

Perinatal Cytomegalovirus Hepatitis in Saudi Infants: A Case Series

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ABSTRACT

Background/Aim: Cytomegalovirus (CMV) is the most common congenital viral infection, occurring in 0.4%–2.3% of all live births. The clinical manifestations of CMV are multiorgan involvement. Currently, the numbers of studies of hepatic CMV infection in immunocompetent infants are insufficient and little information exists in the medical literature about the hepatic manifestations and complications of CMV. **Patients and Methods:** Nine infants diagnosed with hepatic CMV infection were included in the study. The diagnosis was based on the presence of IgM anti-CMV antibodies titer in serum and detection of CMV-DNA in blood. The authors identified clinical characteristics, biochemical characteristics, immunologic markers, and the outcome of hepatic CMV with or without treatment. **Results:** Jaundice was the most common clinical feature of CMV infection in infancy (100%). Hepatic abnormalities in the form of cholestasis (defined as a serum conjugated bilirubin concentration greater than 17.1 μmol/L or greater than 20% of the total serum bilirubin) were found in all patients (100%), hepatitis (77%), hypoalbuminemia (55%), elevated alkaline phosphatase, and gamma-glutamyltransferase (77%). Other findings showed hepatosplenomegaly (44%), thrombocytopenia (22%) and low birth weight (11%) The treatment of hepatic CMV infection was indicated in 66% and was not indicated in 33%. Both of them had resolved cholestasis and hepatitis. **Conclusion:** Jaundice and cholestasis were the most common clinical features of hepatic CMV infections. Hepatic CMV infection in young infants is often a self-limited illness that does not require antiviral therapy. Most of the patients with hepatic CMV infection had a favorable outcome.

Key Words: Alanine aminotransferase, cytomegalovirus, polymerase chain reaction

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Cytomegalovirus (CMV) is the largest member of the herpesvirus family, with a double-stranded DNA genome, capable of encoding more than 200 potential protein products. CMV is the most common congenital viral infection, occurring in 0.4%–2.3% of all live births, and is probably a common cause of mental retardation and nonhereditary sensorineural deafness in children.^[1]

Infants may acquire CMV infection from the mother as a result of intrauterine infection (congenital infection), or

through contact with infected genital secretions during passage through the birth canal (perinatal infection), or postpartum through breastfeeding (postnatal infection).^[2] Postnatally acquired CMV infection in immunocompetent patients is generally subclinical but may sometimes give rise to a mild and self-limited mononucleosis-like syndrome.^[2]

CMV hepatitis is relatively common in early ages, especially in early infancy, and in this period is associated with cholestasis.^[3] CMV infection in infancy is important since it might result in cirrhosis and even death.^[4]

Clinical manifestations in symptomatic newborns range from severe multiorgan involvement with jaundice thrombocytopenic purpura, hepatomegaly, splenomegaly, pneumonia, and encephalitis.^[5] However, little information exists in literature about the hepatic manifestations of CMV infection in infancy.

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In our report we present 9 infants with hepatic CMV due to perinatal CMV infection with no other organ involvement. Therefore, the aim of this study was to describe a series of patients with hepatic manifestations of CMV infection and to identify clinical and biochemical profiles, immunologic markers, and the outcome of hepatic CMV with or without treatment.

PATIENTS AND METHODS

Patients

During an 11-year period (January 2000–May 2011) all newborns and infants with diagnosis of hepatic CMV were recruited in the study as retrospective chart review. Our sample population was derived from a retrospective cases series of patients with hepatic dysfunction that correlated with documented CMV infection.

Enrolled patients fulfill the following criteria: (1) Age between 0 and 12 months; (2) the diagnosis was based on the presence of specific IgM CMV antibodies titer in serum or detection of CMV-PCR in blood or liver tissue.

Exclusion criteria include the following: (1) Age more than 12 months; (2) congenital and acquired immunodeficiency; (3) metabolic liver disorders; (4) other viral hepatitis infections; and (5) abdominal and hepatic surgical causes.

Methods

This case series of perinatal CMV hepatitis in Saudi infants was carried out at National Guard Hospital, Jeddah, between 2000 and reviewed 2011. The authors identified hepatic CMV and they reviewed medical records of the patients with hepatic CMV for details of clinical presentation, laboratory data, radiologic and histologic findings, and the results of the treatment.

