Clinical and Epidemiological Aspects of Human Parvovirus B19 Infection in an Urban Area in Brazil (Niterói City Area, State of Rio de Janeiro, Brazil)

Solange Artimos de Oliveira/+, Luiz Antonio Bastos Camacho*, Antonio Carlos de Medeiros Pereira, Tereza Filomena Faillace, Sérgio Setúbal, Jussara Pereira do Nascimento*****

Disciplina de Doenças Infecciosas e Parasitárias, Hospital Universitário Antonio Pedro, Rua Marques do Paraná 303, 2º. andar, 24030-210 Niterói, RJ, Brasil *Departamento de Epidemiologia, Escola Nacional de Saúde Pública-Fiocruz, RJ, Brasil **Policlínica Comunitária Santa Rosa, Fundação Municipal de Saúde de Niterói, Niterói, RJ, Brasil ***Instituto Biomédico, Universidade Federal Fluminense, Niterói, RJ and Departamento de Desenvolvimento Tecnológico, Biomanguinhos-Fiocruz, Rio de Janeiro, RJ, Brasil

This study was designed to analyse the clinical and epidemiological data from human parvovirus B19 cases in a six-year study of rash diseases conduct in an urban area in Brazil (Niterói city area, State of Rio de Janeiro). A total of 673 patients with acute rash diseases were seen at two primary health care units and at a general hospital. A clotted blood sample was collected from all subjects at the time of consultation. Forty-nine per cent (330 cases) of the patients were negative for dengue, rubella and measles IgM or for low avidity IgG to HHV-6. Of these 330, 105 (31.8%) were identified as IgM positive to parvovirus B19 by using an antibody capture EIA. During the study period, three distinct peaks of parvovirus infection were detected, suggesting that the disease appears to cycle in approximately 4-5 years. B19 infection was characterized by variable combinations of fever, flu-like symptoms, arthropathy, and gastrointestinal symptoms. Frequency of fever and arthropathy was substantially higher in adults, 75% [χ^2 (1 D.F.) = 11.39, p = 0.0007] and 62.5% [χ^2 (1 D.F.) = 29.89, p = 0.0000], respectively. "Slapped-cheek" appearance and reticular or lace-like rash were seen in only 30.1% of the children. No adult presented this typical rash. The lack of the typical rash pattern in a large proportion of parvovirus B19 and the similarity of clinical manifestations to other rash diseases, specially to rubella, highlight the difficulty of diagnosing B19 infection on clinical grounds alone.

Key words: human parvovirus B19 - diagnosis - IgM - epidemiology - clinical features - Niterói, Rio de Janeiro - Brazil

Human parvovirus B19, discovered by Cossart et al. (1975) in 1974, commonly infects children, causing erythema infectiosum, a mild rash illness characterized by a facial rash ("slapped-cheek") and a lacy, reticular, evanescent macular eruption over the trunk and proximal extremities (Anderson et al. 1983). Adults, particularly females, with erythema infectiosum, frequently present joint symptoms (Reid et al. 1985). Parvovirus B19 also causes transient aplastic crisis in patients with underlying hemolytic anemia (Pattison et al. 1981), persistent anemia in immunocompromised patients (Kurtzman et al. 1989) and hydrops fetalis and fetal loss during pregnancy (Brown et al. 1984).

Although the association between parvovirus B19 and erythema infectiosum has been established since 1983 (Anderson et al. 1983), reports on B19 infections have been scarce in Brazil. Notwithstanding, prevalence studies conducted by Nascimento et al. (1990), Freitas et al. (1993, 1999) have shown that the infection is widespread in some states of the country.

The objective of the present study is to analyze the clinical and epidemiological data from B19 cases in a six-year study of rash diseases conducted in the municipality of Niterói, State of Rio de Janeiro, Brazil. Analysis of the other rash diseases were presented elsewhere (Oliveira et al. 2001b).

