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ASSOCIATION BETWEEN HUMAN PARVOVIRUS B19 AND ARTHROPATHY IN BELÉM, PARÁ, NORTH BRAZIL

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SUMMARY

A total of 220 patients with arthropathy were selected in Belém, Pará between January 1994 and December 2000, and screened for the presence of human parvovirus B19 IgM and IgG antibodies by enzyme-linked immunosorbent assay (ELISA). A subgroup (n = 132) of patients with high levels of antibodies (either IgM+/IgG+ or IgM-/IgG+) were examined for the presence of DNA by polymerase chain reaction/nested PCR. Recent/active infection (detection of IgM and/or IgG-specific antibodies and presence of viral DNA) was identified in 47.7% of the 132 individuals with arthropathy. In our study, women were significantly more affected (59.7%) than men (35.4%) (P = 0.0006). The age group of 11-20 years (84.6%), among female patients, and 21-30 years (42.1%), among male, were those with the highest incidence rates. The analysis of the temporal distribution of B19-associated arthropaties showed a cyclic pattern, with peak incidence rates occuring at 3-5 year intervals. Significant diference (P = 0.01) was observed when comparing both the highest (39.0%) and the lowest (11.0%) seropositivity rates for the years of 1995 and 2000, respectively. The interfalangial joints of hands and feet were mostly affected, with 50.0% and 48.0% of cases among both women and men, respectively. In a smaller proportion, other joints such as those of knee, ankle, pulse and shoulder were affected. As for the duration, symptoms lasted 1 to 5 days in 54.0% of the individuals, whereas in 46.0% of them the disease lasted 6-10 days, if considered the subgroup (n = 63) of patients with recent/active infection by parvovirus B19. In our study, joint clinical manifestations occurred symmetrically. Our results indicate that B19 may be an important agent of arthropathies in our region, and this underscores the need for specific laboratory diagnosis when treating patients suffering from acute arthropathy, mainly pregnant women.

KEYWORDS: Parvovirus B19; Acute arthropathy.

INTRODUCTION

Human parvovirus B19, discovered by COSSART *et al.*[15] , belongs to the family Parvoviridae, genus Erytrovirus[39]. The B19 transmission occurs mainly through respiratory secretions following human-to-human close contacts[4,50]. The B19 infection is quite common, affecting children and adults, often being asymptomatic[13,53]. The erythema infectiosum (EI)[7] is the most common clinical presentation of the B19 infection in children. In adults, the primary B19 infection has been associated with arthropathy, transient aplastic crises (TAC) in patients suffering from chronic haemolytic anemia, and chronic anemia in immunocompromised patients. Hydrops fetalis may develop as a consequence of infection during the second trimester of the pregnancy[11,16,42,45,52].

Several viral agents have been implicated in the occurrence of the acute and chronic arthropathies. In the Amazon region, arthropathy is a common finding in rubella, arboviral diseases (ex.: Oropouche and Mayaro fevers), Epstein-Barr virus infection and cytomegalovirus infection[1,23,38,51]. Among of the parasitic and bacterial agents, *Toxoplasma gondii* and *Streptoccocus* species may also cause arthropathy[19,31].

The pathogenesis of B19 arthropathy needs to be fully elucidated. Previous studies support the assumption that the joint lesions are associated with immune complexes[40,47]. In addition, the tissue joint lysis caused by parvovirus B19 has been postulated[33]. The chronic joint lesions has been associated with persistence of the viral agent in the tissue and synovial fluid[20,34,35].

Several studies conducted in temperate countries[2,7,10,24,36,40,44,47] have reported the joint involvement in association with recent/active B19 infections, with rates ranging from 30.0 to 59.0% among male and female adult patients, respectively. Furthermore, joint involvement has been reported in 8.0% children of both sexes. In tropical climate countries, like Brazil, there have been a few reports associating these viral agent with cases of arthropathy. Overall, these studies[37,38] have shown that arthropathy is present among individuals with exanthematous illness, namely E.I, and the positivity rates usually range from 10.0 to 40.0% in men and women, respectively. It is therefore of our interest to improve our knowledge on the epidemiology/clinical features of parvovirus B19 infection in our region focussing on its potential for developing arthropathies.