The epidemiologic data and results were expressed as means, ranks, and percentages.

Definition of hepatic CMV infection

The classic tissue histologic finding in cytomegalic disease is the inclusion cell; however, viral culture, serology, antigenemia, and nucleic acid detection systems (e.g., PCR) generally have much better sensitivity for the diagnosis of CMV-associated diseases.^[4]

Anti-CMV IgG and IgM were performed using microenzyme immunoassay on the Abbott AxSYM machine (Abbott Laboratories, Abbott Park, IL, USA).

Viral DNA was extracted from blood samples using the MagNa-Pure extraction system (Roche Applied Sciences). CMV-PCR was performed using CMV Quant kit for quantitative detection of CMV-DNA in blood samples

(Roche Applied Sciences). The quantitative standards were defined as copies/mL.

This study was approved by the Ethics and Research Committee of National Guard Health Affairs.

RESULTS

We identified 9 patients in the present study. The study population comprised 5 females (56%) and 4 males (44%). The median age at presentation was 2 months (range, 0–5 months). The overall fatality rate was 11%. Other demographic data are shown in Table 1.

Clinical characteristics of hepatic CMV infection

Jaundice was the most common clinical feature of CMV infection in infancy, and was noted in all patients (100%). Maternal CMV and maternal fever were not noted in the present study. Eight patients were spontaneously delivered at term (38–41 weeks gestation) with a normal birth weight (2.6–3.3 kg). One was born as preterm at 34 weeks with birth weight (2.1 kg). Six patients (66%) were breastfed. None of the patients received a blood transfusion. No other organ involvement (lung, brain, and eyes) was detected in any patient. Gastrointestinal symptoms included vomiting in patient 2, dark urine in patient 4, and abdominal distension in patient 7. Hepatosplenomegaly was noted in 4 patients (44%). Pneumonia, seizures, fever, and lymphadenopathy were not noted in the present study. Other symptoms are shown in Table 1.

Biochemical characteristics of hepatic CMV infection

The hematologic findings of hepatic CMV infection revealed that hemoglobin, white blood cell and lymphocytes counts were normal in all patients. Thrombocytopenia (platelet count $<150 \times 10^9/L$) was noted in 2 patients (22%) and thrombocytosis (platelet count $>450 \times 10^9/L$) was noted in 1 patient (11%).

Hepatic abnormalities in the form of cholestasis, identified by elevated serum total and direct bilirubin levels, were found in all patients (100%).

Hepatic abnormalities in the form of hepatocellular injury, identified by elevated serum (liver enzymes) transaminases level, were found in 7 patients (77%). Hypoalbuminemia (serum albumin $<38 \text{ G/L}$) was noted in 5 patients (55%). Coagulopathy with prolonged INR were noted in 3 patients (33%). Serum alkaline phosphatase and gamma-glutamyltransferase were elevated in 7 patients (77%). Other laboratory findings showed that hypoglycemia (serum glucose $<4 \text{ mmol/L}$) was noted in 4 patients (44%). Normal serum ammonia was done in only 2 patients.

