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Cytomegalovirus hepatitis in 49 pediatric patients with normal immunity

Hasan TEZER[1], Saliha KANIK YÜKSEK[2,*], Belgin GÜLHAN[2], Aslı Nur ÖZKAYA PARLAKAY[2], Ceyda TUNA KIRSAÇLIOĞLU[3]

[1]Department of Pediatric Infectious Diseases, Faculty of Medicine, Gazi University, Ankara, Turkey
[2]Department of Pediatric Infectious Diseases, Ankara Hematology Oncology Children's Training and Research Hospital, Ankara, Turkey
[3]Department of Pediatric Gastroenterology, Ankara Hematology Oncology Children's Training and Research Hospital, Ankara, Turkey

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Background/aim: Cytomegalovirus (CMV) hepatitis is generally asymptomatic or rarely can lead to severe complications in immunocompetent hosts. This study aims to evaluate CMV hepatitis in immunocompetent young children, which is discussed relatively rarely in the literature.

Materials and methods: A retrospective review of 49 pediatric patients with CMV hepatitis from January 2005 to December 2010 was performed.

Results: The median age of the patients was 5.81 ± 6.49 months and 57.1% were female. Complaints were prolonged jaundice, vomiting, diarrhea, and abdominal distension. Seventeen patients (34.6%) had congenital or probable congenital CMV infection, while 32/49 (65.3%) had perinatal CMV infection. CMV hepatitis was accompanied by other system findings in 22 patients (44.9%), and only liver involvement was present in 27/49 (55.1%). Alanine aminotransferase and aspartate aminotransferase were elevated together in all patients. Cholestatic hepatitis was present in 13 patients (26.5%). Four patients (8.16%) were treated with ganciclovir. Complete improvement of hepatitis occurred in 48/49 (97.95%). The recovery time of liver function tests was 7–180 days (mean: 53.92 ± 40.8).

Conclusion: CMV hepatitis is usually mild and has a good outcome in immunocompetent individuals. However, cases should be carefully evaluated due to the important role of CMV in the etiology of infantile and neonatal hepatitis.

Key words: Cytomegalovirus, hepatitis, children, immunocompetent

1. Introduction

Cytomegalovirus (CMV) infection in individuals with effective immunity is generally asymptomatic or may occur as a mononucleosis syndrome but rarely leads to severe and life-threatening organ complications such as gastrointestinal, cardiovascular, hepatic, and neurologic manifestations (1). CMV hepatitis is a component of heterophil-negative mononucleosis syndrome and usually has a good prognosis; it is frequently encountered in patients with symptomatic CMV infection (2). However, hepatitis in congenital and perinatal CMV infections may cause progressive liver disease, cirrhosis, and death rarely (3). CMV hepatitis is relatively common especially in early infancy, and it is accompanied by cholestasis in this group (4). The pathogenesis, features, and treatment of CMV hepatitis in immunocompromised hosts is well documented, but liver disease of CMV infection in infants with normal immunity is poorly elucidated (5). This study aims to analyze and evaluate CMV-associated hepatitis in young immunocompetent children, in light of the limited knowledge about this issue, and to contribute to the literature.

2. Materials and methods

Forty-nine children diagnosed with CMV hepatitis from January 2005 to December 2010 in the Ankara Hematology Oncology Children's Training and Research Hospital were retrospectively examined. Children with immunodeficiencies or a specific immunocompromised state were excluded. Age, sex, complaints, hospitalization, blood transfusion histories, and prenatal, natal, and postnatal stories of the patients and physical examination findings were recorded. Accompanying involvements of other systems within 2 years and data of clinical and laboratory follow-up were evaluated.

The diagnosis of CMV infection was based on serum anti-CMV specific IgM positivity (ELISA [DiaSorin, Italy]) or increase of anti-CMV specific IgG titers by more than 4-fold, and/or CMV DNA positivity in blood and/or urine via polymerase chain reaction (PCR)

