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CASE STUDY

DIAGNOSTIC PROBLEMS OF CYTOMEGALOVIRUS INFECTIONS IN PREMATURE NEWBORNS

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ABSTRACT

Introduction. Cytomegaly is an infectious**,** widespread viral disease. It is caused by *Cytomegalovirus* (CMV), which belongs to the DNA viruses group from the *Herpesviridae* family. The virus is human specific. Once infected, a person remains seropositive to the end of life and the virus remains latent particularly in leukocytes, which are its main reservoir. Many different disease manifestations, which depend partially on a patient's age, but mostly on an immunological state, may be caused by CMV.

Aim. The aim of this work was the assessment and histoclinical analysis of CMV infection in a male newborn with a congenital anomaly syndrome.

Case study and examination results. A male newborn, born in the 30th week of gestation, diagnosed with congenital anomaly syndrome, Apgar score was 2. In the neonatal period hypertrophic cardiomyopathy involving the right ventricle, esophageal atresion, esophagotracheal fistula, hepatosplenomegaly, respiratory insufficiency and hyperechogenic periventricular structures in the brain were diagnosed. During the entire hospitalization period a progression of inflammatory changes in the lungs was observed. The results of serological tests to detect anti-CMV and toxoplasmosis specific antibodies were: CMV–IgG 21.00 IU/mL; CMV–IgM negative; Toxo–IgG 4.0 IU/mL; Toxo–IgM negative. Restoration of esophageal continuity and repair of the fistula were performed surgically. Follow-up serological test was positive for anti-CMV antibodies in the IgG and IgM classes. The patient died on the 79th day following hospital admission. Autopsy and histopathological tests confirmed generalized cytomegalovirus infection.

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Discussion. Most advanced histopathological changes were observed in lungs, liver, spleen and brain. Characteristically changed cells, confirming generalized cytomegalovirus infection were found in all the aforementioned organs.
Conclusions. CMV infections, particularly congenital infections in premature newborns are challenging diagnostic and therapeutic problems. Routine diagnostic procedures to detect CMV infections seem to be necessary in risk groups, particularly for premature infants. Negative anti-CMV antibodies result in patients with an insufficient immune system, does not exclude the presence of this infection. Early diagnosis and treatment of congenital cytomegaly may positively affect a patient's clinical condition and prolonged prognosis.

Key words: cytomegaly, premature newborn, infection

INTRODUCTION

Cytomegaly is an infectious**,** globally widespread viral disease. It is caused by *Cytomegalovirus* (CMV), which belongs to the DNA viruses group from the *Herpesviridae* family [8, 10]. The virus is human specific. It remains in a human organism in a latent form for a long time [1]. In the reactivation period it penetrates into bodily fluids and consequently is easily transmitted into the host environment [6].

The name of the virus comes from the changes which it causes in a cell. An infected cell is markedly enlarged, with characteristic intranuclear and cytoplasmic inclusion bodies.

Cytomegaly may be manifested in many various ways, depending on a patient's age and immunological state. In adults and older children, with a normally functioning immune system, its course is usually asymptomatic, rarely mononucleosis-like [3, 6]. However, in people with a lowered immunity, i.e. in patients with immunodeficiency, patients undergoing immunosuppressive treatment, patients who have undergone surgical treatment, and in fetuses and newborns, CMV infection poses a serious threat which may lead to death.

CMV infection may occur via a number of mechanisms, among others, intraplacental mechanism (congenital cytomegaly), via secretion from the female reproductive tract and mother's milk (perinatal cytomegaly), saliva, sexual intercourse, secretion form respiratory tract, "dirty hands", and iatrogenic transmission [2, 4, 5].

Infections during pregnancy are especially dangerous because the virus may lead to serious congenital abnormalities of the fetus. Complications involving newborns most frequently include: generalized infection (sometimes fatal) with enlarged liver and spleen (hepatosplenomegaly), jaundice, thrombocytopenia, hemolytic anemia, rash, loss of hearing, retinitis, choroiditis, optic nerve atrophy, hepatitis, pneumonia, mental retardation of various degrees, microcephaly, periventricular calcifications and intracranial hemorrhages [10].

Due to its common prevalence and a wide range of adverse manifestations, cytomegaly is a serious clinical challenge.

