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Original Article

Positive correlation between VCA-IgM and Th1/Th2 immunocytokines in children with infectious mononucleosis

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Abstract: Objective: To analyze the correlation between immunoglobulin M (IgM) against viral capsid antigen (VCA) of Epstein-Barr virus (EBV) and T helper 1 and 2 (Th1/Th2) immunocytokines (ICKs) in children with infectious mononucleosis (IM). Methods: This is a retrospective study. A total of 40 children with IM treated in our hospital from August 2019 to August 2021 were included in the research group, and another 42 children with upper respiratory tract infection treated during the same period were selected as the control group. The VCA-IgM positive (+) rate and Th1/Th2 ICKs in two groups were detected, and the correlation of VCA-IgM with Th1/Th2 ICKs in IM patients was analyzed. Results: The research group was found to have an evidently higher VCA-IgM+ rate than the control group. Moreover, the accuracy of VCA-IgM in detecting IM was as high as 91.46%. In addition, tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin (IL)-6 and IL-10 presented markedly elevated levels in the research group than in the control group, and in VCA-IgM negative (-) patients compared with VCA-IgM+ patients. There was a positive connection between VCA-IgM and Th1/Th2 ICKs. Conclusions: IM children showed high VCA-IgM+ rate and imbalance of Th1/Th2 ICKs, and their VCA-IgM and Th1/Th2 ICKs are positively correlated. In addition, VCA-IgM has certain diagnostic value for IM.

Keywords: Infectious mononucleosis in children, VCA-IgM, Th1/Th2 immunocytokines, TNF-α, IFN-γ, IL-6, IL-10

Introduction

Infectious mononucleosis (IM) is an acute and infectious systemic proliferative disease due to Epstein-Barr virus (EBV) infection, usually occurs in children [1, 2]. Essentially, EBV is a DNA herpesvirus, which can invade squamous epithelial cells and transmit from person to person with oropharyngeal secretion as the source of infection [3]. According to IM-related epidemiological statistics, the global EBV positive (+) rate is estimated to be as high as 90%. In China, EBV mainly affects children aged 4-6 years [4, 5]. Children with IM may present typical clinical symptoms such as fever, sore throat, lymphadenectasis, rash and eyelid edema, as well as complications like spleen rupture, malignant tumor and EBV-related hemophagocytic syndrome in severe cases [6-8]. In addition, viral capsid antigen (VCA), as an anti-EBV, secretes immunoglobulin M (IgM) antibodies in the acute stage of IM, showing significantly increased concentration of IgM [9]. VCA-IgM is shown to be feasible for specific antibody test to diagnose EBV-induced IM [10]. Hence, revealing the nosogenesis of IM and VCA-IgM expression in IM can provide new clues for clinical detection and treatment of IM.

T-helper cells (Ths) are essential in the body's defense and protection following viral invasion, among which type 1 Ths (Th1s) help the host defend against intracellular pathogens and mediate the progression of certain autoimmune diseases, and type 2 Ths (Th2s) assist to resist invermination and are closely related to allergic diseases [11]. Th1s mainly secrete tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), which can enhance the toxicity of CD8 T cells, stimulate natural killer (NK) cells and promote the regulation of cellular immunity, thus exerting antiviral immunity [12]. Mainly expressing interleukin (IL)-6 and IL-10, Th2s can participate in humoral immune response and

induce antibody production [13]. Imbalance of Th1/Th2 immunocytokines (ICKs) can not only lead to pathological changes, but also cause low infection clearance and host susceptibility to immune-mediated diseases [14]. Th1/Th2 ICKs are reported to mediate EBV-related idiopathic thrombocytopenic purpura and aplastic anemia, but there are few reports about their roles in EBV-related IM [15, 16]. A previous animal study indicated a close association between VCA-IgM and Th1/Th2 ICKs in the course of infectious diseases in mice [17].

We hypothesized that VCA-IgM in IM has a certain correlation with Th1 (TNF-α, IFN-γ)/Th2 (IL-6, IL-10) ICKs in IM. Understanding the impact of VCA-IgM on Th1/Th2 ICKs have the potential to provide reference for the clinical diagnosis and treatment of IM in children.