* Correspondence: salihakanik@gmail.com

method (Rotor-Gene Q, QIAGEN, Germany). CMV hepatitis was defined as a 2- to 3-fold increase in serum transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT], or AST and ALT). Cholestasis was defined as high conjugated bilirubin more than 15%–20% of the total bilirubin (if the total bilirubin level was >5 mg/dL) or high conjugated bilirubin level of 1 mg/dL (if the total bilirubin level was <5 mg/dL). A CMV IgG avidity test was used for distinguishing and classifying acute and previous infection. Congenital CMV infection was defined in patients who were diagnosed in the first 3 weeks of life (6). Perinatal CMV infection was defined in patients who were diagnosed after the postnatal third week by the demonstration of viral nucleic acids or virus excretion in samples (6). Probable congenital CMV infection was defined in patients who were diagnosed after the postnatal third week, but with clinical signs of disease similar to those of congenital CMV infection such as chorioretinitis, hearing loss, or intracranial calcification (6). These patients were children who did not have a history of blood transfusion and had positive serum CMV antibodies, and/or positive CMV DNA PCR in blood and/or urine, and/or high CMV IgG avidity level, and positive CMV IgG antibodies in the mother's serum. All patients enrolled in the study were investigated for possible causes of hepatitis other than CMV infection (hepatitis markers for hepatitis A, B, and C viruses; human immunodeficiency virus (HIV); TORCH group infections; congenital metabolic diseases and storage diseases; and cystic fibrosis), and other factors that were examined were excluded. In addition, thyroid function tests were analyzed for the purpose of hypothyroidism screening in patients presenting with prolonged jaundice.

SPSS 15.0 (SPSS Inc., Chicago, IL, USA) was used for analysis of data. $P < 0.05$ was considered statistically significant.

3. Results

The age of patients ranged between 7 days and 32 months (mean: 5.81 ± 6.49 months) and 28/49 (57.1%) of the patients were female. Complaints of the patients were prolonged jaundice in 14/49 (28.57%), diarrhea in 22/44 (22.44%), vomiting in 5/49 (10.2%), and abdominal distension in 14/49 (28.57%). Fourteen patients (28.57%) had no active complaints but were referred due to increase in liver enzymes from pediatric outpatient clinics (Table). In the history of the patients, postpartum hospitalization (26.5%), prematurity (14.2%), recurrent pulmonary infections (8.16%), and blood transfusion (2.04%) were present. The physical examination findings of patients were as follows: hepatomegaly in 42.8%, jaundice in 30.6%, splenomegaly in 20.4%, growth retardation in 6.12%, microcephaly in 4.08%, and chorioretinitis in 2.04%. The physical examination was completely normal in seven patients (14.28%).

Seventeen patients (34.69%) were diagnosed with congenital CMV (2/49 [4.08%] congenital CMV infection and 15/49 [30.61%] probable congenital CMV infection), and 32 (65.3%) of the total cases were perinatal or postnatal CMV infection. There were accompanying findings of other system (leukocytosis [20.4%], thrombocytopenia [18.36%], central nervous system [CNS] involvement [4.08%], chorioretinitis [2.04%]) in 22 patients (44.9%), and isolated liver involvement of CMV infection was present in 27/49 (55.1%). In patients with isolated liver involvement, 7/49 (29.92%) had congenital infection, 18/27 (66.6%) had perinatal infection, and two patients (7.4%) had postnatal infection.

AST and ALT were elevated together in all patients. AST values were between 64 and 2950 (mean: 300.1 ± 476.3) IU/L and ALT values were between 69 and 2085 (mean: 256.6 ± 350.4) IU/L. High total bilirubin was detected in 19/49 (38.7%) patients with a mean of 3.26 ± 5.24 (0.3–21) mg/dL. Eight patients (16.3%) had a total bilirubin level

Table. Complaints of the patients on admission.

Complaint	Congenital or probable congenital CMV infection n (%)	Perinatal or postnatal CMV infection n (%)	Total n (%)
Prolonged jaundice	5 (10.2)	9 (18.36)	14 (28.57)
Diarrhea	1 (2.04)	10 (20.4)	11 (22.44)
Vomiting	2 (4.08)	3 (6.12)	5 (10.2)
Abdominal distension	3 (6.12)	2 (4.08)	5 (10.2)
No complaint (referred for increase in liver enzymes)	6 (12.24)	8 (16.32)	14 (28.57)
Total	17 (34.69)	32 (65.3)	49 (100)

of >5 mg/dL with a mean of 13.97 ± 5.01 (8–21) mg/dL. Mean conjugated bilirubin was 1.67 ± 3.59 (0–14) mg/dL. High conjugated bilirubin levels were present in 23 patients (46.9%) and values were 1.1–19 (mean: 1.95 ± 3.43) mg/dL. Mean GGT values were 146.48 ± 118.20 (18–566) IU/L and high GGT was detected in 26/49 (53.06%) with a mean of 218.19 ± 119.3 (133–566) IU/L. Hepatitis was accompanied by cholestasis in 13/49 (26.5%) patients. The average age of patients with cholestasis was 4.88 ± 4.83 (0–15) months. The mean age of patients with cholestasis was younger compared to patients with hepatitis, but this was not statistically significant (P > 0.05). Liver biopsy was not required in any patient.