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MATERIAL AND METHODS

The study was conducted in Belém, Pará between January, 1994 and December, 2000. A total of 220 blood samples were collected from individuals with arthropathies (arthritis and/or arthralgy) at the Virology Section of "Instituto Evandro Chagas". This subgroup of patients (n = 220) was selected from 3,000 individuals with arthropathies who tested negative for the following agents: measles, rubella, cytomegalovirus, Epstein-Barr virus, arbovirus (Mayaro, Oropouche and dengue), *Toxoplasma gondii* and *Streptococcus*. Of these, 114 patients were female and 106 were male, with ages ranging from 2 to 68 years (mean age, 35 years). The blood samples were collected by antecubital venepuncture. Sera were kept at - 20°C until processing.

The detection of IgM and IgG antibodies to parvovirus B19 was made using a commercial enzyme-linked immunosorbent assay (ELISA) developed by DENKA SEIKEN™ (Tokyo, Japan). This is an assay that includes a solid-phase multiple-wells system coated with anti-human IgM monoclonal antibody, as previously described[6,43]. Lyophilized, purified human parvovirus B19 recombinant antigen was used. Sensitivity and specificity of this assay have been found to be 100% and 97%, respectively, as based on its comparison with the (gold standard) radioimmunoassay[14]. Sera were tested at a (single) dilution of 1:200, according to the manufacturer. The results of ELISA were calculated dividing optical density (O.D) values of serum samples by the mean absorbance of cut-off. The serum samples with IgM antibodies with absorbance ≥ 1.00 were regarded as positive.

A subgroup (n = 132) of individuals with B19 IgM+/IgG+ antibodies (absorbance, ≥ 1.00) and IgM-/IgG+ (O.D of serum samples >5 times the mean O.D of cut-off) were selected for the B19 DNA detection, using the polymerase chain reaction (PCR). The PCR technique was performed in two steps, essentially as reported before[18,32]. First, amplification was done using a mixture of external oligonucleotide primers (P1 and P6), followed by a second amplification (the nested PCR) that involved a mixture of the internal primers P2 and P5. The B19 recent/active infection was defined as the presence of IgM+ and/or IgG specific antibodies plus viral DNA detection in this subgroup (n = 132) of selected individuals. Conventional ELISA and immunofluorescence indirect assays were used for the detection of both IgM and IgG antibodies to rubella, measles, Epstein-Barr virus, cytomegalovirus and *Toxoplasma gondii*, as previously reported[8,12,17,25,29]. Serum specimens were also tested by haemagglutination-inhibition (HI), as described before[46], for the determination of antibodies to Mayaro, Oropouche and dengue viruses, which are well-know viral agents of exanthematous illnesses in the Amazon region. The latex assay was used for the detection of the antiestreptolysin O, for the diagnosis of infection by *Streptococcus* as a possible cause of rheumatic fever, as previously described[30], in a subgroup (n = 12) of patients that presented with tonsillar pharyngitis.

The data were analysed using the EPI-INFO software, version 6.0 (Atlanta, GA, USA). Rates were compared by using the Mantel-Haenszel chi square test of association or Fisher's exact test, as appropriate. Significance was defined as $P < 0.05$.

RESULTS

Nineteen (8.6%) of the 220 patients were IgM and IgG positive (IgM+/IgG+) to B19 (Table 1). One hundred and sixty nine patients (76.8%) were identified as being immune, since they were IgM-/IgG+, and 32 (14.6%) of them had neither IgM nor IgG antibodies (IgM-/IgG-). The results of PCR and nested PCR are shown in the Table 2. The viral DNA was detected in 17 (12.9%) and 46 (34.8%) of the 132 patients who were either IgM+/IgG+ (n = 19) and IgM-/IgG+ (n = 113), respectively. The detection of B19 DNA among female and male patients were 59.7% and 35.4%, respectively (Table 2). Significant difference was observed when comparing the joint involvement in the subjects of both sexes: $P = 0.0006$ (a vs b) and $P = 0.005$ (c vs d) for the age groups 11-20 years and the subtotal, respectively (Table 2). In the children ≤ 10 years of age, B19 DNA positive rates ranged from 50.0 to 75.0%. The age groups 11-20 years (84.6%), among female patients, and 21-30 years (42.1%), among male, were those with the highest incidence rates. Significant difference was observed when comparing these two age groups ($P = 0.01$).

The analysis of the temporal distribution of B19-associated arthropathies shows a cyclic pattern, with peak incidence rates at 3-5 years intervals. Significant difference ($P = 0.01$) was observed when comparing both the highest (39.0%) and the lowest (11.0%) seropositivity rates, corresponding to 1995 and 2000, respectively (Fig. 1).