Table 1: Clinical and demographic characteristics of the patients

Variable	Pat 1	Pat 2	Pat 3	Pat 4	Pat 5	Pat 6	Pat 7	Pat 8	Pat 9
Age	2 mo	1 mo	2 mo	2 mo	1 mo	Day 1	4 mo	5 mo	2 mo
Sex	F	F	F	M	F	M	F	M	M
Birth weight (kg)	3.3	2.6	3.1	2.8	3.4	2.1	2.8	2.9	3.0
Length (cm)	53	51	50	49	49	43	51	50	48
HC (cm)	36	37	35	33	36	30	37	35	36
Full/preterm	FT	FT	FT	FT	FT	34wk	FT	FT	FT
Delivery: (vagina/CS)	Vaginal	Vaginal	Vaginal	Vaginal	Vaginal	Vaginal	Vaginal	Vaginal	Vaginal
Maternal CMV	-ve	-ve	-ve	-ve	-ve	-ve	-ve	UK	UK
Maternal fever	No	No	No	No	No	No	No	No	No
Blood transfusion	None	None	None	UK	None	None	None	None	None
Breast feeding	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No
Symptoms									
Jaundice	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pneumonia	No	No	No	No	No	No	No	No	No
Seizures	No	No	No	No	No	No	No	No	No
Fever	No	No	No	No	No	No	No	No	No
Abdominal distension	Yes	No	No	No	No	No	Yes	No	No
URT infection	No	No	No	No	No	No	No	No	No
GI symptoms	No	VM	No	DU	No	No	No	No	No
Skin symptoms	No	No	No	No	No	Pet	No	No	No
HSM	No	No	Yes	No	No	Yes	Yes	Yes	No
Lymphadenopathy	No	No	Yes	No	No	No	No	No	No
Ascites	Yes	No	No	No	No	No	No	No	No
Neurologic examination	NL	NL	NL	NL	NL	NL	NL	NL	NL
Eye Examination	NL	NL	NL	NL	NL	NL	ND	NL	NL

Mo: Months, F: Female, M: Male, FT: Full term, HC: Head circumference, wk: Week, CS: Cesarean section, UK: Unknown, URT: Upper respiratory tract, GI: Gastrointestinal, VM: Vomiting, DU: Dark urine, Pet: Petechia, HSM: Hepatosplenomegaly, NL: Normal, ND: not done, Pat: Patient

Table 2: Biochemical characteristics of the patients at baseline

Variable (Normal Range)	Pat 1	Pat 2	Pat 3	Pat 4	Pat 5	Pat 6	Pat 7	Pat 8	Pat 9
Hemoglobin (12.2–15.3 g/dL)	7.6	12.5	12.7	8.4	13.7	14.6	13.8	14.4	12.5
Platelet (150–450 × 10 ⁹ /L)	102	333	1053	297	620	20	338	201	238
WBC (6–16 × 10 ⁹ /L)	7.0	14.9	16.7	7.6	15.6	4.0	8.8	9.3	8.9
Lymphocytes	4.6	4.7	6.1	5.4	11.5	1.1	6.2	5.1	6.6
Atypical lymphocytes	+ve	ND	ND	+ve	ND	ND	ND	ND	ND
Albumin (38–54 G/L)	33	35	23	40	42	31	44	37	41
Total bilirubin (<20.5 μmol/L)	315	136	30	74.1	131	153	60	159	60
Direct bilirubin (<9 μmol/L)	114	73	27	53	94	28	45	38	41
AST (5–34U/L)	28	218	244	78	92	47	225	147	25
ALT (5–55 U/L)	16	165	186	73	615	88	312	98	12
GGT (12–64 U/L)	26	273	477	81	78	101	208	101	20
ALK (30–220 U/L)	2216	280	140	737	615	312	1198	392	119
INR (0.8–1.1)	3.7	1.0	1.3	1.0	1.1	1.6	1.1	1.0	1.1
Ammonia (40–80 μg/dL)	36	ND	ND	54	ND	ND	ND	65	ND
Glucose (4–7 mmol/L)	2.4	3.8	5.6	5.3	4.7	3.9	5.8	3.0	5.8

WBC: White blood counts, INR: International normalized ratio, ALT: Alanine transaminase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyltransferase, ALK: Alkaline phosphatase, ND: Not done, -ve: Negative, +ve: Positive, Pat: Patient

Positive atypical lymphocyte was done in only 2 patients. Other laboratory findings were shown in Table 2.

Immunologic markers and other investigations of hepatic CMV infection

Serum CMV IgM was positive in all patients (100%) while serum CMV IgG was elevated in 6 patients (66%). Serum CMV PCR was elevated in 8 patients (88%). PCR detection of CMV in the liver tissue was performed only in patient 5 with positive result.

Abdominal ultrasonography was unremarkable on 7 patients. Patient 1 showed increased echogenicity of liver and patient 2 showed hepatomegaly and increased echogenicity of liver. Percutaneous Liver biopsy was done in 1 patient only (patient 5) because of suspected biliary atresia. The biopsy showed that mild fibrosis and ductopenia were present. It revealed evidence of giant cell transformation.

