polymerase chain reaction (PCR) was positive. The avidity index (IgG), an immunoassay, was less than 34%. This index is a measure of the binding strength of the antibody with the antigen. IgG immunoglobulins appear later than IgM immunoglobulins, which are elicited early in the primary immune response. IgG accumulates in large quantity and possesses high avidity.

Detection in test serum of IgG antibody with an avidity index less than 30 - 35% indicates a fresh primary infection. A level greater than or equal to 40% indicates anamnestic antibodies of high avidity, evidencing past infection; a level in the range of 31 - 39% suggests a late stage of a primary infection or a recent recovery (Volodin et al., 2001). Thus, the determination of antibody avidity permits the differentiation of primary infection from reactivation or secondary infection. This is especially important for pregnant women, since primary CMV infection (and other TORCH infections) can lead to intrauterine defects, stillbirths, and other significant complications.

The avidity index in this patient speaks not for primary infection, but for an insubstantial and deficient immune response. For treating this at-risk pregnant patient, a supportive, supplementary metabolic treatment was instituted with the following:

1. A 10-day intravenous course of Inosine, a purine nucleoside precursor to adenosine triphosphate, 2% solution, 5 ml. in 250 ml. 0.9% NaCl;
2. A 10-day intramuscular course of Actovegin, a protein-free extract of calf blood containing essential phospholipids and probiotics, 2.5 ml. dissolved in 5 ml. 0.9% NaCl;
3. As an immunomodulator, Viusid was chosen, considered permissible for use in pregnancy, from the second trimester. Viusid is a compound of glycyrrhizic acid and multivitamins, given orally.

After a month of this treatment, the patient showed slight subjective improvement. Analysis of blood was marginally improved. Unfavorable circumstances in the family prevented regular follow-up at our center.

The delivery of twin girls occurred at 37 weeks gestation. There were signs of early maturity and respiratory distress. One child expired on the sixth postnatal day; the other on the twenty-first day of life. They were diagnosed with disseminated intrauterine CMV infection with bronchopneumonia.

One year and seven months later the patient returned to our center pregnant. In the first trimester of this second pregnancy she appeared toxic with generalized weakness, malaise, nausea, vomiting, lower blood pressure (90/60 mm Hg) and mild hyperthermia (37.2 - 37.8 degrees C). There was edema of the lower extremities. Bilateral lumbar flank pain was elicited on percussion. The blood plasma was positive for the genomes of CMV and HSV Types 1 and 2. Qualitative urine analysis was positive for protein and leukocytes and epithelial cells were seen in large quantities throughout the microscopic field but no crystals or casts. Urine specific gravity was 1.025. The serum creatinine was normal at 115 $\mu\text{mol/L}$. Ultrasound scan was consistent with pyelonephritis. Her avidity index was still low (however, pertinent to this patient we already knew that this was not a primary infection). Her living conditions were unchanged, entailing considerable psychosocial stresses and a poor quality of life.

The second pregnancy continued under a constant threat of miscarriage. The uterus was in a tonic state, with a notable discharge containing some blood. Twice she was admitted to an outside obstetrical center. She was treated supportively with glucose and ascorbic acid, Inosine, and a prenatal multi-vitamin, magnesium and vitamin B6. This pregnancy concluded in an emergency delivery of a 2800-gram baby girl born at term with Apgar scores of 3 and 5. In the early neonatal period the baby developed the first signs of disseminated CMV infection- interstitial pneumonia, respiratory insufficiency, and hepatitis. CMV genome was found in blood plasma and mononuclear cells. The neonate underwent resuscitative measures during which fresh blood, plasma and albumin were repeatedly transfused. With improvement in their general condition the mother and child were discharged home. However in two months the baby was re-hospitalized with bronchopneumonia, hepatosplenomegaly, elevated transaminases, renal failure and hyperthermia, consistent with disseminated CMV infection. The infant was transferred to intensive care at the Virology Institute for further supportive treatment. Initiation of specific antiviral therapy was complicated by the evident hepatic and renal pathology, which was deemed a contraindication to Gancyclovir. The infant's status improved somewhat, and she was released home on the 45th hospital day. However, she was hospitalized again 10 days later with hyperthermia and febrile convulsions. Elevated transaminasemia, hyperbilirubinemia, splenomegaly were noted, and urine analysis revealed a large number of fresh RBCs. Despite resuscitative measures the infant expired at five months of age.

The third pregnancy for this woman came five months after the death of the third child. The entire pregnancy passed under threat of spontaneous abortion. Qualitative plasma analysis for CMV remained positive; iron deficiency anemia persisted. She manifested generalized weakness, fatigability and depression. Psychosocial living conditions remained unsatisfactory. In view of her prior experience with pregnancies, she was offered an elective Caesarean section to mitigate the risk of intrapartum infection.

An infant boy was delivered by C-section with Apgar scores of 8 and 9, and was immediately put to breast. Outwardly the infant seemed healthy. Mother and child were discharged from the obstetrical service on the seventh day.