AIM

The aim of this work is the assessment and histoclinical analysis of CMV infection in a male newborn with a congenital anomaly syndrome.

CASE STUDY AND EXAMINATION RESULTS

A male newborn, birth weight of 1300 g, born in the first pregnancy, single birth, in the 30th week of gestation, by caesarean section due to the risk of fetal asphyxia, preterm outflow of amniotic fluid, and a risk of intrauterine infection. Apgar score was 2. In the neonatal period, the newborn was diagnosed with: hypertrophic cardiomyopathy involving the right ventricle, esophageal atresion, suspicion of esophagotracheal fistula, hepatosplenomegaly, respiratory insufficiency and hyperechogenic periventricular structures in the brain. Antibiotic therapy of a wide spectrum was administered. For further diagnostic procedures and specialist treatment, the newborn was transferred on the 3rd day of life to the Provincial Specialist Children's Hospital in Olsztyn. After admission several examinations were performed which confirmed esophageal atresion and changes to the brain structures in the form of numerous calcifications of periventricular structures and 2nd degree left-sided hemorrhage. A cyst within the spleen was detected. Changes in the liver were not observed. Immunochemical tests to detect anti-CMV and toxoplasmosis specific antibodies in the IgG and IgM classes were ordered. The results were as follows: CMV–IgG 21.00 IU/mL; CMV–IgM negative; Toxo–IgG 4.0 IU/mL; Toxo–IgM negative. On the 3rd day of hospitalization the newborn underwent a procedure to restore esophageal continuity. Throughout the entire hospitalization the patient's condition was unstable, with periodic improvements. However, after 37 days of hospitalization the baby's condition "broke down". Further examinations were carried out which revealed parenchymal density of an inflammatory nature. Within the following days, the patient's condition worsened, the skin became grey, edema appeared as well as meteorism and hardness of the abdomen. The presence of right-sided pneumothorax and tracheoesophageal fistula were revealed. USG of the abdominal cavity showed markedly enlarged liver and spleen. After 68 days of treatment it was decided to close the fistula. Within the following days the baby's condition exacerbated progressively. After a careful analysis of clinical data and the course of disease, fungal superinfection and cytomegaly infection were proposed, despite the first serological test in the IgM class being negative. Immunochemical diagnostic tests were performed again and this time the following results were obtained: CMV–IgG 13 IU/mL; CMV–IgM –2.27 TV. The patient died on the 79th day following admission.

DISCUSSION

Congenital cytomegalovirus infection is diagnosed on average in 1% of newborns, and it is the most frequent infection in humans [2, 6, 8]. In the majority of adults its course is mild and asymptomatic. However, in people with a lowered immunity it may cause serious health problems, not infrequently leading to death, as in the aforementioned described case. In pregnant women a risk of passing the infection to the fetus is estimated to be 40–50%, while the development of a fully symptomatous disease is estimated to be 10–15%. The remaining 85–90% of newborns infected with the virus *in utero* are at risk of delayed manifestations of the peripheral nervous system defects as well as sight and hearing defects [9, 10]. The most serious course is observed in infections acquired in the I trimester of pregnancy. They are characterized by an increased incidence of congenital anomalies, including: microcephaly, intracranial calcifications, low birth weight. Acquiring an infection in the last period of pregnancy increases the risk of an acute form of the disease with intraorgan localization, interstitial pneumonia, interstitial myocarditis, hepatocellular damage, spleen damage, thrombocytopenia and purpura. Changes in the organs in the case observed by us indicate the mother's infection in an early period of pregnancy.

Perinatal infections are generally asymptomatic. However, after some months or even years neurological consequences may appear involving a delayed onset of mental retardation and hearing impairments [9]. The course of the disease in the herein described case indicates that perinatal infection could not have occurred.

The course of infection correlates with the gestation period: the more immature the fetus, the higher probability of developing a fully symptomatous disease, requiring a long-term, multi-directional treatment. It is necessary for the CMV diagnosis to be established as soon as possible after birth. In our case, diagnostic procedures were correct, however the fact that the disease did not manifest itself in the first examination hindered the therapeutic process.

