

Original Article

Correlation between infection of herpes virus family and liver function parameters: a population-based cross-sectional study

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Abstract

Introduction: To evaluate the relationship between seropositivity to herpes virus family and liver function parameters in children from southwest China.

Methodology: A 2-year cross-sectional retrospective study of 6,396 children aged 6 months to 12 years was performed. All participants underwent physical examination and liver function tests.

Results: Of the children, 622 were positive for EBV, HSV, or CMV IgM, with dramatic changes in liver function parameters. Aspartate aminotransferase and alanine aminotransferase levels were negatively correlated with EBV-IgM and hepatocellular injuries in children < 3 years of age, whereas a positive correlation between lactate dehydrogenase (LDH) and EBV-IgM and hepatocellular injuries was documented in children < 1 year of age. In those < 1 year and 3–6 years of age, HSV-IgM seropositivity was positively correlated with indirect bilirubin and γ -glutamyl transferase. The percentage of children < 1 year of age with positive CMV-IgM was 72.8% (158/217), approximately five times higher than that in those 1–3 years. Sixty-three children were infected with two pathogens simultaneously. Abnormal levels of LDH were observed in 85.71% of children simultaneously infected with CMV and HSV, 77.78% for CMV and EBV, 83.33% for EBV and HSV, and irregular levels of AST were noted in 69.19% of children infected with CMV and HSV, 77.78% for CMV and EBV, and 83.33% for EBV and HSV.

Conclusions: Seropositivity to herpes virus family was correlated with abnormal liver function parameters across years of age. Clinicians should aim to protect the liver function of children infected with herpes viruses.

Key words: herpes virus infection; liver function; seropositive IgM antibody; correlation.

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Introduction

Infection with the herpesvirus family, consisting of several ubiquitous pathogens, can result in inevitable morbidity and mortality in severely infected cases [1–5]. Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpes virus (HSV) are the major members of herpes virus family.

Approximately 90%–95% of patients infected with EBV are asymptomatic [6], especially infants and children < 6 years of age. Symptomatic diseases are clinically characterized by the classical triad of fever, sore throat, and lymphadenopathy, known as infectious mononucleosis [7,8]. Kofteridis DP [9] reported that EBV infection is associated with hepatitis, which is extremely common but asymptomatic [10]. In some cases, EBV infection still leads to the incidence of fatal

fulminant hepatitis despite asymptomatic presentation [11].

CMV is a common cause of virus infection in children worldwide, potentially leading to hearing loss, neurological deficit, and viral hepatitis. Hence, the mortality of CMV infection is relatively high and deserves widespread attention [12,13].

A cross-sectional investigation conducted in Chengdu, China, demonstrated that the mean prevalence of CMV in infants < 1 year of age was 52%, and 60% in children 4–7 years of age [14]. Additionally, CMV infection, which has high morbidity and mortality, has been regarded as the most common cause of intrauterine and perinatal infections [15].

Among those infected with the herpes virus family, approximately 60% to 95% are infected by HSV [16]. Although hepatic involvement in HSV-infected patients

is rarely encountered in clinical practice, it may progress into a severe disease. Nevertheless, related investigations have been extremely insufficient.

EBV, CMV, and HSV, as ubiquitous pathogens, lead to the incidence of pediatric hepatitis. Patients infected with such viruses commonly present with liver dysfunction [7,17,18]. Multiple biomarkers have been utilized to predict the risk of these viral infections in children, whereas the association between these biomarkers and liver function remains to be elucidated. Therefore, the aim of this study was to evaluate the relationship between pediatric liver function and IgM-positive EBV, HSV, and CMV infections in southwest China.

Methodology

Study design

In total, 622 children between 6 months and 12 years of age, admitted to West China Second University Hospital from September 2011 to August 2013, were enrolled in this retrospective study.

