

# The correlation between cytokine concentrations and IgG/IgM antibodies to viruses of the Herpesviridae family in children with rheumatic heart disease

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*Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are still urgent medical issues in developing countries and in some communities of high-income countries. The aim of our study was to evaluate plasma cytokine concentrations in children with RHD and their correlation with antibody concentrations to viruses of the Herpesviridae family. Sixty-two patients with RHD aged 8 to 17 years were included in the study. The concentrations of TNF- $\alpha$ , IL-4, IL-8, IL-10 and IFN- $\gamma$  were evaluated; IgG and IgM antibodies to cytomegalovirus (CMV), herpes simplex virus (HSV) groups I-II and Epstein-Barr virus (EBV) in serum were determined by ELISA method. A significant increase of cytokine concentrations (TNF- $\alpha$ , IL-8, IL-4 and IL-10) was recorded in RHD patients. Antibodies to intracellular Herpesviridae family viruses were detected in all children with RHD. Children with RHD were significantly more likely to have IgG HSV I-II antibodies, and IgG and IgM EBV antibodies compared to controls ( $p < 0.05$ ). The concentration of IgM antibody to CMV showed positive correlation with TNF- $\alpha$ ; the concentration of IgG antibody to EBV showed negative correlation with TNF- $\alpha$ ; and the concentration of IgG and IgM antibodies to EBV showed positive correlation with IL-10 levels. Considering positive correlation of IL-10 concentration with IgG and IgM antibody concentrations to EBV, and the significance of IL-10 in the progression of RHD, the possible predisposing role of EBV in the progression of RHD can be postulated, which needs further study.*

**Key words:** CHILD; CYTOKINES; HERPESVIRIDAE; RHEUMATIC HEART DISEASE

## INTRODUCTION

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) are still urgent issues in developing countries and some communities of high-income countries (1-3). ARF is an autoimmune disorder caused by group A streptococcal (GAS) infection, whereas RHD is a consequence of ARF (4-6). In the development of RHD, recurrent rheumatic fever (RF) is of great significance (2, 6, 7). RHD developed in 40%-50% of ARF patients (8). Poor secondary prophylaxis is one of the main reasons for recurrent RF (2, 9), although recent literature shows that poor secondary prophylaxis is not associated with an increased risk of RHD in developed countries (10). Some social and environmental factors in GAS infection and progression of ARF and RHD have been studied

comprehensively (2, 9, 11, 12). Among them, household crowding, poor hygiene, living in a rural area, unemployed status, illiteracy, low monthly income, maternal employment, and less access to good quality healthcare are pointed out (10, 11, 13). However, other authors have noted that the role of social factors is not fully understood (14).

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Some authors hypothesize that herpes simplex virus (HSV-1) infection may also be involved in RHD (15). Earlier studies showed that anti-HSV serum prevented bacterial adherence, meaning that HSV infection could lead to superinfection, especially GAS (16, 17). Many investigations have demonstrated the role of cytokines in immune regulation and progression of RHD (18-20). High levels of inflammatory cytokines interleukin (IL)-6 and tumour necrosis factor alpha (TNF- $\alpha$ ) are associated with severe valve dysfunction, whereas high IL-10 and IL-4 levels correlate with adverse outcome (21).

In our research, we tried to identify other factors that can influence the disease progression. Herpesviridae are a large family of DNA viruses with nine herpesvirus types known to infect humans. Among them, HSV-1, HSV-2, cytomegalovirus (CMV), and Epstein-Barr virus (EBV) are widespread in humans. In addition, their primary target are epithelial cells, which also are a portal of entry for the *Streptococcus* bacterium. Moreover, they demonstrate tropism to heart tissue. Therefore, these viruses were considered in this study.

The impact of viruses on the pathological process, including cytokine production, may show a new approach in the prevention of disease progression. Our study aimed to evaluate plasma cytokine concentrations in children with RHD and their correlations with the concentrations of antibodies to viruses of the Herpesviridae family.

## PATIENTS AND METHODS

Sixty-two patients with RHD aged 8-17 years were included in the study. The male to female ratio was 1.4 (36/26). Patients were defined as having RHD according to the World Health Organisation criteria (22) and World Heart Federation criteria (23) for echocardiographic diagnosis of RHD. The control group consisted of 30 healthy children.

The concentrations of cytokine TNF- $\alpha$ , interleukins IL-4, IL-8, IL-10, and interferon gamma (IFN- $\gamma$ ) were evaluated by enzyme-linked immunosorbent assay (ELISA) using calibration curves. Quantitative determination of immunoglobulins (Ig)G and IgM antibodies to CMV; IgG and IgM antibodies to HSV I-II; and IgG and IgM antibodies to the capsid antigen (VCA) of EBV in serum was performed by ELISA method. IgG antibody concentrations of 0-6 U/mL were considered negative, 6-10 U/mL doubtful, and >10 U/mL positive result. IgM antibody concentrations of 0-10 IU/mL were considered negative, 10-15 IU/mL doubtful, and >15 IU/mL positive result.