Treatment outcomes of hepatic CMV infection

The treatment of hepatic CMV infection was indicated in 6 patients (66%). The decision of treatment of hepatic CMV infection appeared to be quite individualized or subjective rather than based on fixed criteria. The decision was based on the severity of biochemical or clinical hepatic abnormalities and elevated serum CMV-PCR.

In treated infants, ganciclovir at dose 10–20 mg/kg/day was used in 5 of 6 patients (83%). The mean duration of treatment was 3 weeks. Three out of six patients treated with ganciclovir (50%) had resolved cholestasis and hepatitis. One

out of six patients treated with ganciclovir (16%) progressed to liver failure necessitating liver transplantation. One out of six patients treated with ganciclovir (16%) died because of multiorgan failure and sepsis. Other antiviral drug, valganciclovir was used in 1 patient only and the cholestasis and hepatitis were resolved. No side effects of ganciclovir or valganciclovir therapy were observed.

Three out of nine patients (33%) who were not treated with antiviral drugs showed excellent outcome. All of them had resolved cholestasis and hepatitis. In untreated infants, it indicated possible milder clinical condition thus not needing therapy rather than conclude that lack of treatment leads to better outcome.

Other investigations and immunologic markers are shown in Table 3.

In 6 of 9 patients, ursodeoxycholic acid was administrated as a therapeutic agent to treat cholestasis (patients 1, 3, 5, 6, 7, and 9). Seventy-seven percent of the patients had favorable outcomes, with symptomatic support only.

DISCUSSION

After primary CMV infection, which is usually asymptomatic, CMV establishes a latent infection in polymorphonuclear cells, T lymphocytes, endothelial vascular tissue, renal epithelial cells, and salivary cells.^[6] Hepatic involvement by CMV may be noted as part of multiple system involvement or as an isolated liver involvement, such as neonatal hepatitis or

Table 3: Investigations, immunological markers and treatment outcomes:

Variable (Normal Range)	Pat 1	Pat 2	Pat 3	Pat 4	Pat 5	Pat 6	Pat 7	Pat 8	Pat 9
Serum CMV IgG (-ve)	40.4	-ve	-ve	110.8	-ve	685.8	483.7	285.8	183.7
Serum CMV IgM (-ve)	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve
Serum CMV PCR (<200copies/mL)	54	474	38000	1100	7040	984	2300	4984	230
Abdominal ultrasonography	IE of liver	NL	NL	NL	NL	NL	HM,IE of liver	NL	NL
Liver biopsy	ND	ND	ND	ND	No BD GT	ND	ND	ND	ND
Liver CMV PCR	ND	ND	ND	ND	43000	ND	ND	ND	ND
Treatment	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No
Name of antiviral drug	GCV	None	GCV	None	GCV	GCV	VCV	GCV	None
The dose of drug	15 mg/kg/d	None	10 mg/kg/d	None	10 mg/kg/d	6 mg/kg/d	20 mg/kg/d	10 mg/kg/d	None
Duration of treatment	10 days	None	15 days	None	21 days	26 days	21 days	21 days	None
Outcome	LT	RCH	Died	RCH	RCH	RCH	RCH	RCH	RCH
Ursodeoxycholic acid	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes

CMV IgG: Cytomegalovirus immunoglobulin IgG, CMV IgM: Cytomegalovirus immunoglobulin IgM, CMV PCR: Cytomegalovirus polymerase chain reaction, IE: Increased echogenicity, HM: Hepatomegaly, BD: Bile duct, GT: Giant transformation, GCV: Ganciclovir, VCV: Valganciclovir, LT: Liver transplant, RCH: Resolved cholestasis and hepatitis, NL: Normal, ND: Not done, Pat: Patient

cholestasis.^[7] The pathogenesis of hepatic CMV is obscure, in spite of the fact that the virus replicates thoroughly in both hepatocytes and cholangiocytes.^[8] The clinical spectrum of CMV infection in infancy varies from an asymptomatic infection or a mild disease to severe systemic involvement, including the central nervous system.^[9]

Our study identified clinical characteristics, biochemical profile, immunologic markers, and treatment outcomes of perinatal hepatic CMV infection in infancy.

