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Original article

Frequency of antiparvovírus B19 antibodies in rheumatoid arthritis and systemic lupus erythematosus

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ARTICLE INFO

ABSTRACT

Objective: To determine the frequency of antiparvovírus B19 (B19) antibodies in patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), and the possible correlation of anti-B19 seropositivity with disease activity and quality of life.

Patients and methods: Serum samples from 57 patients with RA, 45 with SLE and 65 healthy controls were used. We applied protocol with clinical data, and the Disease Activity Score 28 (DAS 28), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Health Assessment Questionnaire (HAQ) indexes. The anti-B19 serology was done by enzyme-linked immunosorbent assay (ELISA).

Results: The mean age of patients was 42.74 ± 14.09 years, and of controls was 38.38 ± 13.42 years. 79 patients had active disease (77.5%), and 23 had inactive disease (22.5%). Anti-B19 (IgG) was positive in 49 (86.0%; CI 95% 77.0 – 95.0) RA patients, 38 (84.4%; CI 95% 73.9 – 95.0) SLE patients, and 40 (61.5%; CI 95% 49.7 – 73.4) controls (p = 0.002). Anti-B19 (IgM) was positive in 3 (5.3%; CI 95% 0.0 – 11.1) RA patients, in 7 (15.6%; CI 95% 5.0 – 26,2) SLE patients, and in 1 (1.5%; CI 95% 0.0 – 4.5) control (p = 0.011). There was no correlation of anti-B19 reactivity with disease activity and with DAS 28, HAQ and SLEDAI indexes.

Conclusion: This study demonstrated that the studied population is exposed to infection by B19, which demands attention with its manifestations, especially among patients at greatest risk, such as those immunosuppressed.

Frequência de anticorpos antiparvovírus B19 em artrite reumatoide e lúpus eritematoso sistêmico

RESUMO

Objetivo: Determinar a frequência de anticorpos antiparvovírus B19 (B19) em pacientes com artrite reumatoide (AR) e lúpus eritematoso sistêmico (LES), e a possível correlação da soropositividade anti-B19 com a atividade das doenças e a qualidade de vida.

Pacientes e métodos: Foram utilizadas amostras séricas de 57 pacientes com AR, 45 com LES e 65 controles sadios. Empregou-se protocolo com dados clínicos, os índices Disease Activity

Score 28 (DAS 28), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) e Health Assessment Questionnaire (HAQ). Realizou-se a sorologia anti-B19 por ensaio imunoenzi-mático (ELISA).

Resultados: A média de idade dos pacientes foi de 42,74 +/- 14,09 anos, e a dos controles foi de 38,38 +/- 13,42 anos. Tinham doença ativa 79 (77,5%) pacientes, e doença inativa 23 (22,5%). Anti-B19 (IgG) foi reagente em 49 (86,0%) IC 95% (77,0 – 95,0)% pacientes com AR, em 38 (84,4%) IC 95% (73,9 – 95,0)% com LES e em 40 (61,5%) IC 95% (49,7 – 73,4)% controles (p = 0,002). Anti-B19 (IgM) foi reagente em 3 (5,3%) IC 95% (0,0 – 11,1)% pacientes com AR, em 7 (15,6%) IC 95% (5,0 – 26,2)% pacientes com LES e em 1 (1,5%) IC 95% (0,0 – 4,5)% controle (p = 0,011). Não houve cor-relação da reatividade anti-B19 com a atividade das doenças, os índices DAS 28, SLEDAI e HAQ.

Conclusão: O presente estudo demonstrou que a população avaliada está exposta à infecção pelo B19, o que demanda atenção com suas manifestações, principalmente entre os pa-cientes que apresentam maior risco, como os imunossuprimidos.

Introduction

Human parvovirus B19 (B19), accidentally discovered in 1974,[1] is a small, non-enveloped, single strand DNA virus, family Parvoriridae, gender *Erythrovirus*. The viral particle has icosahedral symmetry, measuring between 22 and 24 nanometers, composed of two structural (VP1 and VP2) and one nonstructural (NS1) protein. The VP1 protein represents less than 5% of the viral capsid, while VP2 protein corre-sponds to more than 95%.[2] B19 only infects humans, and its transmission occurs mainly by respiratory and transpla-cental via. The transmission of B19 may occur occasionally, possibly through blood and blood products transfusions[3] and organ transplants.[4]

B19 is the cause of erythema infectiosum (EI),[5] and is also responsible for conditions of severe anemia in patients with hemolytic diseases such as sickle cell anemia,[6,7] and bone marrow aplasia in immunocompromised hosts. [8,9] Further-more, allegedly B19 is charged as the main agent of non-im-mune hydrops fetalis, besides miscarriage and stillbirth.[10-12]

Some studies associate B19 to neurological diseases[13,14] and hearing loss,[15] and this viral infection can cause pri-marily manifestations that resemble those of autoimmune rheumatic diseases such as rashes, cytopenias, arthritis and autoantibodies.[16-19] This makes it difficult to distinguish be-tween B19 infection and autoimmune manifestations of the disease itself. At present, B19 is considered one of the pos-sible agents of RA [20-22] and SLE[23] in predisposed individuals.