The interfalangial joints of hands and feet were mostly affected, with 50.0% and 48.0% (data not shown in Fig. 2) of cases among both women and men, respectively. In a smaller proportion of patients, other

Table 1
Detection of antibodies to parvovirus B19 in patients suffering from arthropathies, Belém, Pará, 1994-2000.

Sex/age (years)		Total tested	Serological status (%)		
			IgM+/IgG+	IgM-/IgG+	IgM-/IgG-
≤ 10	F	19	3 (15.8)	11 (57.9)	5 (26.3)
	M	19	0 (0)	14 (73.7)	5 (26.3)
11-20	F	28	1 (3.6)	21 (75.0)	6 (21.4)
	M	27	2 (7.4)	19 (70.4)	6 (22.2)
21-30	F	26	4 (15.4)	20 (76.9)	2 (7.7)
	M	21	3 (14.3)	17 (80.9)	1 (4.8)
31-40	F	20	3 (15.0)	17 (85.0)	0 (0)
	M	19	0 (0)	17 (89.5)	2 (10.5)
> 40	F	21	2 (9.5)	17 (81.0)	2 (9.5)
	M	20	1 (5.0)	16 (80.0)	3 (15.0)
Subtotal	F	114	13 (11.4)	86 (75.4)	15 (13.2)
	M	106	6 (5.7)	83 (78.3)	17 (16.0)
Total		220	19 (8.6)	169 (76.3)	32 (14.6)

Table 2
Distribution of recent/active B19 infections associated with arthropathies, according to sex and age. Belém, Pará, 1994-2000.

Sex/age (years)	Total * tested	IgM+/IgG+ (%) DNA+	IgM+/IgG+ (%) DNA-	IgM-/IgG+** (%) DNA+	IgM-/IgG+** (%) DNA-
F ≤ 10	4	3 (75.0)	0 (0)	0 (0)	1 (25.0)
M	8	0 (0)	0 (0)	4 (50.0)	4 (50.0)
F 11-20	13	2 (15.4)	0 (0)	9 (69.2)[a]	2 (15.4)
M	15	0 (0)	1 (6.7)	3 (20.0)[b]	11 (73.3)
F 21-30	22	4 (18.2)	0 (0)	6 (27.3)	12 (54.5)
M	19	2 (10.5)	1 (5.3)	6 (31.6)	10 (52.6)
F 31 –40	19	3 (15.8)	0 (0)	8 (42.1)	8 (42.1)
M	12	0 (0)	0 (0)	5 (41.7)	7 (58.3)
F > 40	9	2 (22.2)	0 (0)	3 (33.3)	4 (44.5)
M	11	1 (9.1)	0 (0)	2 (18.2)	8 (72.7)
F Subtotal	67	14 (20.9)	0 (0)	26 (38.8)[c]	27 (40.3)
M	65	3 (4.6)	2 (3.1)	20 (30.8)[d]	40 (61.5)
Total	132	17 (12.9)	2 (1.5)	46 (34.8)	67 (50.8)

* A total of 88 serum samples not screened by PCR/ nested PCR .
** O.D of specimens, > 5 times that O.D mean of cut off.
[a vs b] Significant difference between the results (P = 0.0006).
[c vs d] Significant difference between the results (P = 0.005).

joints such as those of knee, ankle, pulse and shoulder were affected. As for the duration, symptoms lasted 1 to 5 days in 54.0% of the individuals, whereas in 46.0% of them the disease lasted 6-10 days, if considered the subgroup (n = 63) of patients with recent/active infection for the parvovirus B19. In our study, joint involvement occurred symmetrically (data not shown in Fig. 2).

Negative results were yielded when testing sera for antibodies to a variety of other pathogens that might be related to arthropathies in our region, including dengue virus.

