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Cytomegalovirus disease in neonates and infants – clinical presentation, diagnostic and therapeutic problems – own experience

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Background:

The aim of the study was to present diagnostic problems, different clinical presentations and results of treatment of cytomegalovirus infections in neonates and infants.

Material/Methods:

The study was carried out in a group of 31 children from 10 days to 12 months of age (17 boys, 14 girls). The diagnosis was based on serological investigations (presence of specific IgM antibodies and/or increasing titer of IgG antibodies), presence of intermediate or early CMV antigen in peripheral blood leukocytes or positive blood or urine PCR results. The treatment of 25 cases involved intravenous administration of gancyclovir at 5–7 mg/kg daily doses for 14–21 days. In 1 case, hyperimmunized anti-CMV serum – Cytotect was used.

Results:

The most common clinical symptoms were jaundice, hepato- and splenomegaly. Clinical investigations demonstrated increased aminotransferase activity and the signs of cholestasis. Other frequent findings included anemia, leukocytosis with atypical lymphocyte forms present, as well as thrombocytopenia. In majority treated patients, rapid regression of the clinical symptoms and normalization of transaminases activity was observed. Good outcome of the therapy was confirmed by immunological investigations. The effects of the therapy were similar irrespective of the dose and duration of gancyclovir treatment. The tolerance of the drug was good – no indications for discontinuation of the treatment were observed in any of the patients.

Conclusions:

The clinical presentations of cytomegalovirus disease in infants are varied, the diagnosis of the disease should be considered in children with persistent jaundice, especially if it is accompanied by hepatomegaly and increased aminotransferase activity or signs of cholestasis. Despite relatively good tolerance of the drug by children, the patients should be monitored for possible side effects, especially myelo- and nephrotoxic.

key words:

cytomegalovirus disease • infants • cholestasis • gancyclovir

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BACKGROUND

Human cytomegalovirus (CMV) is common all over the world, and the incidence of infections in various regions is dependent on the level of civilisational development. Specific anti-CMV antibodies are found in ca. 50–70% of the populations of industrial countries and in over 90% of inhabitants of the developing countries [1–3].

According to the moment of infection, congenital and acquired cytomegalovirus infections are distinguished. In the first months of life, there is a possibility of both congenital and acquired infections. According to American authors, cytomegalovirus infections are the most common congenital viral infections occurring in ca. 1% of live births. The infection can be contracted during pregnancy (transplacental transmission, especially in women with primary infection – risk rate reaching 40%), labor (the microorganisms are present in reproductive organ secretions), or during the neonatal period through infected milk or if sanitary and hygienic principles are neglected, by the contact with mother secreting the viruses through other routes: in urine, saliva, etc [2,4–8]. If the child under 3 weeks of age presents with the clinical symptoms such as damage of the central nervous system, liver, cholestasis, retinitis or choroiditis, splenomegaly, hemorrhagic diathesis, pneumonia, and CMV infection is confirmed by laboratory tests, the diagnosis of congenital cytomegalovirus disease can be established [7]. The results confirming cytomegalovirus infection include: obtaining growth of the microorganism in culture, the presence of specific IgM antibodies or increasing IgG titer, the presence of viral antigen in peripheral blood leukocytes or positive PCR results confirming the presence of viral genetic material in the blood, urine or cerebrospinal fluid [1,9–12]. However, if the above clinical symptoms and confirmation of the infection occur between 4 weeks and 12 months of age, the diagnosis of 'possible congenital cytomegalovirus disease' should be established [7].

Acquired infections in immunocompetent infants usually take a much milder course than the congenital form and are often completely asymptomatic. Post-transfusion infections, especially in neonates with low birth weight, are an exception to that rule, and the disease may even be fatal [2].

In the symptomatic forms of acquired cytomegalovirus disease, the first signs are observed at the age of 2–3 months. They most commonly include hepatosplenomegaly, jaundice, enlarged lymph nodes, and laboratory investigations indicate liver damage or hematological abnormalities (hemolytic anemia, thrombocytopenia) [6,13–15].