In all our patients, CMV infection was proved by direct CMV-DNA detection in the blood and by positive specific CMV IgM [Table 3]. The diagnosis of congenital CMV infection requires identification of the virus in a culture specimen acquired before age 3 weeks because perinatally acquired infections may also begin to manifest at this time. Hence, a positive viral culture obtained in infants older than 3 weeks may simply represent perinatal or breast milk acquisition and may not be interpreted as evidence of congenital CMV infection.

The data of Horwitz *et al*^[2] taken together with the observation in our patients suggest that postnatally acquired CMV infection in immunocompetent patients is generally subclinical but may sometimes give rise to a mild and self-limited disease.

The clinical manifestations of perinatal hepatic CMV infection include hepatosplenomegaly (60% of cases) and thrombocytopenia (65% of cases), and delayed intrauterine growth with low birth weight (65% of cases).^[5]

Our report demonstrates that hepatosplenomegaly (44%), thrombocytopenia (22%), and low birth weight (11%) are the clinical manifestations of perinatal hepatic CMV infection.

Our report demonstrates that jaundice is the most common clinical feature of CMV infection in infancy. Hyperbilirubinemia or cholestasis (100%) and increased aminotransferases activities in serum (77%), were commonly observed in our patients, similar to the results obtained by Liberek *et al*,^[10] which showed that increased aminotransferases activities in serum (83%), and hyperbilirubinaemia and cholestasis (over 40%) were commonly observed.

Our data showed that hypoalbuminemia, coagulopathy and elevated serum alkaline phosphatase and gamma-glutamyltransferase were common findings of hepatic abnormalities while hypoglycemia and hyperammonia were uncommon. However, 1 out of 9 patients (11%) developed coagulopathy and progressed to liver failure needing liver transplantation.

In spite of elevated alkaline phosphatase which is common finding in growing children due to osteoblastic activity, mildly elevated alkaline phosphatase is considered as hepatic abnormalities of CMV hepatitis.

The laboratory tests used for serologic diagnosis of hepatic CMV are CMV-IgM antibody, CMV-PCR, and virus cultures. We could obtain both CMV-IgM antibody and CMV-PCR in all patients in our study, but liver biopsy in 1 patient suggested CMV hepatitis.

Treatment of CMV infection with ganciclovir is indicated in certain situations but the guidelines for this specific treatment, especially in immunocompetent patients, newborns, and infants have not yet been established.^[11] The necessity of treatment of CMV infection is controversial, as spontaneous recovery is expected in most cases unless severe systemic disease occurs.^[3,11]

Our limited experience with the treatment of hepatic CMV infection in infants showed that 50% of our patients who were treated with antiviral drugs had resolved cholestasis and hepatitis, whereas 33% of our patients who were not treated with antiviral drugs had resolved cholestasis and hepatitis. However, the relapse of infection after the cessation of the antiviral drug was not observed in our case series. Our data indicated that the decision for treatment was individualized based on the severity of hepatic abnormalities and elevated serum CMV-PCR.

We believe that CMV-DNA quantity is not useful for identifying the patients who will likely benefit from antiviral therapy, in contrast to Lanari *et al*^[12] who demonstrated the importance of high CMV-DNA titer on development of sequelae.

Although CMV infection during infancy is usually associated with mild manifestations, it may be fatal.^[4] It has been reported that hepatic CMV infection could progress to portal hypertension and cirrhosis.^[13] In our study, 1 patient died because of multiorgan failure and sepsis and 1 patient required liver transplantation because of hepatic failure.

Ganciclovir is the drug of choice for the management of CMV infection.^[14] Severe adverse effects (neutropenia, allergic reactions, and diarrhea) requiring the cessation of the treatment were not reported in this case series.

CONCLUSIONS

1. CMV infection should be considered in the differential diagnoses of neonatal cholestasis or hepatitis in infancy.
2. Jaundice is the most common clinical feature of hepatic CMV infection.
3. Hepatic CMV infection in young infants is often a self-limited illness that does not require antiviral therapy regardless of the CMV-PCR quantity.

4. Most of the patients with hepatic CMV infection had favorable outcomes.

Further studies are required to elucidate the pathogenesis of perinatal or postnatal hepatic CMV infection and treatment outcome.

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