DISCUSSION

The analysis of the serologic "status" in the group (n = 220) of subjects with arthropathies made it possible the selection of a subgroup (n = 132) of patients who had presented high IgM+/IgG+ and IgM- / IgG+ antibody levels for B19. Overall, 132 of these serum samples were examined by PCR/nested PCR techniques, according to previous

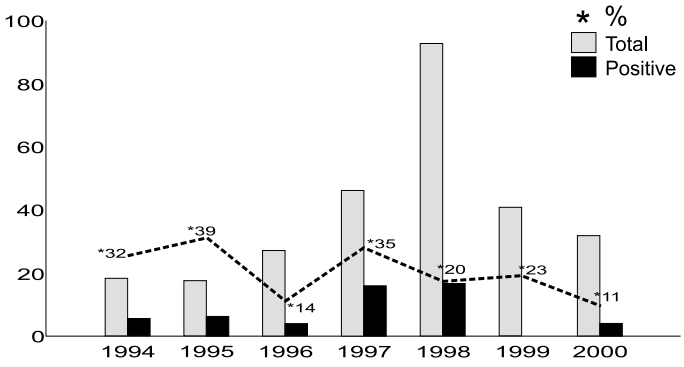

Fig. 1 - Temporal distribution of seropositivity to parvovirus B19 in patients suffering from arthropathies. Belém, Pará, 1994-2000.

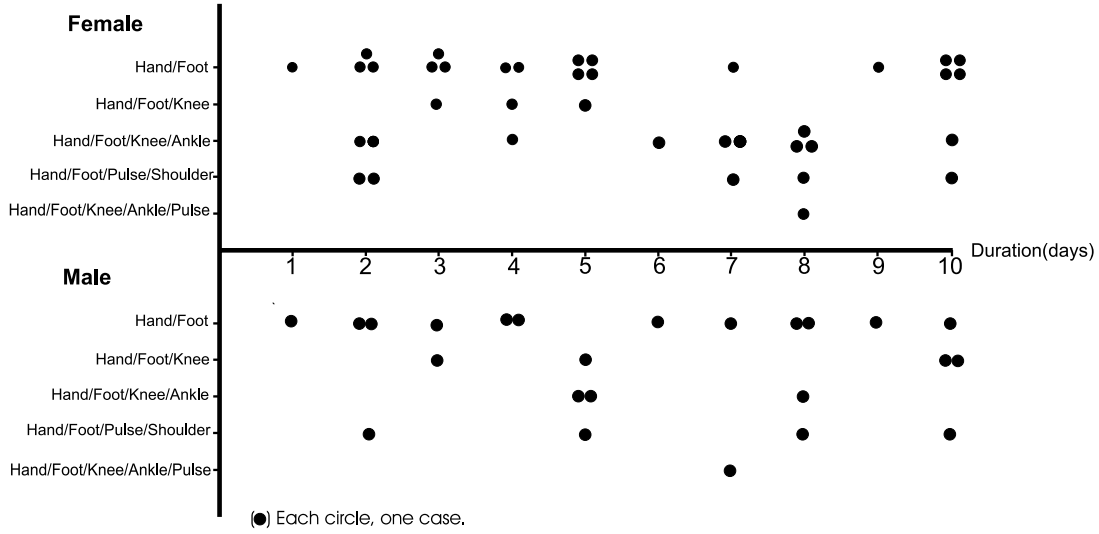

Fig. 2 - Anatomic localization and duration of the arthropathies associated with recent/active B19 infections, according to sex in 63 patients. Belém, Pará, 1994-2000.

studies[10,32]. These techniques present greater sensitivity than the ELISA, mainly in situations that require the diagnosis of recent/active B19 infection leading to joint manifestations[9,26]. This fact was confirmed by the results of this investigation, when comparing the number of recent/active infections detected by ELISA and those detected by nested PCR: significant difference, as indicated by P = 0.0001. The absence of IgM antibodies for B19 in sera doesn't rule out the possibility of recent/active infection, since these sera may have B19 DNA if it contains high levels of IgM-/IgG+ antibodies. This condition, observed in our study, has already been demonstrated by CASSINOTTI *et al*.[9]. The sera not examined (n = 88) by PCR/nested PCR were those showing either no B19 specific IgG or low levels of B19 specific IgG antibodies detected by ELISA. In this study, the arthropathies prevailed among female patients (c vs d, P = 0.005, Table 2), mainly among young women (a vs b, P = 0.0006). A smaller proportion of male adults were affected, and cases of polyarthritis and polyarthralgy also involved children < 10 years. The frequency of joint manifestations associated with parvovirus B19 infection in our investigation was similar to that recorded for adults of both sexes in temperate countries[24], with rates of positivity ranging from 30.0 to 59.0%. However, for the children aged < 10 years our rates were higher than they were for countries with temperate climate[7]. The explanation for this might be related to the rates of B19 primo-infections, recorded by FREITAS *et al.*[22], among children with ages < 5 years in Belém, Brazil, in general higher than those for temperate countries[5].