Gancyclovir is a drug whose effectiveness against cytomegalovirus has been proved. It is a synthetic guanosine analog, inhibiting replication of the virus. Because of its relatively low assimilability, intravenous injections are the preferred route of administration, especially in young children. Gancyclovir therapy, requires continuous monitoring of peripheral blood para-

eters, as well as hepatic and renal function, because of its myelo-, hepato- and nephrotoxic effects [16,17].

Moreover, because of the lack of prospective studies assessing distant adverse effects of the therapy (e.g. teratogenic) the often emphasized variability of doses administered to children, each decision to start treatment must be considered carefully.

The only indication to institute antiviral treatment in neonates and infants is symptomatic cytomegalovirus disease.

Aim of the study

The aim of the study was to present diagnostic problems, different clinical presentations and results of treatment of cytomegalovirus infections in neonates and infants.

MATERIAL AND METHODS

The study was carried out in a group of 31 children hospitalized in the Department of Pediatrics, Pediatric Gastroenterology and Oncology of the Medical University of Gdańsk from 1996 to 2000. The studied group comprised 17 boys and 14 girls from 10 days to 12 months of age. Figure 1 presents the numbers of children in particular age groups. In 5 neonates the diagnosis was established during the first 3 weeks of life, in the remaining cases most frequently between the 4th week and the 3rd month of life. Six patients were born before the 37th week of pregnancy (4 – 32/33Hbd, 2 – 34/35 Hbd) with birth weight below 2500 g (including 4 weighing below 1800 g). In 3 cases they were born at term, but their birth weight was low.

The diagnosis of cytomegalovirus infection was based on the presence of specific IgM antibodies and/or increasing titer of IgG antibodies detected by Vidas immunoenzymatic test, in some patients also on the presence of intermediate or early CMV antigen in peripheral blood leukocytes, and in 4 patients hospitalized most recently on positive PCR results (CMV-DNA present in urine and blood). In the case of youngest patients with high titers of anti-CMV IgG class antibodies with nega-

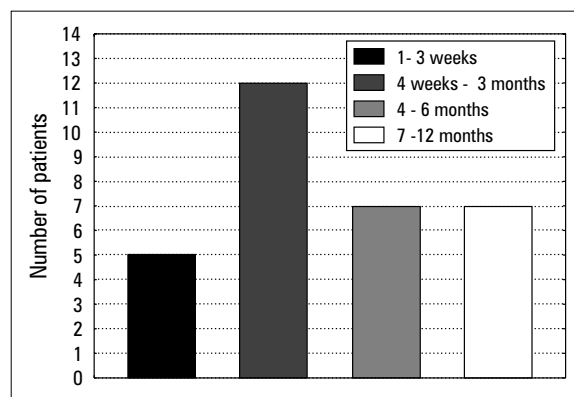


Figure 1. The patients' age.

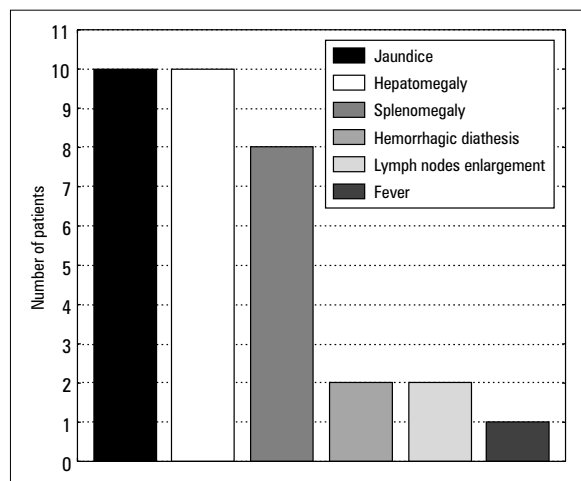


Figure 2. Clinical symptoms of cytomegalovirus disease presented by the patients.

tive IgM, maternal antibody status was also assessed. Additionally, laboratory investigations assessing liver function and cholestasis were performed (AlAT, AspAT, GGTP, FALK, total bilirubin and its bound fraction concentrations), whole blood count, abdominal ultrasonography, and in some patients also transfontanellar USG of the brain, with neurological and ophthalmological consultation. If laboratory tests indicated the signs of liver damage and/or cholestasis, the diagnostics was also extended by testing for the presence of other infectious diseases (toxoplasmosis, urinary tract infections, HBV, HCV) and some metabolic disorders (blood levels of alpha-1-antitrypsin, iron, ferritin, ceruloplasmin, urine and serum levels of galactose, galactose-1-phosphate uridiltransferase, chlorides in sweat and GC-MS metabolic screening of urine samples).