Hedman and Franssila (2006) [21] reported that during the course of infection with B19, serum autoantibodies can be detected in some patients, as rheumatoid factor (RF), anti-neutrophil cytoplasm (ANCA), anti-nuclear (ANA), anti-DNA, antimitochondrial (anti-M), antiphospholipid (anti-PL), anti-Sm, anticardiolipin (aCL) and anticollagen autoantibodies. Other authors detected in the serum of patients with per-sistent B19 infection, peptides homologous to those found in viral proteins and human cytokeratins, which favors the development of autoimmunity.[24]

Although some authors reported high levels of B19 in-fection worldwide,[25,26] most studies on this virus in patients with rheumatic diseases are conducted in European and Asian countries. In Latvia, [27]an European country, a study evaluated the prevalence of B19 infection in patients with RA *versus* a control group of healthy blood donors, with anti-B19 (IgG and IgM) serology by enzyme immunoassay (ELISA) and by a search of viral DNA in patients' samples of plasma, peripheral blood leukocytes and cells of the synovial fluid, as well as in controls' plasma and peripheral blood leukocytes. The result was the detection of anti-B19 (IgG) in 79% of pa-tients' plasma samples and in 77.7% of controls, and of anti-B19 (IgM) in 24% of patients' plasma samples and in 16% of controls. Viral DNA was detected in 16% of patients' plasma samples and in 2.1% of controls ($p = 0.00086$), and in 18% of patients' leukocytes and in 4.3% of controls ($p = 0.0049$) . The presence of B19 infection among patients with active and in-active disease was similar. However, the presence of anti-B19 (IgM) was shown to correlate with complications in clinical manifestations.

In a Taiwan study[28] the authors investigated anti-B19 (IgG and IgM) antibodies and DNA in plasma and synovial fluid of RA patients and of healthy controls. The presence of anti-B19 (IgG and/or IgM) in plasma was positive in 93.6% of pa-tients and in 32.7% of controls ($p <0.001$), in 55.6% of samples of synovial fluid of patients and in 19.2% of samples from controls ($p = 0.005$). The viral DNA was positive in 30.6% of samples of plasma from patients and in 9.1% of controls ($p = 0.005$), and in 75.0% of synovial fluid samples of patients and in 26.9% of the controls ($p = 0.015$). Among patients with RA, a correlation between the presence of viral DNA and HLA DR4 was found.

In another study, it was demonstrated an association between presence of IgM anti-protein NS1 of B19 and cyclic citrullinated antipeptide IgG (anti-CCP) in patients with RA, particularly among those with persistent viral DNA in joint tissues. Moreover, the presence of anti-NS1 did not correlate with the activity index DAS 28.[29]

Due to a possible association between B19 infection and rheumatic diseases, and in view of the scarcity of studies on this virus in patients with RA and SLE in our scenario, we consider appropriate an investigation on this subject.

We also consider as relevant the evaluation of the staging of these diseases and the immune status in patients with RA and SLE affected by this viral infection, since the literature indicates the possibility of immunological changes caused by the virus.

Objective

To evaluate the frequency of anti-B19 (IgG and IgM) in patients with RA and SLE compared with healthy controls, and to evaluate the possible correlation of anti-B19 seropositivity with disease activity, activity indexes (DAS 28 and SLEDAI) and quality of life (HAQ).

Patients and methods

167 volunteers were included in this study: 57 patients with RA and 45 with SLE treated at the Department of Rheumatology, Hospital das Clínicas, Federal University of Goiás (UFG-HC), and a control group of 65 healthy volunteers. For inclusion in the study, patients had to fulfill the classification criteria for RA of the American College of Rheumatology (ACR),[30] or, for SLE,[31,32] could not present other rheumatic diseases, malignancies or any infectious disease, and should have > 18 years of age.

The activity of RA was assessed by Disease Activity Score 28 (DAS 28),[33] which considers active disease when its value exceeds 2.6, and quality of life was measured by the Health Assessment Questionnaire (HAQ).[34] The activity of SLE was assessed by Systemic Lupus Erythematosus Disease Activity Index (SLEDAI),[35] which considers the presence of active disease when the value is > 3.