Data and methods

General data

This retrospective study, approved by the Ethics Committee of the Huadu District People's Hospital of Guangzhou, selected 40 pediatric IM patients admitted from August 2019 to August 2021 as the research group, and 42 pediatric upper respiratory tract infection (URTI) patients during the same period as the control group. The male-to-female ratio and the mean age of children were 22:18 and (4.98±2.55) years, respectively in the research group, and 28:14 and (4.62±2.26) years, respectively in the control group. The two groups of children differed insignificantly in sex and average age, indicating comparability ($P > 0.05$).

Inclusion criteria: children who aged under 10 years old and underwent EBV specific antibodies and EBV-DNA load determinations, with confirmed diagnosis of IM; children in normal growth and development; children with three of the following clinical symptoms: fever, pharyngeal tonsillitis, lymphadenectasis, splenomegaly and hydroblepharon; children who did not use hormones or immunomodulators during treatment. Exclusion criteria: children with malignant tumor or blood system diseases; children with congenital immunodeficiency or immune system diseases; children who used glucocorticoids, cytotoxic agents or other immunosuppressants within 3 months; children with IM-like syndrome caused by other viruses, such as cytomegalovirus, adenovirus or hepatitis virus; referrals or those who discharged himself/herself against medical advice. The inclusion criteria and exclusion criteria were applicable to the research group. For the control group, all inclusion criteria except "confirmed diagnosis of IM" and all the exclusion criteria were applicable to this group.

Endpoints

After collecting fasting cubital venous blood from children on the 6th-10th day of the treatment, the serum was obtained by centrifugation (1500 x g, 4°C) for 10 min and refrigerated for later use. IgM serum antibodies against EBV-VCA were analyzed by enzyme-linked immunosorbent assay (ELISA), with kits from by Wenzhou Kemiao Biotech (KMEHu 012318). The experimental steps were in strict accordance with the kit's operating instructions.

Th1/Th2 ICKs such as TNF-α, IFN-γ, IL-6 and IL-10 were also detected by ELISA kits (Beijing Solarbio, SEKH-0047, SEKH-0046, SEKH-0013, SEKH-0018), and then the sample contents were detected by a microplate reader (Shenzhen Haisi'an Biotech, HSA-M1812). The detection process strictly followed the manufacturer's recommendations of the kit or instrument.

Calculation of indicators related to diagnostic value

Sensitivity is the number of true positives measured by VCA-IgM divided by the number of true positives measured by the gold standard.

Specificity is the number of true negatives measured by VCA-IgM divided by the number of true negatives measured by the gold standard.

Positive predictive value is the number of true positives measured by VCA-IgM divided by the number of positives measured by the method used.

Negative predictive value is the number of true negatives measured by VCA-IgM divided by the number of negatives measured by the method used.

Accuracy rate is the sum of true positives and true negatives measured by VCA-IgM divided by the sum of true positives and true negatives measured by the gold standard.

Table 1. Patient baseline data [n (%), mean ± SD]

Factors	n	Control group (n=42)	Research Group (n=40)	χ^2/t	P
Sex				1.172	0.279
Male	50	28 (66.67)	22 (55.00)		
Female	32	14 (33.33)	18 (45.00)		
Average age (years)	82	4.62±2.26	4.98±2.55	0.677	0.500
Course of disease (days)				0.802	0.371
< 3	39	22 (52.38)	17 (42.50)		
≥ 3	43	20 (47.62)	23 (57.50)		
Height (cm)				0.802	0.371
< 90	39	22 (52.38)	17 (42.50)		
≥ 90	43	20 (47.62)	23 (57.50)		
Weight (kg)				1.179	0.278
< 18	36	16 (38.10)	20 (50.00)		
≥ 18	46	26 (61.90)	20 (50.00)		
Season of onset				0.235	0.972
Spring	26	14 (33.33)	12 (30.00)		
Summer	24	12 (28.57)	12 (30.00)		
Autumn	19	10 (23.81)	9 (22.50)		
Winter	13	6 (14.29)	7 (17.50)		
Single parent family				1.411	0.235
No	63	30 (71.43)	33 (82.50)		
Yes	19	12 (28.57)	7 (17.50)		
Family medical history				0.965	0.326
None	73	36 (85.71)	37 (92.50)		
Yes	9	6 (14.29)	3 (7.50)		
Place of residence				0.105	0.746
Urban	56	28 (66.67)	28 (70.00)		
Rural	26	14 (33.33)	12 (30.00)		