The treatment of cytomegalovirus disease was instituted in 26 cases – in 25 gancyclovir (Cymevene, Roche) was used and in 1 – hyperimmunized anti-CMV serum (Cytotect, Biotest).

RESULTS

Jaundice, observed in 32% (10/31) patients, was the most common clinical symptom in the studied group of children. In 32% (10/31), hepatosplenomegaly (from moderate, palpable 1.5–2 cm below the right costal margin to marked, extending to the iliac crest) was revealed by physical examination and/or USG.

In 2 cases, peripheral lymph node enlargement was observed in addition to hepatosplenomegaly, and in 2 signs of hemorrhagic diathesis on the skin. One 8-month-old boy was admitted to the Department in poor general condition, febrile, pale, with marked hepatosplenomegaly. The above symptoms had been observed for 4–5 days prior to hospitalization, with no improvement after antibiotic therapy instituted on outpatient basis. Differential diagnosis considered, among others, sepsis and proliferative diseases of the hematopoietic system.

Figure 2 presents in detail the clinical symptoms observed in the studied group.

The most common abnormality detected in accessory investigations was increased activity of aminotransferases (AlAT and/or AspAT), observed in 24/31 cases (77%). In 20 patients, the values of at least one enzyme activity were 2-fold higher than the upper normal limit. Mean AlAT activity in that group of children reached 156 U/l (values from 48 to 624 U/l; normal range from 1 to 37 U/l), and AspAT – 169 U/l (values from 43 to 471 U/l; normal range from 8 to 40 U/l). As it has been mentioned above, jaundice was observed in most cases (mean total bilirubin level reached 5.45 mg/dl – values from 1.8 to 10.2 mg/dl; normal range from 0.1 to 1.0 mg/dl). In 10 cases it was due to cholestasis (direct bilirubin concentrations exceeding 1.5 mg/dl), additionally in 8 biochemical parameters of cholestasis without clinical signs of hyperbilirubinemia were demonstrated (GGTP, FALK, bile acids). Mean GGTP activity in children with cholestasis was 210 U/l (values from 40 to 800 U/l; normal range from 6 to 50 U/l), whereas FALK values ranged from 311 to 800 U/l – mean 348 U/l, normal range from 30 to 300 U/l. The concentration of bile acids in blood was also determined in some patients. The obtained values ranged from 18.7 to 158 μ M/l, whereas the normal ones range from 0 to 6 μ M/l.

Anemia was a relatively frequent finding – 9/31 (with reticulocytosis in 5 children with the evidence of hemolysis). Additionally, WBC demonstrated leukocytosis in 6/31 cases, and atypical lymphocytes were present in blood smears in 13 patients. Thrombocytopenia (thrombocyte counts below 100,000) was observed in 2 cases.

Abdominal USG was performed in all patients. It revealed hepatomegaly in 10 cases, including 4 with coincident congenital atresia of extrahepatic bile ducts and signs of intrahepatic cholestasis.

In 3 cases of intrahepatic cholestasis (2 – alpha-1-antitrypsin deficiency, 1 – cholestasis of unclear etiology) USG demonstrated additionally enhanced echogenicity of the organ. Splenomegaly was observed in 8 cases.

Transfontanellar brain USG was performed in 23 children with no significant abnormalities found (in 2 cases slightly smoothed outlines of the anterior horns of the lateral ventricles). Ophthalmological examination performed in 25 patients revealed changes typical of retinopathy occurring in premature infants in 2 cases.