The temporal distribution of B19 infection throughout our study period support the cyclic pattern proposed for the occurrence B19 infections, as recorded by FREITAS *et al*.[21] in Belém, Pará, with peaks of viral activity at 3-5 year intervals. Of note, the high number of arthropathies recorded in 1998 were not associated with the B19 and other bacterial and/or parasitic agents investigated. This fact raises the possibility that pathogens not investigated in our study be associated with the disease, as demonstrated in others regions[37,41,48,49]. Because of situations like this, [36,38,40] it has been stressed the importance of making differential diagnosis with arthropathies due to other pathogens, so that proper therapeutic measure can be taken. In our study, interfalangial joints of hands and feet were mostly affected. Less often, other joints such as those of knee, ankle, pulse and shoulder were affected. The arthropathies associated with the recent/active B19 infection presented short duration (maximum of 10 days), symmetrical distribution and disappeared without sequelae. These clinical features have been recorded in previous studies[36,38]. In our study, the absence of chronic arthropathies associated with parvovirus B19, as previously described[34,36], could be explained by the fact that a low number of patients (n = 13) with chronic joint symptoms (lasting months or years) were enrolled in the present study. Therefore, arthropathies due to collagen or connective tissue diseases seemed not having prevailed among our study patients and there was no evidence that such cases were recent/active B19 infection.

In our study, arthralgy was more frequent than arthritis. The interfalangial joints (hands and feet) were more related arthralgy, mainly among women. These results were also reported in other studies[36,38]. Viruses other than B19, bacteria or parasitic agents capable to produce acute arthropathies in our region were ruled out as possible aetiological agents.[36,38]

In our investigation, the frequent joint manifestations associated with parvovirus B19, mainly among women, indicate the need for laboratorial diagnosis of this viral agent, therefore avoiding unproper treatment.

The arthritis/arthralgy in pregnant women may constitute an important indicator of B19 infection, known to be potentially hazardous for the concept[3,27,28].

RESUMO

Associação entre parvovírus B19 e artropatias em Belém, Pará, norte do Brasil

Um total de 220 indivíduos portadores de artropatias foi selecionado em Belém, Pará, entre janeiro de 1994 e dezembro de 2000 e, posteriormente, examinado com o propósito de se detectarem anticorpos IgM e IgG para o parvovírus B19, utilizando-se a técnica imunoenzimática (ELISA). Um subgrupo (n = 132) de indivíduos com amostras de soro apresentando altos níveis de anticorpos (IgM+/IgG+ e IgM-/IgG+) foi usado para detecção de DNA do B19 através da reação em cadeia da polimerase (PCR) e do "nested" PCR. Infecção recente/ativa (detecção de IgM e/ou IgG mais a presença de DNA viral) foi diagnosticada em 47,7% dos 132 indivíduos apresentando comprometimento das articulações. O sexo feminino foi mais afetado (59,7%) que o masculino (35,4%), com diferença estatisticamente significativa (P = 0,0006). Os grupos etários mais atingidos foram os de 11-20 anos (84,6%), no sexo feminino, e 21-30 anos (42,1%), no masculino. A análise da distribuição temporal mostrou um padrão cíclico, com períodos de maior e menor atividade viral que variam de 3 a 5 anos. Diferença estatisticamente significativa (P = 0,01) foi observada quando comparadas as freqüências de positividade mais alta (39,0%) e mais baixa (11,0%) para os anos de 1995 e 2000, respectivamente. As articulações mais atingidas foram, em ordem de freqüência, as interfalangianas de mãos e pés, com 50,0% e 48,0% para o sexo feminino e masculino, respectivamente. Em menor proporção outras articulações tais como as do joelho, tornozelo, pulso e ombro foram afetadas. Quanto à duração das manifestações articulares, 54,0% evoluíram por 1-5 dias, e 46,0% ao longo de 6-10 dias, considerando o subgrupo (n = 63) de indivíduos com infecção recente/ativa para o B19 em ambos os sexos. Em nosso estudo, o comprometimento das articulações apresentou caráter simétrico. Os resultados encontrados demonstraram o freqüente acometimento articular associado às infecções recentes/ativas por parvovírus B19, ressaltando a necessidade do diagnóstico laboratorial dessa virose, principalmente entre gestantes.

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