Considering the prevalence of the virus in the European population, all pregnant women should be examined in the III trimester so that the initial status of the newborn is established when some non-specific symptoms appear. In newborns and babies an abnormal course of inogenous jaundice, intestinal disorders, non-specific skin rash, and mostly systemic infections should be seen as indicators for performing examinations. Moreover, manifestations of congenital anomalies already described (as in the discussed case – *esophageal atresia*), hepatosplenomegaly or intracranial calcifications should also lead to examinations to detect the virus's presence. It should be a routine examination in diagnostics involving prematurity, fetus defects and abortions.

Detecting the infection is based on serological tests. The presence of specific antibodies in the IgM class indicates a primary infection. However, serological methods

are of less significance presently, because in order to confirm cytomegaly consecutive tests should be carried out in 2-week intervals, whereas a rapid therapeutic intervention is of vital importance. Only the detection of specific antibodies in the IgM class allows for establishing the diagnosis. It should be remembered that antibodies for other viruses from the *Herpesviridae* family may produce cross-reactions with CMV antigens and give false positive results [10].

In the remaining cases more modern examinations detecting the virus or an element of its structure should be carried out – antigens with the use of various methods of molecular biology. One of them is the polymerase chain reaction (PCR) method which involves multiplication and then identification of the genetic material of the virus in blood, saliva or cerebrospinal fluid. Detecting the virus in amniotic fluid, or antibodies of the IgM class in blood confirms the diagnosis, although negative results of these tests do not always exclude this diagnosis [10].

In the discussed case we deal with a congenital CMV infection. Diagnosing symptomatous cytomegaly was indicated by the changing picture of liver and spleen. During hospitalization the liver displayed disconcerting changeability in USG images, alternately from sizes indicating pathology to those within norm. Spleen displayed a picture of enlarging hyperechogenic changes. Another reason for diagnosing the viral infection were hyperechogenic foci that repeatedly appeared in transfontanelle ultrasonography of the brain, suggesting calcifications or necrotic foci.

Autopsy and histopathological tests of the specimens revealed changes indicating a generalized CMV infection. Histopathological tests revealed the presence of characteristic, enlarged cells with intranuclear inclusion bodies – "owl's eye" in: lungs, liver, spleen, kidneys and pancreas (Fig. 1–6).

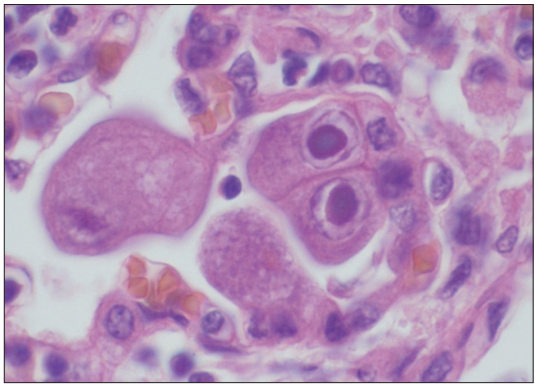

Fig. 1. Intranuclear viral inclusions in alveolar lung cells [HE 400×]

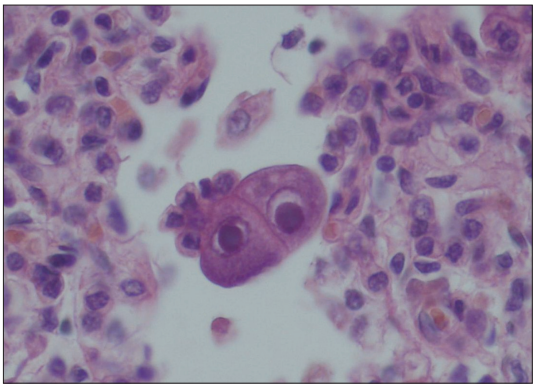

Fig. 2. Intranuclear viral inclusions in spleen cells [HE 400×]

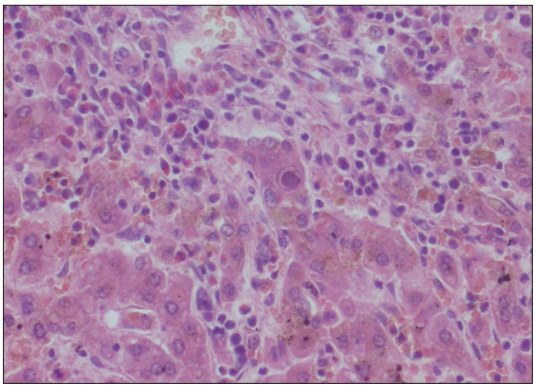

Fig. 3. Intranuclear viral inclusions in liver cells [HE 200×]