Figure 3 presents in detail the abnormalities detected in accessory investigations in cytomegalovirus infection patients.

Confirmation of the diagnosis was usually based on the presence of specific IgM antibodies and intermediate or early CMV antigen in peripheral blood leukocytes. In the remaining cases, the diagnosis was confirmed by the titer of IgG antibodies increasing in the subsequent determinations (in some cases supplemented with positive early antigen) or, in 4 cases, by

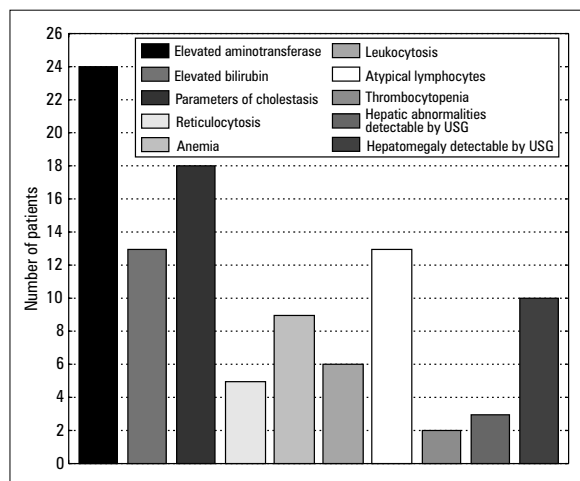


Figure 3. Abnormalities of clinical investigations in the patients.

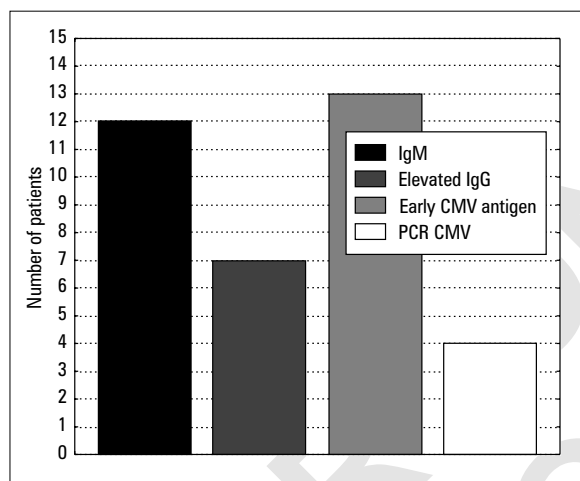


Figure 4. The basis for CMV infection diagnosis.

positive PCR results (including 3 with positive blood and urine findings).

Figure 4 presents in detail the results confirming cytomegalovirus infection.

The treatment was instituted in 26 cases – in 25 cases with intravenous gancyclovir and in 1 with hyperimmunized anti-CMV serum – Cytotect. Gancyclovir was administered at 5 mg/kg doses twice daily in 14 patients and at 6–7 mg/kg doses twice daily in 11. The therapy was continued for 14 days in 17 patients and for 21 days in 8. Cytotect was used in a 8-month-old boy with severe, generalized course of the disease. The drug was administered i.v. according to the following schedule: 4 ml/kg/daily on day 0, 4 and 8; 2 ml/kg/daily on days 12 and 16.

In 1 patient treated with gancyclovir, abdominal USG revealed enlarged kidneys without any abnormalities in biochemical tests performed to assess renal function, and in 3 other patients transient increase of aminotransferase activity. There were no indications for discontinu-

ation of the therapy. Most treated patients, especially those without coincident disorders responsible for liver damage and cholestasis (e.g. alpha-1-antitrypsin deficiency, extrahepatic bile duct atresia), demonstrated relatively rapid regression of clinical symptoms and 'biochemical' improvement confirmed by immunological investigations. The results of treatment were similar in children receiving 10 mg/kg and 12–14 mg/kg daily doses for 14 and 21 days. Cytotect, administered to 1 patient with good, lasting results, was also well-tolerated.