Complete improvement of hepatitis occurred in 48/49 patients (97.95%) whether associated with cholestasis or not. The recovery time of liver function tests was between 7 and 180 days (mean: 53.92 ± 40.8) in these patients. One patient who had no improvement in liver function tests was found to have a metabolic disease (amino acid metabolism disorder [tyrosinemia type I]) together with CMV infection. Due to lack of anticipated decline in liver enzymes in spite of decrease in the CMV viral load with the detection of tyrosinemia type I disease, the current hepatic involvement was considered to be due to congenital metabolic disease in this patient. A liver biopsy was scheduled for definitive diagnosis of hepatitis; however, the process could not be completed due to technical deficiencies and lack of family consent. The recovery time of hepatitis was between 10 and 90 days (mean: 39.17 ± 30.4) in patients with congenital or probable congenital CMV infection. A total of four patients (8.16%) were treated with intravenous ganciclovir (10 mg/kg daily, in divided doses at 12-h intervals). Of the patients treated with ganciclovir, one patient had congenital CMV infection and the other three patients had perinatal CMV infection. Two of these four patients had cholestatic hepatitis. Patients treated with ganciclovir had involvement of other systems together with CMV hepatitis (CNS involvement in 2 patients [1 = intracranial calcification, 1 = polymicrogyria], chorioretinitis in 1 patient, and pneumonia in 1 patient). The duration of treatment with ganciclovir was between 14 and 21 days (mean: 18.45 ± 3.53). Treatment-related side effects developed in one patient as bone marrow inhibition with neutropenia and thrombocytopenia. There was no patient that needed recurrent ganciclovir treatment. Recovery time of elevated transaminases and cholestasis in these patients was between 10 and 30 days (mean: 21.25 ± 10.2). When patients treated with ganciclovir and patients that were not treated were compared, the recovery time of liver function tests was found shorter in the treated group, but this was not statistically significant (P > 0.05). No relapse or recurrence of hepatitis was detected in 2-year follow-ups of the patients, except the patient detected to have a congenital metabolic disease.

4. Discussion

Manifestations, follow-up findings, and treatment approaches of CMV infection in immunocompromised individuals have been extensively revised and reported in the literature, but these specified conditions in immunocompetent individuals have received less attention (7,8). This study is important as it aimed to contribute to the literature about CMV hepatitis in immunocompetent infants and young children. CMV infection is usually characterized as a mononucleosis-like syndrome with fever, cervical adenopathy, and elevation in liver enzymes in immunocompetent hosts (9). Elevations in transaminases is the most common subclinical finding in these patients. High bilirubin and alkaline phosphatase levels are not often expected laboratory findings (10,11). In our study, there were high indirect bilirubin levels in 23 patients (46.9%). This result shows that CMV hepatitis may have been accompanied by elevated levels of unconjugated bilirubin, different than the literature. CMV hepatitis is more likely to be accompanied by cholestasis in early infancy, as indicated in the literature (4), and association of cholestasis and hepatitis was present in the early infancy period. Our study was consistent with such data, but a statistically significant relationship for this condition was not detected. It should also be noted that CMV infection should come to mind primarily as an infectious agent in infants presenting with prolonged jaundice, especially during early infancy, as a result of this study. Although available reports state that a more severe clinical course of patients with cholestatic hepatitis was seen (2,12), all of our patients with cholestatic hepatitis had been observed to have complete recovery without any chronicity or relapse. In addition, complaints such as vomiting, diarrhea, and abdominal distension, which are more pronounced in perinatal or postnatal CMV infection, should be noted among frequent complaints of CMV hepatitis, as shown in our study in the Table and consistent with the literature (1,2,6). A remarkable result in our study that must not be overlooked is that about 28% of patients were referred for transaminase elevations when seen for any other reasons while asymptomatic. Therefore, CMV hepatitis is an important factor in asymptomatic patients with elevated transaminases, especially in early infancy, and should be ruled out.

The diagnosis of CMV hepatitis is based on results of serologic studies, molecular methods, liver biopsy, or all of them (1,10). Multinucleated giant cells with mononuclear portal and parenchymal inflammatory cell infiltrates and cholestasis are commonly seen on liver biopsies and large nuclear inclusions called "owl's eye" inclusions may be

seen in specimens (2,10,12). Evidence of CMV hepatitis was not demonstrated with a liver biopsy in any of our cases due to lack of an indication requiring liver biopsy or family consent, and the diagnosis of CMV infection was made by serology and nucleic acid testing in peripheral blood samples.