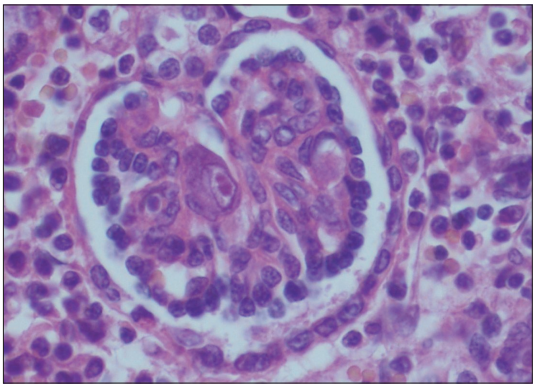

Fig. 4. Characteristic intranuclear viral inclusions in mesangial kidney cells [HE 400×]

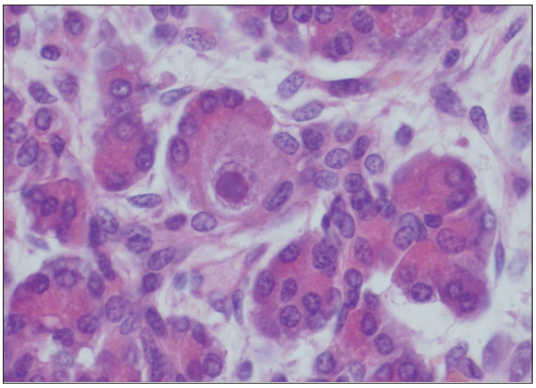

Fig. 5. Intranuclear viral inclusions in pancreas cells [HE 400×]

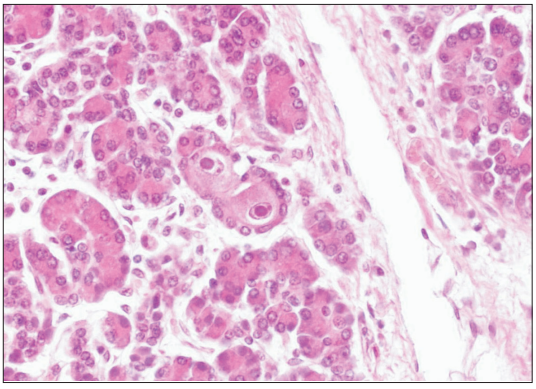

Fig. 6. Inflammation and fibrosis in the pancreas [HE 200×]

Autopsy detected: interstitial pneumonia, hepatitis, splenitis, interstitial nephritis and glomerulonephritis, as well as pancreatitis. In the generalized course of the cytomegovirus infection all parenchymal organs were involved, which was the major cause of death.

There is no vaccine thus far, or a fully effective, safe medication for this disease. Past disease does not prevent reinfection. It is a major cause of congenital infections in newborns, and also the most frequent cause of mental retardation, deafness, and many other developmental defects. All these factors make it a common but underestimated medical problem which warrants further studies.

In Poland compulsory, systematic serological tests to detect cytomegaly in the entire population of pregnant women have not been introduced thus far. Sporadically performed examinations are not consulted by physicians specializing in infectious

diseases. At the time of compulsory screening performed routinely in newborns with the use of just a few drops of blood on filter paper, correlating the detection of cytomegaly with tests focused on more than 20 various metabolic and genetic defects seems to be the modern 3rd degree preventive method, recommended globally [7].

CONCLUSIONS

1. A clinical course of CMV in children is correlated with the route of transmission to the organism and with an age when the infection occurs.
2. It seems that introducing routine diagnostic procedures to detect CMV infections in risk groups, especially for premature newborns, is justifiable.
3. Negative anti-CMV antibodies result in patients with insufficient immune system, does not exclude the presence of infection.
4. Early diagnosis and treatment of congenital cytomegaly may positively affect a patient's clinical condition and prolonged prognosis.
5. Pathomorphologic evaluation of the specimen or a biopsy of a lymph node or parenchymal organs enables the establishment of a final diagnosis.

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