DISCUSSION

Despite advances in diagnostic methods, the diagnosis of cytomegalovirus infection in neonates and infants is still difficult. It results primarily from the variability of clinical symptoms and frequent ambiguity of the results of accessory investigations, allowing no unequivocal interpretation. Additionally, other infections, caused e.g. by Toxoplasma gondii or rubeola virus may be responsible for similar clinical presentations and abnormalities of laboratory parameters [2,7,18,19]. According to most authors, cytomegalovirus disease can be diagnosed on the basis of immunological investigations (serology, early antigen), or of the abnormalities of biochemical parameters, but always in connection with the clinical presentation. It should also be remembered that the demonstration of CMV presence in biological material only does not provide a basis for the diagnosis of cytomegalovirus disease. CMV is known to cause frequently latent infections only [6,11,12]. It is also difficult to determine the type of the infection: congenital, possibly congenital or acquired. Some clinical symptoms, e.g. jaundice, are so common in the neonates that they do not arouse anxiety if observed in such patients. Only the persistence of the above symptoms prompts the physicians to start diagnostic investigations. In the studied group, congenital cytomegalovirus disease was diagnosed in 5 neonates only. However, as it follows from anamnesis, the symptoms which might have been suggestive of the disease had been observed during the first weeks of life in additional 7 patients who were diagnosed much later.

Cytomegalovirus infections in mothers can be responsible for premature births. In the studied group, 6 patients were born from premature labor, 3 at term but with signs of intrauterine dystrophy. Their condition at birth was assessed as good or quite good (Apgar scores of minimum 7).

In view of multidirectional effects of cytomegalovirus infection, the condition of the liver, kidneys, nervous system, organ of vision and peripheral blood was assessed in our patients [2,6,13,14].

In accordance with other reports, persistent jaundice, cholestasis, hepatosplenomegaly, as well as increased transaminase activity, cholestasis parameters (GGTP, FALK, hyperbilirubinemia) and anemia in accessory investigations were observed as the most common clinical findings suggestive of cytomegalovirus disease. The incidence of infantile cholestasis in the course of CMV

infections is estimated by some authors even at 17%. As emphasized by Tarra et al. and own observations, the infection coincides relatively often with congenital extrahepatic bile duct atresia and other cholestatic syndromes. This can give rise to considerable diagnostic problems, which result in delayed diagnosis and institution of treatment [15,20].

It should be emphasized, however, that the clinical presentations and laboratory results obtained in the studied group may create an inobjective bias indicating high incidence of 'hepatologic abnormalities' in infants with cytomegalovirus disease. The above situation resulted probably from the specialization of our center (gastroenterology and hepatology) and the fact that children with the above abnormalities were most frequently referred here for diagnostics and treatment.

Hemorrhagic diathesis associated with thrombocytopenia, described by Istars et al. was observed in 2 cases in our group [7]. Anemia with signs of hemolysis was observed much more frequently.

Our observations concerning abnormalities in brain USG are similar to those made by other authors. Distended anterior horns of the lateral ventricles with no abnormal neurological signs were found in 2 patients [13].

In the diagnostics of CMV, similarly to other infections, the infection may be confirmed by demonstrating the presence of the virus or virus-specific systemic immune response. Numerous authors emphasize the value of serological methods, most frequently used in practice because of their cost and availability [3,6,9]. Also in the studied group, the diagnosis was based in most cases on serological investigations detecting specific antibodies. IgM antibodies were found in 12 cases, whereas in 7 high and increasing IgG titers were demonstrated.

The assessment of maternal IgG antibody status was necessary in a lot of cases in order to exclude passive transplacental transmission of the antibodies detected in the infant's blood.

In case of diagnostic problems, intermediate or early antigen determinations were performed or search for the viral genetic material by PCR. It should be taken into consideration that premature infants and children with immune deficits may not produce specific IgM antibodies. According to Cederequist, the younger the organism is at the time of infection, the weaker the humoral response may be. Some authors also point to the possibility of immune response inhibition by infectious factors belonging to the TORCH group [7,18]. For the above reasons, patients with clinical presentation and laboratory results suggesting cytomegalovirus infection despite negative serological results require determination of early CMV antigen or of CMV-DNA by PCR.