Statistical processing

Statistical analysis was performed using SPSS *v*20.0 (IBM Corp, Armonk, NY, USA), and images were exported via GraphPad Prism *v*7. In this paper, differences of $P < 0.05$ were deemed significant. Categorical and quantitative data were presented in the form of n (%) and mean ± SD, respectively. As to the statistical methods, the categorical data were compared using a Chi-square test, and the quantitative data between groups were compared by the t-test. The correlation of VCA-IgM with Th1/Th2 ICKs was analyzed by Spearman's correlation coefficients.

Results

Patient baseline data

The two cohorts of children differed insignificantly in sex, average age, course of disease, height, weight, onset season, single parent family, family history, place of residence and other baseline data ($P > 0.05$) (**Table 1**).

VCA-IgM positive (+) rate in two groups

We analyzed the VCA-IgM+ rate and found a positive rate of 7.14% in the control group, versus 90.00% in the research group, indicating a statistically higher VCA-IgM+ rate in the research group ($P < 0.05$). The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of VCA-IgM in identifying IM were 90.00%, 92.86%, 92.31%, 90.70%, and 91.46%, respectively (**Tables 2**, **3**).

Th1/Th2 ICKs in two groups

The detection results of Th1/Th2 ICKs TNF-α, IFN-γ, IL-6 and IL-10 revealed markedly higher concentrations of the above parameters in the

Table 2. VCA-IgM positive rate in two groups [n (%)]

Groups	n	VCA-IgM positive	VCA-IgM negative	χ^2 value	*P* value
Control group	42	3 (7.14)	39 (92.86)	56.396	< 0.001
Research group	40	36 (90.00)	4 (10.00)		

Note: VCA, Viral Capsid Antigen; IgM, Immunoglobulin M.

Table 3. Diagnostic value of VCA-IgM for IM

Detection method	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
VCA-IgM	90.00	92.86	92.31	90.70	91.46

Note: VCA, Viral Capsid Antigen; IgM, Immunoglobulin M.

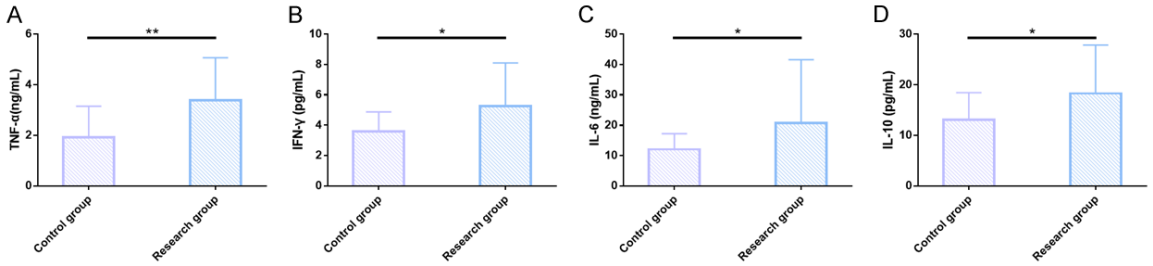

Figure 1. Th1/Th2 ICKs in two groups of patients. A. The research group showed a statistically higher TNF-α level than the control group. B. The research group showed a statistically higher IFN-γ level than the control group. C. The research group showed a statistically higher IL-6 level than the control group. D. The research group showed a statistically higher IL-10 level than the control group. Note: **P* < 0.05, ***P* < 0.01. Th1/Th2, T helper 1 and 2; ICKs, Immunocytokines; TNF-α, Tumor Necrosis Factor-α; IFN-γ, Interferon-γ; IL, Interleukin.