Demographic data, including age, gender, season the blood sampling occurred, and alternative results are illustrated in Table 1. Liver function parameters included total protein (TP), albumin (ALB), globulin (GLB), prealbumin (PA), alkaline phosphatase (ALP),

alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), direct bilirubin (DBIL), indirect bilirubin (IBIL), lactate dehydrogenase (LDH), and γ -glutamyl transferase (γ -GT). Multiple antibodies, including CMV-IgM, EBV-IgM, and HSV-IgM, were detected. The fasting venous blood sampling was obtained from the same child at the same time point. Abnormal liver function tests were determined using corresponding reference ranges after adjustment for age and gender. Based upon the concentration of respective IgM antibodies, all children were divided into three groups. In group I, serum CMV-IgM antibody concentration > 30 U/mL was defined as positive CMV. In group II, serum EBV-IgM antibody level exceeding 40 U/mL was defined as positive EBV. In group III, the concentration of serum HSV-IgM antibody > 1.1 index was deemed as positive HSV. The presence of IgM was used for diagnosing the recent occurrence of CMV/EBV/HSV infection [19]. All blood samples positive for hepatitis virus A, B, C, and E, and enteroviruses and respiratory viruses were excluded from subsequent analysis.

Laboratory tests

All tests were conducted in a laboratory accredited by ISO15189 (CNAS) and the College of American

Table 1. Clinical characteristics of children infected by CMV, EBV, or HSV.

Parameters	Group		
	CMV	EBV	HSV
n (%)	271 (40)	289 (42)	125 (18)
Age (years)	3.29 ± 2.61	4.35 ± 3.10	3.01 ± 3.61
Sex (male/female)	161/128	142/129	67/58
Season of blood sampling (n)*			
Spring	29	45	28
Summer	76	60	31
Autumn	111	96	27
Winter	73	70	39
Liver function parameters			
ALB (g/L)	41.2 (38.2–44.5)	43.5 (40.4–45.7) ⁺	43.3 (40.2–46.1) [¶]
ALP (U/L)	284.5 (219.7–448.0)	192 (151–252) ⁺	211.5 (144–310) [¶]
ALT (U/L)	49 (27–108)	26 (14–64) ⁺	34 (14–71) [¶]
AST (U/L)	65 (45–145)	30 (30–68) ⁺	47 (32–85) ^{¶ §}
DBIL (μmol/L)	4 (2.5–20.4)	2.2 (1.6–3.0) ⁺	2.7 (1.6–4.1) ^{¶ §}
GLB (g/L)	21.4 (18.7–25.7)	27.8 (20–315) ⁺	23.5 (20.4–28.1) ^{¶ §}
IDIL (μmol/L)	5.7 (3.3–13.2)	3.7 (2.7–4.9) ⁺	4.1 (2.8–6.8) ^{¶ §}
LDH (U/L)	342 (289–410)	354 (274–475) ⁺	330 (280–438.5)
PA (mg/L)	184 (135–234)	164 (118.5–323.5)	187 (133–237)
TB (μmol/L)	10 (6.2–42.3)	6 (4.3–8.2) ⁺	6.8 (4.6–11.7) [¶]
TP (g/L)	64 (58.4–68.4)	71.7 (76.3–76.4) ⁺	67 (62.8–72.3) ^{¶ §}
γ -GT (U/L)	73 (31–169.5)	16 (11–38) ⁺	23 (14–73) ^{¶ §}

CMV: cytomegalovirus; EBV: Epstein-Barr virus; HSV: herpes simplex virus; TP: total protein; ALB: albumin; GLB: globulin; PA: prealbumin; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TB: total bilirubin; DBIL: direct bilirubin; IBIL: indirect bilirubin; LDH: lactate dehydrogenase; γ -GT: γ -glutamyl transferase; Values are presented as means, total ranges, or total n and percentages; *Spring is from March to May; summer from June to August; autumn from September to November; winter from December to February; ⁺p < 0.05 EBV vs. CMV; [¶]p < 0.05 HSV vs. CMV; [§]p < 0.05 EBV vs. HSV.

Pathologists (CAP). CMV-IgM, EBV-IgM, and HSV-IgM were analyzed on Liaison (DiaSorin, Saluggia, Italy), and control materials (Bio-Rad, Hercules, USA) were used for quality control to ensure the accuracy of daily measurement. Liver function tests were analyzed on ADVIA 2400 automatic biochemical analyzer (Bayer, Pittsburgh, USA). Control materials were provided by Bio-Rad (Hercules, USA). All experiments were performed strictly following the manufacturers' instructions.