Use of ganciclovir in children with normal immunity for CMV infections is still controversial with inadequate data and experience, and it is suggested in certain severe conditions (8,9,13). Besides the lack of sufficient data to show the utility and efficacy of ganciclovir in CMV hepatitis (2), there are some studies that support the treatment in patients with acute or persistent/chronic hepatitis or proven histopathological findings of CMV infection (2,12,14,15). In our study, the indication of four patients that received ganciclovir treatment was not only liver involvement of CMV infection; there were also other system involvements such as pneumonia, retinitis, and CNS involvement in all four patients and cholestatic hepatitis was present in two patients. Except for the patient with congenital metabolic disease, all of our patients not receiving ganciclovir treatment showed spontaneous recovery, and there was not a significant statistical difference between patients who received or did not receive treatment. It was thought that this result was due to inadequate numbers of patients in the treated group. However, the duration of recovery in the treated group was noted to be shorter. Although ganciclovir treatment is known to be effective in the prevention of CMV-induced acute liver failure (2,8,13), there are not presently sufficient data regarding long-term effects of ganciclovir. As a result of our study, treatment with ganciclovir should be considered in the patients with severe progressive disease unresponsive to supportive therapy, but serious side effects should also be kept in mind (16), and detailed evaluation of the patients is required prior to treatment.

Although clear data about the duration of anti-CMV therapy in immunocompetent individuals are not present, there are various studies about treatment regimens ranging between 5 and 21 days (2,9,14,15), and even more long-term applications in some cases based on clinical and laboratory findings are present (17,18). Ganciclovir treatment was administered to our patients in the appropriate period specified in the literature. A known and transient side effect of ganciclovir, myelosuppression (19,20), was observed in only one patient.

After primary infection, CMV undergoes latency in the human body through a series of immune escape strategies (6,7,21). CMV infection is well controlled in immunocompetent hosts. However, reactivation or recurrence of infection may be seen associated with various immunological changes in the immune function of individuals during or after recovery from infection, especially depending on CMV viral load, prolonged length of hospital stay, and age, as shown in several adult studies (22–24). CMV reactivation is a defined entity in immune-deficient children, especially in solid organ or bone marrow transplantation patients (25). However, reactivation of CMV infection and CMV hepatitis has not been further documented in immunocompetent children during infancy together with all pediatric ages. Reactivation or recurrence of CMV hepatitis was not detected in any of our patients during 2 years of follow-up. It is notable that all of our patients were immunocompetent children, and this result will contribute to the limited knowledge on this subject in children with robust immunity.

In conclusion, CMV infection should be one of the leading factors that come to mind in cases of acute, persistent, or chronic hepatitis, especially in patients presenting in early infancy. When liver enzymes do not return to normal limits on follow-up, the other causes of hepatitis, especially congenital metabolic disorders, should be investigated in patients with CMV hepatitis detected during early infancy, as exemplified in our patient. There is a need for further controlled randomized studies with larger series of cases in terms of therapeutic approaches in this indication. Until the certain indications of ganciclovir treatment of CMV hepatitis in children are well defined, every patient should be evaluated individually and side effects should be kept in mind during treatment decisions.

References

1. Horwitz CA, Henle W, Henle G, Snover D, Rudnick H, Balfour HH Jr, Mazur MH, Watson R, Schwartz B, Muller N. Clinical and laboratory evaluation of cytomegalovirus-induced mononucleosis in previously healthy individuals. Report of 82 cases. Medicine (Baltimore) 1986; 65: 124-134.
2. Tezer H, Seçmeer G, Kara A, Ceyhan M, Cengiz AB, Devrim İ, Us D, Yüce A, Gürakan F, Yıldırım İ et al. Cytomegalovirus hepatitis and ganciclovir treatment in immunocompetent children. Turk J Pediatr 2008; 50: 228-234.
3. Zuppan CW, Bui HD, Grill BG. Diffuse hepatic fibrosis in congenital cytomegalovirus infection. J Pediatr Gastroenterol Nutr 1986; 5: 489-491.
4. Fischler B, Ehrnst A, Forsgren M, Orvell C, Nemeth A. The viral association of neonatal cholestasis in Sweden: a possible link between cytomegalovirus infection and extrahepatic biliary atresia. J Pediatr Gastroenterol Nutr 1998; 27: 57-64.
5. Eddleston M, Peacock S, Juniper M, Warrell DA. Severe cytomegalovirus infection in immunocompetent patient. Clin Infect Dis 1997; 24: 52-56.