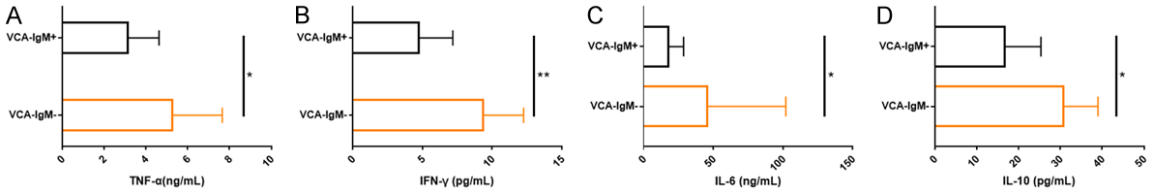

Figure 2. Expression of Th1/Th2 ICKs in VCA-IgM positive (+) and negative (-) patients. A. VCA-IgM+ patients showed statistically lower TNF-α levels than VCA-IgM- patients. B. VCA-IgM+ patients showed statistically lower IFN-γ levels than VCA-IgM- patients. C. VCA-IgM+ patients showed statistically lower IL-6 levels than VCA-IgM- patients. D. VCA-IgM+ patients showed statistically lower IL-10 levels than VCA-IgM- patients. Note: **P* < 0.05, ***P* < 0.01. Th1/Th2, T helper 1 and 2; ICKs, Immunocytokines; VCA, Viral Capsid Antigen; IgM, Immunoglobulin M; TNF-α, Tumor Necrosis Factor-α; IFN-γ, Interferon-γ; IL, Interleukin.

research group than in the control group (*P* < 0.05) (**Figure 1**).

Expression of Th1/Th2 ICKs in VCA-IgM+ or negative (-) patients

We divided IM patients into VCA-IgM+ and VCA-IgM- groups to analyze their differences in Th1/Th2 ICKs. The results determined statistically lower TNF-α, IFN-γ, IL-6 and IL-10 concentrations in VCA-IgM+ patients than in VCA-IgM- patients (*P* < 0.05) (**Figure 2**).

Correlation analysis between VCA-IgM and Th1/Th2 ICKs in IM patients

We set VCA-IgM+ patients as 1 and VCA-IgM- patients as 2 to analyze the correlation between VCA-IgM and Th1/Th2 ICKs by Spearman's correlation coefficients. The results showed a positive correlation of VCA-IgM with TNF-α (r=0.379, *P* < 0.05), IFN-γ (r=0.383, *P* < 0.05), IL-6 (r=0.440, *P* < 0.05) and IL-10 (r=0.484, *P* < 0.05) (**Figure 3**).

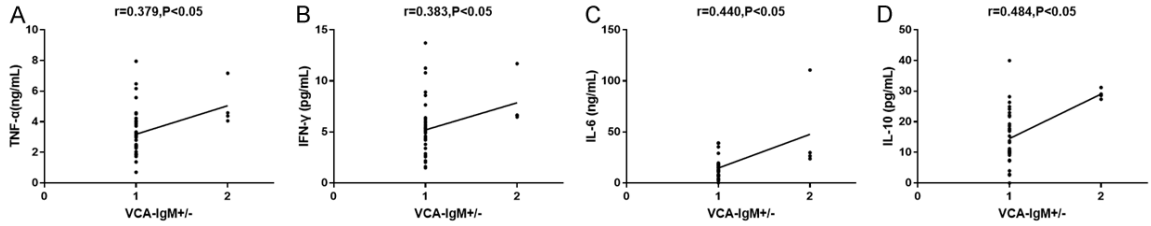

Figure 3. Correlation analysis between VCA-IgM and Th1/Th2 ICKs in IM patients. A. There was a significant positive correlation between VCA-IgM and TNF-α in IM patients (r=0.379, $P < 0.05$). B. There was a significant positive correlation between VCA-IgM and IFN-γ in IM patients (r=0.383, $P < 0.05$). C. There was a significant positive correlation between VCA-IgM and IL-6 in IM patients (r=0.440, $P < 0.05$). D. There was a significant positive correlation between VCA-IgM and IL-10 in IM patients (r=0.484, $P < 0.05$). Note: Th1/Th2, T helper 1 and 2; ICKs, Immunocytokines; VCA, Viral Capsid Antigen; IgM, Immunoglobulin M; TNF-α, Tumor Necrosis Factor-α; IFN-γ, Interferon-γ; IL, Interleukin.