Statistical analysis

All data analysis was performed using SPSS 17.0 statistical software (IBM, Armonk, USA). Data were presented as mean ± standard deviation (SD) when normally distributed, as median and interquartile range when the distribution was skewed, or as frequencies and percentages for categorical variables. Differences between continuous variables were evaluated by student's *t*-test, Kolmogorov-Smirnov Z, and χ^2 . For inferential statistical analyses of the variables CMV/EBV/HSV and parameters of liver function, Pearson's Chi-square test was used. A *p* value < 0.05 was considered statistically significant.

Results

Baseline demographic data

Clinical characteristics of 622 patients between 6 months and 12 years of age are shown in Table 1. In total, 63 children were infected with two pathogens in West China Second University Hospital. When stratified for the season in which sampling was done, a significant difference was noted in terms of seasonal infections (group I: *p* < 0.05; group II: *p* < 0.05; group III: *p* = 0.661). The percentage of CMV and EBV infection in the autumn and winter were significantly higher compared with those in the spring and summer (Figure 1). However, the percentage of CMV and EBV infection did not significantly differ between genders.

Correlation between liver function and EBV/CMV/HSV infection

Patients infected with EBV, CMV, and HSV presented with abnormal levels of LDH (62.17%, 60.86%, and 64.0%, respectively) and AST (50.42%, 48.06%, and 52.20%, respectively), less commonly observed in terms of TP (group I: 15.13%) and DBIL (group II: 7.27%; group III: 13.60%), as illustrated in Figure 2. All patients had significant changes in terms of liver function parameters, but a pronounced pattern was observed in the groups with PA.

Figure 1. Seasonal distribution of children with positive EBV, CMV, and HSV IgM.

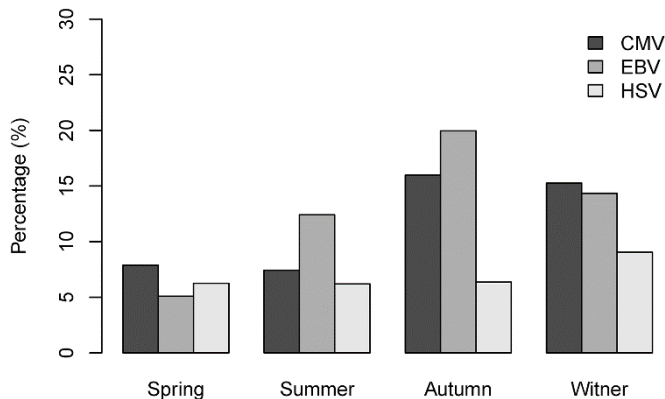
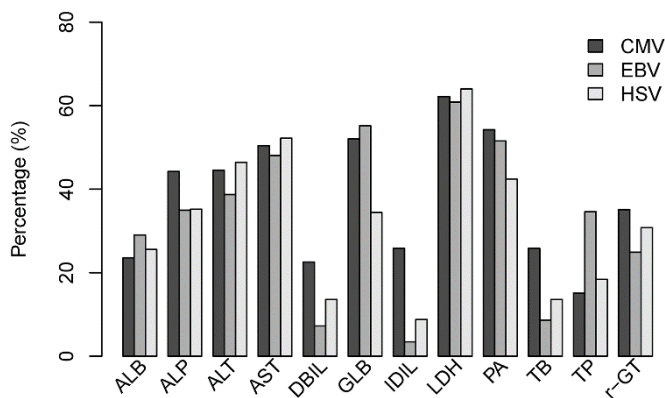


Figure 2. Comparison of percentage of abnormal liver function parameters in children carrying anti-CMV, anti-EBV, or anti-HSV antibodies.



As shown in Table 2, AST and ALT levels were negatively correlated with hepatocellular injuries induced by seropositive EBV-IgM in children < 3 years of age, whereas a positive correlation between hepatic injuries and LDH levels was observed in children < 1 year of age. IBIL was positively correlated with γ -GT in children < 1 year and 3–6 years of age with seropositive HSV-IgM. The percentage of seropositive CMV-IgM in children < 1 year of age was 72.8% (158/217), approximately five times higher than that in children 1–3 years of age. Significant correlation was documented with PA in children < 1 year of age.