The results were analysed by standard procedures using the Statistica StatSoft 6.0 software package. The indices were expressed as mean  $\pm$  standard deviation (SD) for continuous variables. The Student's t-test was used to compare the

means between the groups, and the  $\chi^2$ -test was used to test for difference between frequencies. To determine a rank measure of association, Spearman's correlation coefficient was calculated.

Ethical approval for the study was obtained from the scientific Ethics Committee of I Horbachevsky Ternopil State Medical University. The parents of the children participating in this study signed their informed consent. The study conformed to the Declaration of Helsinki principles.

## RESULTS

The median age of the examined patients was 16 years, range 8-17 years. Duration of the disease ranged from 1 to 10 years, mean duration  $5.8 \pm 3.2$  years. Mitral valve lesions were most common ( $n=60$ , 96.8%). Isolated mitral regurgitation (MR) was detected in 27 (43.5%) cases. Mild heart valve disease was diagnosed in 47 (75.8%) and moderate heart valve disease in 15 (24.2%) patients. Severe heart valve disease was not detected at the time of diagnosis.

The mean cytokine concentrations in the serum of children with RHD are presented in Table 1. A significant increase in cytokine concentrations (TNF- $\alpha$ , IL-8, IL-4 and IL-10) was recorded in patients with RHD. We also determined the number of patients with normal, increased and decreased concentrations of cytokines. The indicator measured in the control group ( $M \pm SD$ ) was considered normal. The increase of TNF- $\alpha$  concentration was observed in 48 (77.4%) patients. Increased IL-4 concentration was recorded in 52 (83.9%) children. However, there was no significant difference in the mean serum IFN- $\gamma$  concentration between patients with RHD and control group children. An increase of IL-10 concentration was observed in half of the children with RHD; in 15 (22.6%) patients it was within the normal range and in 17 (27.4%) it was reduced.

IgG antibodies to viruses of the Herpesviridae family were detected in all children with RHD. Among the examined children, 20 (32.2%) had IgG antibodies to three viruses (CMV, HSV I-II, EBV), 39 (62.9%) to two pathogens, and 3 (4.8%) to one of these viruses. The frequency of antibodies to Herpesviridae viruses in RHD children is presented in Table 2. Only positive results were taken into account and are presented in this table.

Children with RHD were significantly more likely to have IgG HSV I-II antibodies as compared to controls ( $p < 0.05$ ). It should be noted that chronic EBV infection was present in 93.5% of children with RHD, which was significantly more frequent than in controls ( $p < 0.001$ ).

IgM antibodies to VCA EBV were also detected more often in RHD children (in 37.1%) as compared to controls. The fre-

TABLE 1. Mean serum cytokine concentrations in children with rheumatic heart disease (RHD) (M±SD)

Cytokine, pg/mL	Controls (n=30)	RHD (n=62)	p
TNF- $\alpha$	11.6±11.3	128.4±36.1	<0.001
IL-4	26.4±11.3	110.4±52.8	<0.01
IL-8	19.7±8.5	41.7±8.2	<0.001
IL-10	35.9±11.7	93.5±106.4	<0.01
IFN- $\gamma$	6.5±6.1	8.0±4.2	>0.05

TABLE 2. Frequency of IgG and IgM antibody detection (positive results) to Herpesviridae family viruses in children with rheumatic heart disease (RHD)

Antibody (only positive results)	Controls (n=25)		RHD (n=62)		p
	n	%	n	%	
IgM CMV	1	4.0	10	16.1	0.1234
IgG CMV	12	48.0	42	67.7	0.0859
IgM HSV I-II	2	8.0	13	21.0	0.1473
IgG HSV I-II	10	40.0	41	66.1	0.0251
IgM VCA EBV	1	4.0	23	37.1	0.0018
IgG VCA EBV	12	48.0	58	93.5	<0.0001

quency of IgM and IgG antibodies to VCA EBV was significantly higher ( $p<0.001$ ) as compared to the detection of these antibodies to CMV and HSV I-II.

Considering the correlation of cytokine concentration and antibodies to viruses of the Herpesviridae family, there was a positive correlation of IgM antibody concentrations to CMV with TNF- $\alpha$  ( $r=0.453676$ ,  $p<0.05$ ). IgG antibody concentrations to VCA EBV negatively correlated with TNF- $\alpha$  ( $r=-0.386325$ ,  $p<0.05$ ). There was a significant positive correlation of IgG and IgM antibody concentrations with VCA EBV and IL-10 concentrations ( $r=0.44054$  and  $0.4283$ , respectively;  $p<0.05$ ) (Figure 1). IL-10 concentration in patients with IgG antibodies to CMV and EBV, and with IgG antibodies to three viruses (CMV, HSV I-II, EBV) was significantly higher than in patients with RHD and IgG antibodies to HSV and EBV ( $121.1\pm90.3$  pg/mL;  $84.4\pm39.5$  pg/mL, respectively, *versus*  $56.4\pm26.6$  pg/mL;  $p<0.05$ ).