The study of circulating anti-B19 antibodies (IgG and IgM) was performed by enzyme-linked immunosorbent assay (ELISA) with parvovirus B19 RIDASCREEN kit, with sensitivity of 91.3% for IgG and 91.7% for IgM, and with specificity of 97% for IgG and 93.8% for IgM, according to information from r-biopharm, the reagent manufacturer. In the study of anti-B19 (IgM) we employed a precipitant substance for removal of IgG antibodies and rheumatoid factor.

In statistical analysis, the chi square test, Fisher's exact test and logistic regression analysis were applied, using SPSS package version 15.0, considering as significant p values <0.05 and a confidence interval (CI) of 95%.

This study was reviewed and approved by the Research Ethics Committee at Hospital das Clínicas, Federal University of Goiás (UFG-CEP-HC), with the number 093/2010. All volunteers received due explanation on the procedures and signed the Informed Consent Form (ICF).

Results

Patients were aged 18 – 76 years with a mean of 42.74 ± 14.09 years. The controls were aged 18 – 64 years with a mean of 38.38 ± 13.42 years. Among the 102 patients, 79 (77.5%) had active disease, with 37 (46.8%) with SLE and 42 (53.2%) with RA. The mean SLEDAI score between patients with SLE in activity was 9.92 ± 5.32. DAS 28 was calculated for 35 patients with RA activity, with a mean of 5.03 ± 1.19. The value of HAQ for 33 of these patients was determined, with a mean of 1.51 ± 0.91.

The search for circulating anti-B19 IgG was positive in 49 (86.0%; CI 95% 77.0 – 95.0) RA patients, in 38 (84.4%; CI 95% 73, 9 – 95.0) SLE patients and in 40 (61.5%; CI 95% 49.7 – 73.4) controls (p = 0.002). The presence of anti-B19 (IgM) was observed in 3 (5.3%; CI 95% 0.0 – 11.1) RA patients, 7 (15.6%; CI 95% 5, 0 – 26.2) SLE patients and 1 (1.5%; CI 95% 0.0 – 4.5) control (p = 0.011) (Table 1).

The anti-B19 (IgG) reactivity was shown in 69 (87.3%; CI 95% 80 – 94.7) patients with active disease and in 18 (78.3%; CI 95% 61,4 – 95.1) with inactive disease (p = 0.222). The anti-B19 (IgM) reactivity occurred in 8 (10.1%; CI 95% 3.5 – 16.8) of patients with active disease and in 2 (8.7%; CI 95% 0.0 – 20.2) patients with inactive disease (p = 0.600) (Table 2).

In the evaluation of anti-B19 reactivity and of the index of activity in RA (DAS 28), it was observed that in those anti-B19 (IgG) reactive (n = 32) patients, the mean DAS 28 was 4.98 ± 1.15. In anti-B19 (IgG) nonreactive (n = 3) patients, the mean DAS 28 was 5.67 ± 1.65 (p = 0.340). When the anti-B19 reactivity (IgM) was evaluated, only one patient had this antibody, and the value of DAS 28 was 3.40. Among these anti-B19 IgM non-reactive (n = 34) patients, the mean DAS 28 was 5.08 ± 1.17 (p = 0.237) (Table 3).

The quality of life index (HAQ) was calculated for 33 patients with active disease. Among these patients, 29 had anti-B19 (IgG) reactive with a mean HAQ of 1.43 ± 0.92 and four had anti-B19 (IgG) non-reactive with a mean HAQ of 2.05 ± 0.71 (p = 0.216). Anti-B19 (IgM) reactive was observed in only one patient with HAQ = 3.40 and anti-B19 (IgM) non-reactive in 32, with a mean HAQ of 1.54 ± 0.90 (p = 0.293) (Table 4).

Among SLE patients with active disease (n = 37), anti-B19 (IgG) was reactive in 30 (81.1%) with a mean SLEDAI of 9.83 ± 5.04, and among those with anti-B19 (IgG) non-reactive (n = 7) (18.9%), the mean SLEDAI score was 9.94 ± 5.45 (p = 0.965).

Table 1 – Frequency of anti-B19 (IgG and IgM) in patients with RA and SLE and controls in Goiânia, Goiás, between August 2010 and August 2011.