Liver function parameters

In total, 63 patients were infected by two viruses simultaneously. Compared with their counterparts infected with single virus, the percentage of abnormal levels of LDH (group I: 85.71%; group II: 77.78%; group III: 83.33%) and AST (group I: 69.19%; group II: 77.78%; group III: 83.33%) was significantly higher in children co-infected with two pathogens, as

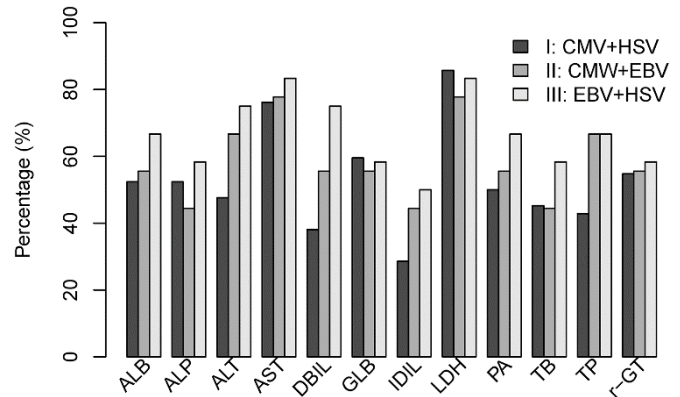
illustrated in Figure 3. The abnormal rates of ALB, ALP, ALT, DBIL, GLB, IBIL, PA, TB, TP, and γ -GT in patients co-infected with two viruses were equally significantly higher compared with those in their counterparts infected with a single pathogen (Figures 2 and 3).

Discussion

Herpes virus family mainly affects the organs derived from ectoderm, including the skin, mucous membranes, and nerve tissues. The pathogenesis of this infectious disease is diverse with a tendency to latent infections, which poses a serious threat to human health [19-22], especially for children. Mixed co-infection by CMV/HSV, CMV/EBV, and EBV/HSV in children may have different primary, co-primary, or secondary pathogens. Previous studies have documented that the severity of infection will be increased in cases of infection by two or more than two viruses (CMV, EBV, and HSV). Therefore, clinical diagnosis should be determined as early as possibly [23]. In this investigation, 63 (approximately 10%) of 622 children were co-infected with CMV/EBV, CMV/HSV, or EBV/HSV. The laboratory test for the diagnosis was accredited by ISO15189 (CNAS) and the College of American Pathologists.

EBV infection first occurs during childhood and affects almost any organs. EBV virus primarily infects B-cells, and is transmitted through intimate contact [8,24]. However, the mechanism underlying EBV infection complicated with hepatitis remains elusive. A possible explanation proposes that the virus induces a systemic and intrahepatic production of pro-

Figure 3. Liver function parameters in 63 children co-infected with two pathogens.



inflammatory cytokines, which interfere with the activity of both the sinusoidal and canalicular transporting systems that probably leads to cholestasis [25]. Other possible mechanisms include infection of biliary epithelial cells and high concentration of enzyme-inhibiting autoantibodies against the anti-oxidative enzymes [26,27].

CMV is a common cause of infections in children worldwide and yields high morbidity in individuals with compromised immunity, such as neonates and liver transplant recipients [15]. Wade *et al.* reported that 60% of the individuals with HSV were asymptomatic or oligosymptomatic; thus, these conditions are difficult for patients to self-recognize [28]. The incidence of disseminated HSV infection is rare and mainly occurs in neonates and immunocompromised individuals, such as patients undergoing renal transplantation or receiving anti-cancer drugs, and leukemia or lymphoma patients, in whom systemic involvement by HSV is the

Table 2. Spearman’s correlation test for liver functions among children infected by CMV, EBV, or HSV.