IgM antibody concentrations to VCA EBV correlated positively with RHD duration and severity of cardiac involvement ( $r=0.92$ , and  $r=0.68$ , respectively;  $p<0.05$ ).

## DISCUSSION

A significant increase of cytokines TNF- $\alpha$ , IL-8, IL-4 and IL-10 in patients with RHD was proved in the study. Other research showed a positive correlation between IL-6 and TNF- $\alpha$  and the severity of RHD (18). The predominant TNF- $\alpha$  and IFN- $\gamma$  expression in the heart has also been reported, and the authors suggest that Th1-type cytokines could me-

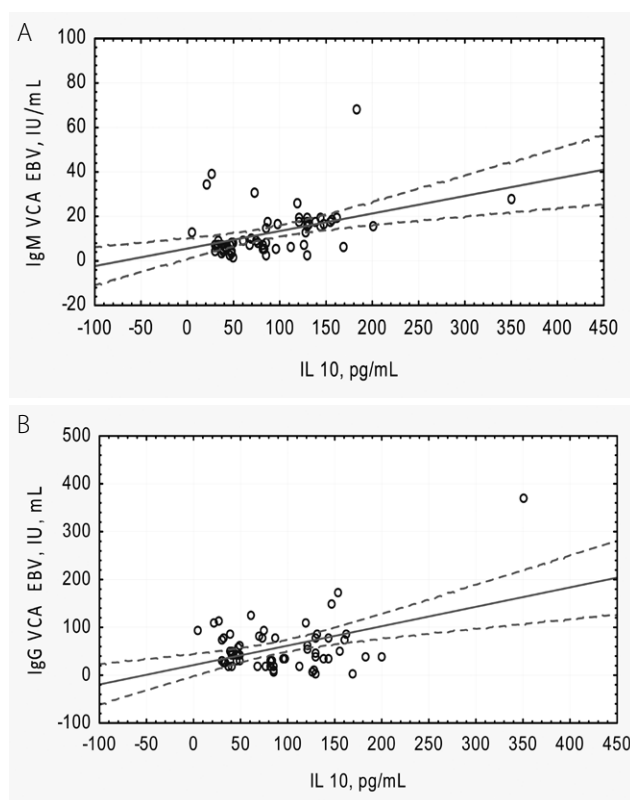


FIGURE 1. Correlation model of antibody concentrations of IgM (A) and IgG (B) to VCA EBV and IL-10 concentrations in children with rheumatic heart disease.

diate RHD (17, 21). TNF- $\alpha$  and IL-10 gene polymorphism has been investigated and was associated with valvular lesions and RHD severity (16). Circulating cytokines can be used as biomarkers of RHD severity (18).

The significance of streptococcal infection in the development of ARF is indisputable (4, 22). However, a small percentage of the disease development even after the invasion with rheumatogenic strains of *Streptococcus (S.) pyogenes* has prompted scientists to search for other predisposing causes of the disease (23, 24).

The viral theory was originated in the 1930s (2) and the search for viruses that contribute to the development of the disease is a topical issue today (12-14). In addition, the mechanisms of developing heart lesions after ARF and transformation to RHD are still not fully understood.

Experimental studies have shown that bacterial adhesion increases in cases of viral infection (25). Influenza and other acute viral respiratory infections are risk factors for invasive *S. pyogenes* infection and occur within one week of influenza diagnosis (26, 27). The correlation between viral and bacterial infections through immune mechanisms is confirmed by the fact that the incidence of haemophilic, meningococcal and pneumococcal infections increases during the influenza epidemic (28).

Another study confirms the significance of recent varicella infection among unvaccinated children as a risk factor of paediatric invasive *S. pyogenes* cases (29). The invasive bacterial infection in cases with chickenpox is commonly manifested by severe infections, including necrotizing fasciitis (30). High risk is caused not only by direct penetration of the bacteria pox lesions but also by significant immunosuppression (29).

Our study showed that the rate of IgM and IgG antibodies to VCA EBV was significantly higher in patients with RHD than in controls. Some researchers also pointed out the possible predispositional role of EBV in the development of RHD (22). Another study did not find any positive correlation to support the synergism theories regarding streptococcal infection and viral infections, such as hepatitis B virus, hepatitis C virus, rubella virus, HSV group 1, and EBV in the development of ARF, but only EBV DNA positivity was found in all ARF cases but not in the control group, suggesting the need of further studies with larger patient series (30). Some authors suggest that one of the indicators of the significance of viruses in the development of ARF is its reduction after antiviral vaccination (31, 32).