Anti-B19 IgG	RA n (%) (CI 95%)	SLE n (%) (CI 95%)	Controls n (%) (CI 95%)	p
+	49 (86.0) (77.0 - 95.0)	38 (84.4) (73.9 – 95.0)	40 (61.5) (49.7 – 73.4)	
−	8 (14.0) (5.0 – 23.1)	7 (15.6) (5.0 – 26.1)	25 (38.5) (26.5 – 50.3)	
Total	57 (100.0)	45 (100.0)	65 (100.0)	0.002
Anti-B19 IgM				
+	3 (5.3) (0.0 – 11.1)	7 (15.6) (5.0 -26.7)	1 (1.5) (0.0 – 4.5)	
−	54 (94.7) (88.9 – 100.0)	38 (84.4) (73.9 – 95.0)	64 (98.5) (95.5 – 100.0)	
Total	57 (100.0)	45 (100.0)	65 (100.0)	0.011

Fisher exact test.
RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; B19, B19 parvovirus, IgG, Anti-B19 IgG; IgM, anti-B19 IgM; CI 95%, confidence interval 95%.

Seven patients had anti-B19 (IgM) reactive, with a mean SLE-DAI score of 9.63 ± 5.73. Among those with anti-B19 (IgM) non-reactive, the mean SLEDAI was 11.14 ± 5.28 (*p* = 0.496) (Table 5).

Discussion

This is the first Brazilian study on the frequency of anti-B19 in SLE and RA. In this study we investigated the presence of circulating antibodies in these patients, compared with the healthy population, and the possible influences of B19 infection in the clinical staging of these patients. In international publications, the inclusion of molecular studies reinforces the serological findings and points to evidence of the influence of this virus in the development of autoimmune diseases.

This study showed a high frequency of anti-B19 in the population evaluated, being greater among patients.

In this group of patients, the anti-B19 serology was not associated with presence of manifestations such as anemia, arthritis, neuropathy and thyroiditis, nor with the development of autoantibodies.

The anti-B19 reactivity (IgG and IgM) observed in patients with RA and SLE in our geographical region was similar to that found in studies of Kozireva et al.,[27] in Latvia, and of Chen et al.,[28] in Taiwan, both evaluating patients with RA. These findings of high frequency of anti-B19 in patients with rheumatic diseases may result from a greater propensity, of these patients, in acquire viral infections due to immunosuppression or by some characteristic of the immune system in these patients, making them more susceptible to infection with this virus. Also, we cannot rule out the possibility of this virus acting as a trigger for RA and SLE.

We are concerned about the fact of the persistence of viral DNA and the presence of IgM antibodies with respect to the diagnosis of infection, a relation with the autoimmune disease activity and the administration of immunosuppressive drugs. There is no definition about the risk of the presence of acute B19 infection and immunosuppressive therapy.

In the present study we found a correlation between anti-B19 (IgG) reactivity and the rheumatic diseases evaluated, similar to that observed by Chen et al.,[31] who, besides a correlation between presence of antibodies and disease, also noted a correlation between presence of viral DNA in plasma and in synovial fluid of RA patients. In the evaluation of anti-B19 reactivity (IgM), we noted a correlation only with SLE. The results found in this study were different from that observed by Kozireva et al.,[30] who showed no correlation between the frequency of anti-B19 (IgG and IgM) and RA antibodies, but showed correlation when evaluating the presence of viral DNA in plasma, in synovial fluid and in peripheral blood leukocytes.

The anti-B19 reactivity (IgG and IgM) in participants of the present study was not significantly associated with disease activity; this was also observed by Kozireva et al.[30] This result suggests that the presence of large amounts of antibodies of the IgG class, as demonstrated in the two studies, prevented

Table 2 – Frequency of anti-B19 (IgG and IgM) in patients with RA and SLE in activity in Goiânia, Goiás, between August 2010 and August 2011.

Anti-B19 IgG	Activity YES (CI 95%)	Activity NO (CI 95%)	*p*
+	69 (87.3) (80.0-94.7)	18 (78.3) (61.4-95.1)	
–	10 (12.7) (5.3-20.0)	5 (21.7) (4.9-38.6)	
Total	79 (100.0)	23 (100.0)	0.222
Anti-B19 IgM			
+	8 (10.1) (3.5-16.8)	2 (8.7) (0.0-20.2)	
–	71 (89.9) (83.2-96.5)	21 (91.3) (79.8-100.0)	
Total	79 (100.0)	23 (100.0)	0.600

Fisher exact test.
B19, B19 parvovirus; IgG, anti-B19 IgG; IgM, anti-B19 IgM; CI 95%, confidence interval 95%.

Table 3 – Frequency of anti-B19 (IgG and IgM) in patients with active RA and mean of DAS 28 in Goiânia, Goiás, between August 2010 and August 2011.