The infant was followed on a daily basis. At 8 - 9 days, there were no external signs, but on pulmonary auscultation there were coarse breath sounds. On the tenth day, abrupt, fulminating respiratory insufficiency developed. He was admitted on an emergency basis to the Virology Institute intensive care unit, where he expired on the twelfth day of life. An autopsy revealed an underdeveloped, rudimentary thymus gland, pulmonary edema, and cerebral edema.

This patient had a fourth pregnancy, which ended in a spontaneous abortion at eight weeks.

The woman experienced a long period of depression, and overall fatigue and weakness during the subsequent eight months. Psychologists were called to assist her after she attempted suicide.

Further therapeutic interventions were directed at, first of all, improving her social conditions, then conducting treatments and rehabilitation. Periodically during two years the patient received various supportive metabolic treatments, such as probiotics, membrane stabilizers, preparations affecting lipid metabolism, essential phospholipids, and detoxifiers. Unfortunately, optimal specific anti-viral therapy was not considered possible. In Uzbekistan the antiviral Gancyclovir, considered specific treatment for CMV, is extraordinarily expensive, and as a result is not accessible for many patients in need of it. Our patient fell into this category. Conditions dictated a combined approach to treat the viral infection and support the patient. How we purported to act was well expressed by Andrewes (1967), that antibiotics can achieve swift sterilizing effects in many infectious diseases, but in others, for example, those caused by herpesviruses, complete elimination of the infectious agent is impossible, and further treatment is accomplished by mobilizing immune factors, which takes time.

We used a combined regimen, starting with intravenous Acyclovir, with inhibitory activity against CMV. Following Acyclovir, Polyoxidonium, an immunostimulant, was administered IM daily in the upper outer gluteal quadrant for four days.

Viusid, an inducer of endogenous interferon, was given orally one packet twice daily for three months.

Improvement of the patient's living conditions, medical treatment, and a long period of rehabilitation have given a good result.

The fifth pregnancy appeared three years later, and proceeded favorably. In the entire course of the fifth pregnancy the CVM genome was measured positive once, following a common cold (URI). We were able to alleviate the pathological process with three courses of Viusid and Viferon, the latter a human recombinant interferon alpha-2b, administered as a rectal suppository. Delivery was by C-section of a healthy girl, weighing 3.40 Kg, with Apgar scores of 9 - 10.

Observation of the child over the first year demonstrated an absence of CMV genome in her blood, although up to three months of age IgG antibodies were detected by EIA. Since the CMV genome was not found in the first year, and at 6 months IgG had disappeared, we considered the immunoglobulins present in the child in the early months to be maternal antibody. Into her third year of life, the girl is developing normally, on a par with her peers both physically and mentally.

It should be noted that in addition to an adequate treatment regimen, improvements in living conditions as well as normalization of the family situation played a signal role in the improvement of the health status of the mother. She experienced greater success in managing psychosocial stressors.

Observation of the patient was conducted from 2003 till the present time.

Conclusion

Observation of the patient illustrated a number of aspects. The first aspect displayed is that the source of the intrauterine cytomegalovirus infection (CVMI) is the mother, ill with the acute form of CVMI or the latent chronic form in a period of reactivation. In such cases transmission to the fetus occurs directly through damaged placenta (prenatal), or during passage through the birth canal (perinatal) (Farber, 1989; Kazantsev and Popova, 1980). Secondly, detection of specific anti-CMV IgG in the newborn or the infant up to one year of age suggests the transplacental transmission of antibodies from the infected mother. In this case we detected the viral DNA by PCR in both plasma and mononuclear cells. Another aspect is that lifelong persistence of CMV virus is possible (Granitov, 2001). Reactivation of the infection occurs in the presence of immunosuppression. In the case we describe, immunosuppression had taken place, associated with a complex of factors: Firstly, the constant condition of stress; secondly, an inadequate diet- unbalanced, vitamin-poor, without sufficient protein; iron-deficiency anemia; a generalized weakening of the central nervous system. Finally it was noted that in the presence of factors promoting immunosuppression and in intrauterine infection of the fetus, congenital cytomegalovirus disease can progress as the disseminated form, with injury of various organs and systems, as took place in all four of the cases of neonatal death presented here.

With the deficit of knowledge on HCMV and its effect on pregnant women and their children in Uzbekistan, such research into the clinical manifestation of the virus is vital to help deter the transmission of the virus, improve the wellbeing of mother and child, and prevent miscarriage and death of the child. Such knowledge is vital due to such a high percentage of the population being infected with the virus. Treatment can be maximally effective in a setting of combined specific antiviral and supportive pathophysiological therapy, together with psychosocial treatment and personal health education. In addition, public information through the media on all aspects of infectious disease prevention is needed to improve public hygienic habits and the quality of life. Further research of

Cytomegalovirus possible clinical manifestation is encouraged along with research into optimal treatment for the virus.

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