Experimental research showed that HSV-1 infected cells adhered precisely to the group A streptococci rather than streptococci of other groups or candida (13). The authors suggested that herpetic infection, which caused about 4% of pharyngitis, could lead to superinfection caused by *S. pyogenes*. Other studies determined HSV-1 in valve tissues obtained during surgery for heart defects in patients with RHD (14). The researchers suggested that streptococcal infection might be secondary to herpetic, with local tissue damage and cytokine inflammatory response to streptococcal infection, which was a potential factor of reactivation of latent herpetic infection (14). The mechanisms of HSV-1 valve damage are still unclear.

Our study proved that children with RHD were significantly more likely to have IgG to HSV I-II and IgG VCA, IgM VCA to EBV. IgG to VCA EBV negatively correlated with TNF- $\alpha$ ; IgG and IgM to VCA EBV positively correlated with IL-10 levels. These changes may indicate suppression of Th1 lymphocyte responses with a predominance of Th2 subpopulation, which can lead to the progression of rheumatic lesions.

Persistence and activation of Herpesviridae family viruses lead to the imbalance of Th1/Th2 cytokine activity, which can cause immune disorders and promote chronicity of the process.

Correlation of antibody levels to viruses of the Herpesviridae family and cytokine concentrations in children with RHD showed an association of persistence of herpes viruses and their reactivation and some changes of the cytokines

and proved the imbalance of cytokine production by T-helper 1 and 2 depending on various pathogens. An imbalance of cytokine responses, with a shift of activity towards Th2 subpopulation that enhances immunosuppression, is aimed at long-term persistence of the pathogen and leads to chronic process.

Many researchers suggest the significance of IL-10 and its polymorphism in immune regulation and progression of RHD (15, 18). The inflammatory response generated by cytokines promotes the chronicity of the disease (15, 17).

A limitation of this study was a small control group (the number of children in the control group was smaller than the number of patients with RHD). Therefore, further studies are needed with a larger number of patients and controls.

## CONCLUSION

The study proved a significant increase of cytokines TNF- $\alpha$ , IL-8, IL-4 and IL-10 in children with RHD. Considering the positive correlation between IL-10 concentrations and IgG and IgM antibody to EBV, and the significance of IL-10 in the progression of RHD, we can suggest the possible predisposing role of EBV in the progression of RHD, which needs further study.

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## SAŽETAK

# Korelacija koncentracije citokina i IgG/IgM protutijela na viruse iz porodice Herpesviridae u djece s reumatskom bolešću srca

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Akutna reumatska vrućica (ARV) i reumatska bolest srca (RBS) još uvijek su hitna medicinska stanja u zemljama razvoju, ali i u nekim sredinama u razvijenim zemljama. Cilj ovoga istraživanja bio je procijeniti koncentracije citokina u plazmi djece s RBS-om te njihovu korelaciju s koncentracijama protutijela na viruse iz porodice Herpesviridae. U istraživanje je bilo uključeno 62 bolesnika s RBS-om u dobi od 8 do 17 godina. Mjerene su serumske koncentracije TNF- $\alpha$ , IL-4, IL-8, IL-10 and IFN- $\gamma$ ; protutijela IgG and IgM na citomegalovirus (CMV), herpes simpleks virus (HSV) I.-II. skupine i Epstein-Barrov virus (EBV) u serumu mjereni su metodom ELISA. Kod bolesnika s RBS-om zabilježen je značajan porast koncentracija citokina (TNF- $\alpha$ , IL-8, IL-4 i IL-10). Protutijela na unutarstanične viruse iz porodice Herpesviridae otkrivena su u sve djece s RBS-om. Prisutnost IgG HSV I-II protutijela te IgG i IgM EBV protutijela bila je značajno vjerojatnija kod djece s RBS-om u usporedbi s kontrolnom skupinom ( $p < 0,05$ ). Koncentracija IgM protutijela na CMV pokazala je pozitivnu korelaciju s TNF- $\alpha$ ; koncentracija IgG protutijela na EBV pokazala je negativnu korelaciju s TNF- $\alpha$ ; koncentracija IgG i IgM protutijela na EBV pokazala je pozitivnu korelaciju s razinama IL-10. S obzirom na pozitivnu korelaciju koncentracije IL-10 s koncentracijama IgG i IgM protutijela na EBV te značajnost IL-10 u progresiji RBS-a može se pretpostaviti predisponirajuća uloga EBV-a u progresiji RBS-a, što zahtijeva daljnja istraživanja.

**Ključne riječi:** DJECA; CITOKINI; HERPESVIRIDAE; REUMATSKA BOLEST SRCA