Anti-B19 IgG	n	DAS 28 Mean ± DP	*p*
+	32 (91.4)	4.98 +/- 1.15	
–	3 (8.6)	5.67 +/- 1.65	
Total	35 (100.0)	5.03 +/- 1.19	0.340
Anti-B19 IgM			
+	1 (2.9)	3.40	
–	34 (97.1)	5.08 +/- 1.17	
Total	35 (100.0)	5.03 +/- 1.19	0.237

Analysis of logistic regression.
DAS 28, Activity index for rheumatoid arthritis.

Table 4 – Frequency of anti-B19 (IgG and IgM) in patients with active RA and mean HAQ in Goiânia, Goiás, between August 2010 and August 2011.

Anti-B19 IgG	n	HAQ Mean ± DP	*p*
+	29 (87.9)	1.43 +/- 0.92	
–	4 (12.1)	2.05 +/ 0.71	
Total	33 (100.0)	1.51 +/- 0.91	0.216
Anti-B19 IgM			
+	1 (3.0)	0.30	
–	32 (97.0)	1.54 +/- 0.90	
Total	33 (100.0)	1.51 +/- 0.91	0.293

Analysis of logistic regression.
HAQ, Index of quality of life in rheumatoid arthritis.

Table 5 – Frequency of anti-B19 (IgG and IgM) in patients with active SLE and mean SLEDAI in Goiânia, Goiás, from August 2010 to August 2011.

Anti-B19 (IgG)	n	SLEDAI - mean ± DP	*p*
+	30 (81.1)	9.83 +/- 5.04	
–	7 (18.9)	9.94 +/- 5.45	
Total	37 (100.0)	9.92 +/- 5.32	0.965
Anti-B19 (IgM)			
+	7 (18.9)	9.63 +/- 5.73	
–	30 (81.1)	11.14 +/- 5.28	
Total	37 (100.0)	9.92 +/- 5.32	0.496

Analysis of logistic regression.
SLEDAI, Index of activity in systemic lupus erythematosus.

that the virus, if present, alter the course of disease, and the disease was observed due to immune status of the individual patient or activity other factors not assessed, and not due to the presence of the virus in patients.

In the present study we found no correlation between anti-B19 (IgG and IgM) reactivity and activity indexes (DAS 28 and SLEDAI) and quality of life (HAQ). These findings demonstrate that the anti-B19 reactivities (IgG and IgM), indicators of previous and acute infection, respectively, did not correlate with clinical and laboratory aspects able to modify the indexes DAS 28, HAQ and SLEDAI. It is also possible that this high frequency of anti-B19 (IgG) reveal only that the studied population is constantly exposed to the presence of the virus without, however, apparent infection.

In a case report conducted by Suzuki et al.,[36] the authors reported the presence of B19 infection in a patient with SLE; its manifestation was similar to active disease, pointing in this publication the occurrence of common symptoms of acute infection and disease activity.

Studies published by Pavlovic et al.[23] and Lunardi et al.[24] suggest the possibility of autoimmunity after B19 infection, due to similarities between molecules of this virus and host molecules. Furthermore, the work of Lunardi et al.[24] suggested that manifestations similar to RA in patients infected with B19 may occur by deposition of viral antigen-antibody complexes in these patients' joints.

In the present study, low reactivity anti-B19 (IgM) was observed, indicating recent infection, both among patients and controls. Although most patients with anti-B19 reactivity (IgM) exhibited disease activity, it was not possible to identify changes in these patients that could be attributed specifically to the viral action. On the other hand, acute infection, identified by the presence of anti-B19 (IgM), may have favored the reactivation of disease. Similar findings were observed by Hsu and Tsai,[37] but with different findings in Kerr and Cuniff.[38]

In this study, we noted that the frequency of anti-B19 (IgG) among controls, a healthy population, was similar to that found in Chilean blood donors,[39] and higher than that observed in women of reproductive age in Goiânia, Goiás, Brazil.[40] These findings indicate that the frequency of prior infection in the healthy population in our region is within the patterns observed in the literature.

However , the finding of a higher frequency of reactivity observed among controls, compared with the study of Rios (2008),[40] may be associated with a higher age group than the observed in the volunteers in our study. Another possibility is the constant presence of the volunteers in this study in a hospital setting, since they were mainly recruited among caregivers and blood donors. Also, we cannot rule out the different characteristics of the evaluated serum samples, since in our study we used freshly harvested samples, unlike the Rios study, who analyzed samples of sera bank.

Conclusion

In the present study, we demonstrated that the analyzed population is exposed to infection by B19; this finding demands attention with its manifestations, especially among immunosuppressed patients at greater risk of acquiring viral infections.

Conflicts of interest

The authors declare no conflicts of interest.

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