Discussion

EBV infection is a high-incidence infectious disease in pediatrics and the most common pathogen of IM [18]. IM is clinically manifested as pharyngitis, lymphadenopathy and fever, and may also cause hematological malignancies such as Burkitt's lymphoma, gastric lymphoma and non-Hodgkin's lymphoma, as well as an increased risk of autoimmune diseases like multiple sclerosis [19, 20]. Research has shown that the immune system can play an antiviral role by requisitioning a group of cytokines beneficial to the host when dealing with virus infections, and the mechanism may be that these cytokines can coordinate the host immune cells to effectively eliminate the invading viruses [21]. This study mainly investigated the VCA-IgM+ rate in IM patients and its correlation with Th1/Th2 ICKs.

First, this study included children with IM as research group (n=40) and those with URTI during the same period as control group (n=42). We found an evidently higher VCA-IgM+ rate in the research group than in the control group (90.00% vs. 7.14%), suggesting that IM children had a significantly higher VCA-IgM+ rate, similar to the findings of Zaki [22]. EBV infection is known to stimulate host B cells to differentiate into plasma cells and produce antibodies, secreting anti-EBV-VCA-IgM in the early stage of the disease [23]. VCA-IgM+ is also regarded as an effective marker for acute EBV infection in IM patients and can be a serum index to indicate primary EBV infection [24]. In our study, it was found that VCA-IgM has a high diagnostic efficiency for distinguishing IM from URTI, with an accuracy rate of 91.46%, and high sensitivity (90.00%) and specificity (92.86%). Subsequently, the detection of Th1/Th2 ICKs showed that compared with those in the control group, TNF-α, IFN-γ, IL-6 and IL-10 concentrations were abnormally up-regulated in the research group, which indicated that the immune regulatory mechanism of children with IM was abnormal. Andersson et al. [25] reported that the secretion of TNF-α IFN-γ and IL-6 in tonsils of patients with fulminant IM increased significantly, suggesting that these cytokines are closely related to the pathological changes of IM and may be related to the cytokine cascade triggered by B lymphocytes under EBV infection stimulation. IFN-γ, as a modulator of cellular immunity, assists in IgM, IgG, and IgA syntheses by activating macrophages [26]. IL-6 and IL-10 are cytokines involved in humoral immunity. The former can activate B cells and promote the production of antinuclear antibody and anti-smooth muscle antibody [27], while the latter, as a cytokine of central immune regulation, is associated with serious complications in IM patients while playing a vital part in maintaining sufficient Th2 immune response during antigen stimulation [21, 28]. Furthermore, we found obviously higher TNF-α, IFN-γ, IL-6 and IL-10 concentrations in VCA-IgM- patients than in VCA-IgM+ patients, suggesting that this immune imbalance may be more serious in IM patients with VCA-IgM-. The subsequent correlation analysis showed that VCA-IgM had a significant positive correlation with the above four Th1/Th2 ICKs in IM patients.

This research demonstrated a significant correlation between VCA-IgM and Th1/Th2 ICKs in IM children, and revealed the influence of VCA-

IgM and Th1/Th2 ICKs on the pathological process of IM as well as the high diagnostic potential of VCA-IgM for IM. But it still has some limitations. First of all, we only included 40 children with IM, which is a small sample from a single center that may have a certain influence on the accuracy of the study results. Second, complications have not been included in the analysis, and additional studies in this aspect will be helpful to further understand the potential correlation of VCA-IgM and Th1/Th2 ICKs with complications in IM children. Third, further research is needed in the future to refine our study.

In conclusion, we propose for the first time the positive correlation of VCA-IgM with Th1/Th2 ICKs in children with IM. TNF-α, IFN-γ, IL-6 and IL-10 concentrations were statistically higher in IM children than in children with URTI. In addition, the above four ICKs are significantly higher in IM children with VCA-IgM- than in those with VCA-IgM+, indicating that IM children with VCA-IgM- were associated with potential serious immune imbalance. Moreover, VCA-IgM has the potential to be an auxiliary diagnostic index for IM.

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Disclosure of conflict of interest

None.

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