PATIENTS AND METHODS

Study population - Data collection was conducted from January 1994 to December 1999. A total of 673 patients with acute rash diseases were seen at the two largest primary health care units (Policlínica Comunitária Santa Rosa and Centro de Saúde Carlos Antonio da Silva) and at a general hospital (Hospital Universitário Antonio Pedro) from the public network with a catchment comprising approximately 50% of the population of the metropolitan area of Niterói. A questionnaire was used to collect demographic, clinical and epidemiological data. Informed consent was obtained for participants and from the parents or guardians of patients younger than 18 years of age. The study protocol was approved by the hospital's Institutional Review Board.

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+Corresponding author. Fax: + 55-21-2719.7262. E-mail: artimos@vm.uff.br

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Laboratory tests - A clotted blood sample was collected from all subjects at the time of consultation. A second sample was also obtained between 7 and 10 days later from 29 patients. The samples were centrifuged and serum was separated and frozen at -20ºC until the serological analysis was performed. All serum samples were tested for the presence of anti-rubella IgM virus antibodies by using a commercial enzyme immunoassay (EIA) (Rubenostika IgM, Organon), for anti-measles virus IgM by using an antibody capture EIA developed at the Centers for Disease Control and Prevention (Atlanta, USA) (Hummel et al. 1992), and for anti-dengue virus IgM by using an in-house EIA (Kuno et al. 1987, Nogueira et al. 1992). Those specimens, negative for rubella, measles and dengue virus antibodies, were also tested for anti-human parvovirus B19 IgM using an antibody capture EIA (MACEIA) (Cubel et al. 1994, Nascimento et al. 1998). Primary infection with human herpesvirus type 6 (HHV-6) was diagnosed by an indirect immunofluorescence test for low avidity HHV-6 IgG (Ward et al. 1989).

Data (statistical) analysis - Age and sex distribution, clinical features and time of occurrence of cases of parvovirus B19 infection were analyzed and compared to those in other rash diseases investigated during the study. The study population was divided in age groups and patients with ≥ 15 years of age were considered as adults. The chi-squared test was used to compare proportions and $p < 0.05$ was considered statistically significant. Data were analyzed using Epi Info Version 6 (Dean et al. 1994).

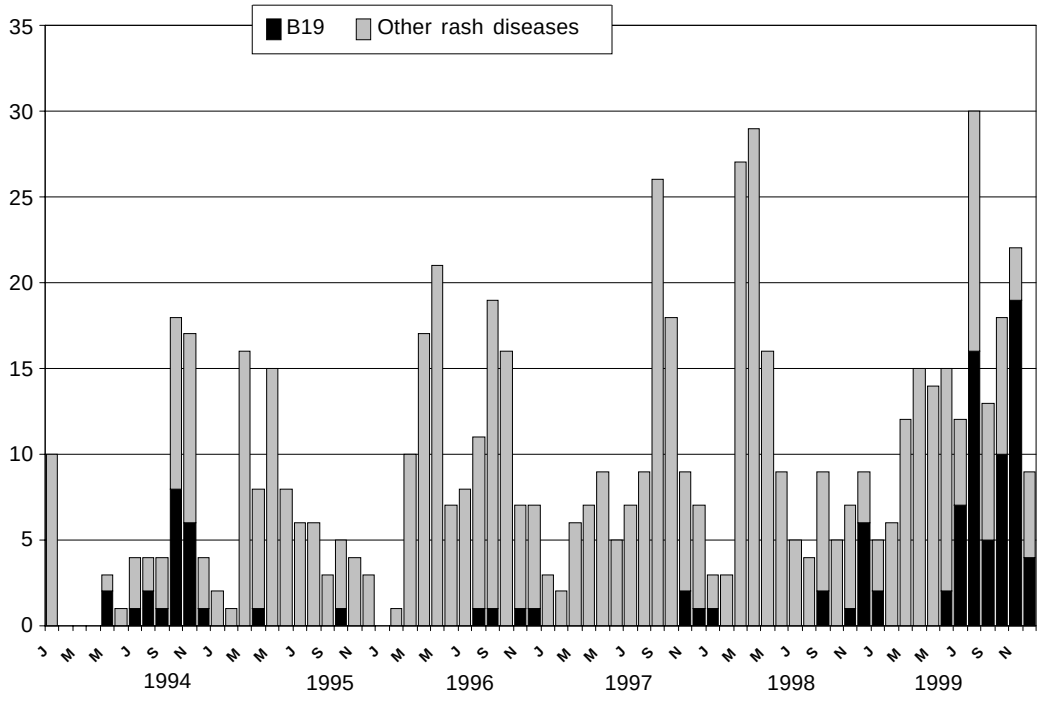
RESULTS

Forty-nine per cent (330 cases) of the patients were negative for dengue, rubella and measles IgM or for low avidity IgG to HHV-6. Of these, 105 (31.8%) were identified as IgM positive to parvovirus B19.