6. American Academy of Pediatrics. Cytomegalovirus infection. In: Pickering LK, Baker CJ, Long SS, McMillian JA, editors. Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL, USA: American Academy of Pediatrics; 2009. pp. 708-709.
7. Rafailidis PI, Mourtzoukou EG, Varbobitis IC, Falagas ME. Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review. Virol J 2008; 5: 47.
8. Vancíková Z, Dvorák P. Cytomegalovirus infection in immunocompetent and immunocompromised individuals–a review. Curr Drug Targets Immune Endocr Metabol Disord 2001; 1: 179-187.
9. Hadaya K, Kaiser L, Rubbia-Brandt L, Gervaix A, Diana A. Ganciclovir for severe cytomegalovirus primary infection in an immunocompetent child. Eur J Clin Microbiol Infect Dis 2004; 23: 218-220.
10. Just-Nübling G, Korn S, Ludwig B, Stephan C, Doerr HW, Preiser W. Primary cytomegalovirus infection in an outpatient setting–laboratory markers and clinical aspects. Infection 2003; 31: 318-323.
11. Zubiaurre L, Zapata E, Bujanda L, Castillo M, Oyarzabal I, Gutiérrez-Stampa MA, Cosme A. Cytomegalovirus hepatitis and myopericarditis. World J Gastroenterol 2007; 13: 647-648.
12. White FV, Dehner LP. Viral diseases of the liver in children: diagnostic and differential diagnostic considerations. Pediatr Dev Pathol 2004: 7; 552-567.
13. Vancíková Z, Kucerová T, Pelikán L, Zikmundová L, Priglová M. Perinatal cytomegalovirus hepatitis: to treat or not to treat with ganciclovir. J Paediatr Child Health 2004; 40: 444-448.
14. Nigro G, Krzysztofiak A, Bartmann U, Clerico A, Properzi E, Valia S, Castello M. Ganciclovir therapy for cytomegalovirus-associated liver disease in immunocompetent or immunocompromised children. Arch Virol 1997; 142: 573-580.
15. Tajiri H, Kozaiwa K, Tanaka-Taya K, Tada K, Takeshima T, Yamanishi K, Okada S. Cytomegalovirus hepatitis confirmed by in situ hybridization in 3 immunocompetent infants. Scand J Infect Dis 2001; 33: 790-793.
16. Kimberlin DW. Antiviral therapy for cytomegalovirus infections in pediatric patients. Semin Pediatr Infect Dis J 2006; 13: 22-30.
17. Pass RF. Cytomegalovirus. In: Long SS, Pickering LK, Prober CG, editors. Principles and Practice of Pediatric Infectious Diseases. Philadelphia, PA, USA: Churchill Livingstone; 2008. pp. 1029-1035.
18. Doan TT, Phung TT, Pham HV, Pham SH, Nguyen LT. Effect of ganciclovir for the treatment of severe cytomegalovirus-associated pneumonia in children without a specific immunocompromised state. BMC Infect Dis 2013; 13: 424.
19. Plosa EJ, Esbenshade JC, Fuller MP, Weitkamp JH. Cytomegalovirus infection. Pediatr Rev 2012; 33: 156-163.
20. Stagno S. Cytomegalovirus. In: Kliegman RM, Stanton B, Geme S, Schor N, Behrman RE, editors. Nelson Textbook of Pediatrics. 19th ed. Philadelphia, PA, USA: WB Saunders; 2010. pp. 1115-1117.
21. Kumar A, Herbein G. Epigenetic regulation of human cytomegalovirus latency: an update. Epigenomics 2014; 6: 533-546.
22. Kano Y, Shiohara T. Current understanding of cytomegalovirus infection in immunocompetent individuals. J Dermatol Sci 2000; 22: 196-204.
23. Limaye AP, Kirby KA, Rubenfeld GD, Leisenring WM, Bulger EM, Neff MJ, Gibran NS, Huang ML, Santo Hayes TK, Corey L et al. Cytomegalovirus reactivation in critically ill immunocompetent patients. JAMA 2008; 300: 413-422.
24. Cook CH, Trgovcich J. Cytomegalovirus reactivation in critically ill immunocompetent hosts: a decade of progress and remaining challenges. Antiviral Res 2011; 90: 151-159.
25. Bontant T, Sedlaçek P, Balduzzi A, Gaspar B, Cesaro S, Einsele H, Peters C, Dalle JH. Survey of CMV management in pediatric allogeneic HSCT programs, on behalf of the inborn errors, infectious diseases and pediatric diseases working parties of EBMT. Bone Marrow Transplant 2014; 49: 276-279.