Despite negative IgM, positive early antigen results were obtained in 13 patients of the studied group, and positive PCR results in 4 (qualitative method). Quanti-

tative PCR or determination of mRNA providing the evidence of active viral replication are particularly valuable. However, these methods are not routinely used because of very high costs [11,12].

Gancyclovir, a guanosine derivative, is the therapy of choice in CMV infections. However, it should be used with caution in children because of the lack of prospective studies in this age group and the possibility of adverse effects.

The optimum therapeutic dose is the most important disputable issue. Literature data point to higher effectiveness of gancyclovir administered at doses higher than those used in adults (5 mg/kg) [16,17,21].

Some authors emphasize that higher doses of the drug (6.0–7.5 mg/kg/dose at 12 h intervals) are justifiable to obtain appropriate therapeutic levels in the blood and tissues. Some authors believe the administration of 3 instead of 2 doses of gancyclovir to be more favorable [2,6,22,23].

The therapy, in the opinion of most authors, should be continued for at least 3 weeks to prevent recurrences and development of viral resistance more effectively. The optimal treatment should be associated with frequent monitoring of drug levels in the serum to ensure appropriate effectiveness and safety of medication. Albrecht et al, who monitored drug levels in neonates with congenital cytomegalovirus disease, administered it at doses ranging from 4.5 mg/kg to 13 mg/kg 2–3 times daily, i.e. at doses exceeding several times those used in adult patients. Unfortunately, only a few centers in Poland have the opportunity to monitor gancyclovir levels [23].

In the studied group, the decisions to start treatment were taken on the basis of a detailed analysis of the clinical presentation and results of accessory investigations. Sometimes (if the clinical condition of the patients was good) the time course of biochemical abnormalities was assessed. In 4 cases, the results of observation and control investigations allowed to abandon the intended therapy because of regression of the clinical symptoms and improvement of biochemical parameters. All the patients were older infants (above 6 months of age) with most probably acquired cytomegalovirus disease. The parents of 1 patient with congenital extrahepatic bile duct atresia did not consent to the therapy despite positive IgM antibodies.

The difficulties in differentiation of various forms of the disease play an important role in the decisions concerning further management. For instance, the diagnosis of congenital infection is an absolute indication for antiviral treatment because of a severe course and serious complications of the disease [6].

In 25 cases, in which the decision to institute treatment was taken, gancyclovir was administered i.v. at 5–7 mg/kg b.w. doses twice daily for 2–3 weeks. In most treated patients, relatively rapid regression of the clinical

cal symptoms and normalization of biochemical parameters was observed, which was confirmed by immunological investigations. In a few cases, recurrent progression of liver damage symptoms was observed after a period of transient normalization of test results. Those cases included children, in whom the duration of the infection had been probably (as it followed from anamnesis data) relatively long and baseline immunological investigations indicated massive infection, or children suffering from coincident chronic diseases leading to liver damage. The above observations are consistent with those reported by other authors [14,15].

The follow-up times after the completion of treatment were different in the investigated group. For that reason, any conclusions concerning the effectiveness and duration of the effects of treatment require further observation and control examinations.

It should be emphasized that the tolerance of the drug was good in the studied group of infants. The above finding has also been confirmed by other studies [14,15,23]. No indications for discontinuation of the treatment were observed in any of the patients.

In one case, control abdominal USG performed after the completion of treatment revealed enlarged kidneys with distinct corticomedullary border, without any evident abnormalities in the results of biochemical tests performed to assess renal function. In the subsequent control USG (after 2 months) the normalization of USG kidney image was observed. Slight and transient decrease of hematological parameters was also observed in single cases.

CONCLUSIONS

1. The clinical presentations of cytomegalovirus disease in infants are varied.
2. The diagnosis of cytomegalovirus disease should be considered in children with persistent jaundice, especially if it is accompanied by hepatomegaly and increased aminotransferases activity or parameters of cholestasis.
3. The treatment should be instituted in symptomatic cases only, after thorough analysis of the clinical presentation and clinical investigation results.
4. Despite relatively good tolerance of the drug by children, the patients should be monitored for possible side effects, especially myelo- and nephrotoxic.

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