The distribution of the cases throughout the years (Figure), showed peaks of occurrence in which different rash diseases prevailed (Oliveira et al. 2001b). Parvovirus B19 infection showed a clear seasonal variation, being most frequent in late winter and spring (July-December): 92.4% of the cases were seen in the second semester of the study years. During the study period, three distinct peaks of parvovirus infection were detected, in the second part of 1994, 1998 and 1999. The 1999 peak of infection, was most prominent, comprising 60% (63/105) of the study cases. The proportion of parvovirus B19 infections among rash diseases varied from 23.1% to 58.7% in the second semester of the years of high incidence. In nonepidemic years, the proportion varied from 3.9% to 5.9%.

Most B19 cases (69.5%) occurred in children, whereas the other rash diseases had a more balanced age distribution (Table I). Male and female gender were equally distributed among parvovirus B19 infections as well as among other rash diseases, in the age group < 15 years old. However, in adult B19 cases there was a clear predominance of females (26/32 - 81.3%), which was less pronounced in other rash diseases (190/291 - 65.3%).

B19 infection was characterized by variable combinations of fever, flu-like symptoms, arthropathy, and gastrointestinal symptoms (Table II). Frequency of fever and arthropathy was substantially higher in adults, 75% [χ^2 (1 D.F.) = 11.39, p = 0.0007] and 62.5% [χ^2 (1 D.F.) = 29.89, p = 0.0000], respectively. Although pruritic rash was reported more frequently in adults (53.1%) than in the age group < 15 years old (35.6%), this difference was not statistically significant [χ^2 (1 D.F.) = 2.14, p = 0.1432].



Time distribution of human parvovirus cases and other rash diseases during the study period (January 1994 - December 1999).

TABLE I

Age and sex distribution of human parvovirus and other rash diseases cases

Age group (in years)	B19			Other rash diseases		
	Female	Male	Total n (%)	Female	Male	Total n (%)
< 1	-	-	-	22	29	51 (9)
1 - 4	9	5	14 (13.3)	59	48	107 (18.8)
5 - 9	21	21	42 (40)	41	28	69 (12.1)
10 -14	6	11	17 (16.2)	24	26	50 (8.8)
Subtotal	36	37	73 (69.5)	146	131	277 (48.8)
15 - 19	2	2	4 (3.8)	25	18	43 (7.6)
20 - 29	7	2	9 (8.6)	73	42	115 (20.2)
30 - 39	15	1	16 (15.2)	45	19	64 (11.3)
40 - 49	2	-	2 (1.9)	32	15	47 (8.3)
50 - 59	-	1	1 (0.9)	12	6	18 (3.2)
≥ 60	-	-	-	3	1	4 (0.7)
Subtotal	26	6	32 (30.5)	190	101	291 (51.2)
Total	62	43	105 (100)	336	232	568 (100)

TABLE II

Distribution of the most common signs and symptoms observed in human parvovirus and other rash diseases cases according to the age groups