Parameters	ALB	ALP	ALT	AST	DBIL	GLB	IDIL	LDH	PA	TB	TP	γ -GT
CMV (N = 217)												
< 1 year (n = 158)	0.057	0.154	0.145	0.104	0.093	-0.073	0.099	-0.371	0.174*	0.104	-0.044	0.116
1–3 years (n = 30)	-0.025	0.292	0.045	0.225	0.120	-0.056	-0.097	-0.118	0.083	0.027	0.032	0.352
3–6 years (n = 11)	0.067	-0.067	-0.750	0.321	0.214	0.143	0.216	0.286	0.214	-0.179	0.143	0.052
> 6 years (n = 18)	-0.321	0.065	-0.070	0.161	-0.111	-0.25	-0.234	0.076	-0.377	-0.169	-0.360	0.130
EBV (N = 289)												
< 1 year (n = 16)	-0.300	-0.500	-0.700*	0.100	-0.600	0.564	-0.600	0.564*	-0.600	-0.002	-0.600	-0.300
1–3 years (n = 124)	0.115	-0.015	0.028	-0.004*	-0.162	0.080	-0.071	-0.155	-0.06	-0.109	0.072	-0.088
3–6 years (n = 91)	-0.038	0.173	0.171	0.046	0.012	0.120	-0.141	0.182	-0.053	-0.061	0.118	0.002
> 6 years (n = 58)	0.104	-0.058	0.108	0.087	0.19	0.395*	0.101	0.153	-0.154	0.161	0.246	0.086
HSV (N = 125)												
< 1 year (n = 53)	-0.080	0.283	0.303	0.245	0.294	-0.056	0.340*	0.121	0.206	0.267	-0.15	0.390*
1–3 years (n = 32)	-0.162	-0.093	0.236	0.176	-0.319	-0.087	0.223	0.175	-0.193	-0.272	-0.172	0.030
3–6 years (n = 18)	-0.026	-0.229	0.265	0.268	0.260	0.257	0.551*	-0.015	0.001	0.410	0.172	0.439
> 6 years (n = 22)	0.071	-0.22	0.209	0.062	-0.371	0.075	-0.377	0.009	0.097	-0.443	0.020	0.153

CMV: cytomegalovirus; EBV: Epstein-Barr virus; HSV: herpes simplex virus; ALB: albumin; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DBIL: direct bilirubin; GLB: globulin; BIL: indirect bilirubin; LDH: lactate dehydrogenase; PA: prealbumin; TB: total bilirubin; TP: total protein; γ -GT: γ -glutamyl transferase; *p < 0.05 was considered statistically significant.

main manifestation and hepatic involvement a part of this process [29]. It has been recognized that children infected by a herpes virus commonly have abnormal liver function [30,31], which is consistent with our findings in this clinical trial. In this investigation, we found that the incidence of abnormal liver function ranged from 3.5% to 64.0%, depending on the type of virus infection. We observed a similar percentage in EBV-IgM-positive individuals with abnormal levels of ALT and γ -GT, and a higher proportion with abnormal levels of LDH compared with the findings proposed by Just-Nübling *et al.* [32]. Moreover, neither CMV seropositivity nor HSV seropositivity was correlated with seasonal variation, in accordance with the results of Evans Gold *et al.* [33]. However, EBV seropositivity was correlated with seasonal variation in HSV-seropositive children < 1 year of age, probably caused by mother-to-infant transmission. The present study found no significant correlation between seropositive virus infection and gender in children.

In the present study, the correlation between virus infection and liver function parameters significantly varied across age. Herpes virus antibodies were negatively correlated with all liver function parameters except in children > 6 years of age, probably due to data insufficiency. A correlation between certain liver function parameters and herpes virus antibodies seropositivity was noted in children < 1 year and those between 1 and 3 years of age. Therefore, our findings may contribute to the identification of herpes virus antibodies seropositivity in children of different ages based on levels of hepatic function parameters, providing certain reference data for identifying optimal parameters for the diseased state. Among a total of 622 infected children, 63 were co-infected with two pathogens, including CMV/HSV, CMV/EBV, and EBV/ HSV, which is consistent with previous reports [34-36]. However, further studies are required to clarify the relationship between liver function and interaction involved in patients co-infected by multiple pathogens.

Study limitations

This study had several limitations. First, the serology of the herpes virus IgM antibodies is complex, and the results in our study remain to be validated by subsequent investigations [37]. Second, false-positive outcomes in serological analysis may influence the test results. Third, blood samples were collected from different children during different seasons, which probably weakened the effect of the season on the titers of herpes virus IgM antibodies.

Conclusions

Liver function abnormalities were observed in children with seropositive IgM antibody of herpes virus. Children < 3 years of age with positive EBV antibodies presented with elevated levels of AST and ALT. However, compared to alternative parameters, increased level of LDH was more commonly seen in children < 1 year of age. A positive correlation between IBIL/ γ -GT and seropositive HSV antibody was documented in children < 1 year and 3–6 years of age. The findings of the present study may have pivotal public health implications.

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