Clinical features	Age group					
	B19			Other rash diseases		
	< 15 years (N = 73) n (%)	≥ 15 years (N = 32) n (%)	Total (N = 105) n (%)	< 15 years (N = 277) n (%)	≥ 15 years (N = 291) n (%)	Total (N = 568) n (%)
Fever	27 (37)	24 (75)	51 (48.6)	226 (81.6)	222 (76.3)	448 (78.9)
Pruritus	26 (35.6)	17 (53.1)	43 (41)	79 (28.5)	122 (41.9)	201 (35.4)
Coryza	21 (28.8)	10 (31.3)	31 (29.5)	08 (39)	89 (30.6)	197 (34.7)
Cough	20 (27.4)	10 (31.3)	30 (28.6)	116 (41.9)	97 (33.3)	213 (37.5)
Lymphadenopathy	19 (26)	8 (25)	27 (25.7)	122 (44)	115 (39.5)	237 (41.7)
Arthropathy	7 (9.6)	20 (62.5)	27 (25.7)	39 (14.1)	143 (49.1)	182 (32)
"Slapped-cheek" appearance	22 (30.1)	-	22 (21)	2 (0.7)	1 (0.3)	3 (0.5)
Reticular rash aspect	22 (30.1)	-	22 (21)	2 (0.7)	1 (0.3)	3 (0.5)
Rash recrudescent	18 (24.7)	1 (3.1)	19 (18.1)	2 (0.7)	4 (1.4)	6 (1.1)
Conjunctivitis	8 (11)	3 (9.4)	11 (10.5)	72 (26)	73 (25.1)	145 (25.5)
Purpuric spots	4 (5.5)	3 (9.4)	7 (6.7)	8 (2.9)	10 (3.4)	18 (3.2)
Headache	2 (2.7)	8 (25)	10 (9.5)	25 (9)	82 (28.2)	107 (18.8)

A large proportion of B19 cases presented with an erythematous maculopapular rash, whereas purpuric spots occurred only in seven (6.7%) cases. "Slapped-cheek" appearance and reticular or lace-like rash were seen in only 30.1% of the children. No adult presented this typical rash. Recrudescence of the rash (precipitated by exercise or heat) occurred in 18.1% of the cases and the vast majority (94.7%) was noted in children. The distribution and recrudescence of the rash showed the most striking contrasts between B19 cases and other rash diseases. Differences in the frequency of other symptoms were narrower and more difficult to interpret given the heterogeneity of the group of rash diseases.

Arthropathy was reported more frequently in adults with B19 infection than in adults with other rash diseases. In general, it was symmetrical, affecting preferentially the small joints of the hands, feet, knees and writs. Less frequently, ankles, elbows and cervical spine were affected. The acute polyarthropathy completely resolved within two weeks, but for one woman it lasted for three months.

Exposure to an exanthematic disease was reported by 46 (43.8%) patients and the most frequently reported site of transmission was home (71.7%). Acquisition of infection at school was reported only in children, occurring in 7 (21.2%) of the 33 cases with available data. Nine of the 13 women who had a known contact acquired the infection from their children. B19 infection was serologically confirmed in 27 (58.7%) of the contacts of the 46 patients that reported exposure to an exanthematic disease.

DISCUSSION

Although some studies (Freitas et al. 1988, 1990, 1993, Miranda et al. 1989, Nascimento et al. 1990, Cubel et al. 1992, Mielle et al. 1995) have been published in recent years, including preliminary results of the first year of this study (Oliveira et al. 1996), clinical and epidemiological aspects of parvovirus B19 are still not widely documented in Brazil. By systematically gathering data on acute rash diseases over the years we disclosed a seasonal pattern of the infection in a mid-sized urban area. During the study period, three distinct peaks of parvovirus infection were detected, suggesting that the disease appears to cycle in approximately 4-5 years. To our knowledge, this is the first time that the cyclical pattern of parvovirus B19 infection has been described in our country. Our finding is similar to those reported in the literature. Rates of infection increase every 3-4 years (Serjeant et al. 1993), although long-term cyclical variation, with peak activity of infection occurring every 4-7 years, is also described (Rodis 1999).

Different from other rash diseases for which specific control measures have been applied, parvovirus B19 incidence fluctuates without interference. Outbreaks of parvovirus B19 infection in temperate climates are more common in late winter and spring months, though cases may be recorded in any month (Cohen 1995). In our study, 92.4% of the cases were recorded during this season, similar to the report by Cubel et al. (1997) for other regions of Brazil. However, different findings were reported in the Amazon region by Miranda et al. (1989), who described higher incidence of the disease during the first half of the year, a season of heavy rainfall and high humidity in the North of our country.

The high proportion of schoolchildren (56.2%) among cases of B19 infections with rash is consistent with that reported in the literature (Brown 1997, Rodis 1999). Most of the B19 cases in adults (81.3%) occurred in females and 9 of the 13 women who had a known contact acquired the infection from their children. In a B19 outbreak, no significant differences in attack rates in males and females were observed by Woolf et al. (1989), although other authors have reported higher rates in females (Ager et al. 1966, Lauer et al. 1976). In a controlled clinical-epidemiological study, Woolf et al. (1989) found that women with B19 infection usually develop an acute arthropathy with rash, often accompanied by flu-like symptoms, whereas men present fewer symptoms, being a flu-like illness often the sole manifestation. Therefore, it is likely that the clear predominance of adult women in our study could be related to the exuberance of clinical manifestations of B19 infection in females and to the study design, which did not allow us to detect subclinical infections caused by the virus.

In general, clinical aspects presented by our patients were in agreement with those reported by other authors. Frequently, the disease was characterized by variable combinations of rash, flu-like symptoms and arthropathy. As described in the literature (Reid et al. 1985), less than 10% of the children had arthralgias or joint swelling, these complaints being substantially higher in adults (62.5%), particularly female adults. The arthropathy was symmetrical, affecting more often small joints of hands, feet, knees, wrists. Although usually brief and self-limiting, in 20% of affected women arthropathy may persist or recur for more than two months (Woolf et al. 1989, Brown 1997). In our study, prolonged joint complaints were seen only in 1 (3.8%) of the 26 adult females studied.

The classical slapped-cheek and lace-like rash have been reported more frequently in children, although they have also been described in adults (Woolf et al. 1989). In our study population, this typical rash pattern was found only in children and, among them, in only 30.1% of the cases. However, for all the other cases that formed our study group the frequency of these rash patterns was very small. This was the only meaningful contrast between B19 cases and the other rash diseases, which were rather heterogeneous. Another finding of this study was the frequency of fever in adults (75%), significantly greater than in children (37%). It is unclear to what extent this difference was real or resulted from ascertainment.

The lack of the typical rash pattern in a large proportion of parvovirus B19 and the similarity of clinical manifestations to other rash diseases, specially to rubella, highlight the difficulty of diagnosing B19 infection on clinical grounds alone. Moreover, parvovirus B19 infection shares the seasonal pattern with rubella and measles, i.e., late winter and spring, which makes clinical diagnosis even more difficult. In Brazil, because of the reduction in measles and rubella incidence rates after the introduction of national mass vaccination campaigns, parvovirus B19 infection has increased its relative importance in the surveillance of rash diseases (Cubel et al. 1997, Ministério da Saúde 1999, Oliveira et al. 2001a). However, without the aid of laboratory methods, the public health relevance is likely to be unnoticed. Symptomatic parvovirus B19 infections are likely to be misdiagnosed as one of the more widely known rash diseases. Our data indicate that the diagnosis of B19 infection should be considered more often, particularly in pregnant women, immunocompromised patients and individuals with underlying hemolytic disorders, as the infection may lead to serious adverse outcomes.

The findings from this study have relevant implications for the epidemiological surveillance of rash diseases. The outbreak of parvovirus B19 in 1999 was missed by routine surveillance, which was conceived mainly for measles control. As measles and rubella cases become rarer, the relative importance of parvovirus B19 and other exanthematic diseases will grow and may eventually have to be targeted by epidemiological surveillance.

Caution should be exercised in the interpretation of findings from an uncontrolled study of a non-probabilistic sample of cases gathered from health care settings and, thus, lacking statistical representativeness. Selective forces acting upon individuals, who ended up in this case series are only partly known. Our study group provided clinical and demographic descriptive data on the subset of parvovirus B19 infections, who presented a maculopapular cutaneous rash, and felt (or was thought to be) ill enough to seek medical care, and managed to get

it in the public health care network. They are likely to represent the most severe cases in the clinical spectrum of the disease. Therefore, the age, sex distribution and the frequency of symptoms may not apply to all those infected. Still, the distribution of cases over time, may be considered a rough representation of the occurrence of the infection in that population, which was substantially covered by the health care units where study participants were recruited.

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