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HUMAN PARVOVIRUS B19 INFECTION: CLINICAL AND EPIDEMIOLOGICAL STUDY OF 24 CASES

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SUMMARY

From March 1994 to November 1995 24 cases of human parvovirus B19 infection were seen at the Infectious Diseases Department of the Hospital Universitário Antônio Pedro, Niterói – RJ. Serum samples for IgM detection (capture enzyme immunoassay) were positive from the 1st to the 27th day after the onset of the exathema. The classical features of erythema infectiosum (slapped cheecked syndrome) were observed in 8 (33.3%) cases all of them children. Eight patients (6 adults and 2 children) presented a symmetrical polyartropathy, seen more frequently in women.

These results show that B19 infection diagnosis is difficult when the disease does not present the classical features and because of the frequent involvement of the joints this infection should be considered in the differential diagnosis of early rheumatoid arthritis.

KEYWORDS: Human parvovirus B19 infection; Exanthema; Arthropathy.

INTRODUCTION

Human parvovirus B19 was first described in 1975 by COSSART et al.[6] while screening serum from healthy blood donors for hepatitis B virus. Since that time parvovirus has been implicated as the causative agent for a range of diseases in humans. It commonly infects children, causing a benign, self limited illness: the erythema infectiosum or fifth disease[2,5]. However, when adults, specially women, are infected, they may often develop acute arthritis[5,33]. The virus also induces aplastic crisis in patients with hemolytic anemias, and prolonged anemia and neutropenia in immunocompromised patients[16]. In pregnant women, B19 can cross the placenta, infect the fetus, and cause miscarriage and hydropsis fetalis[3,5]. On the other hand, many B19 virus infections are asymptomatic[26].

In Brazil, B19 infections were first diagnosed in healthy blood donor in Rio de Janeiro[7] and in erithema infectiosum patients in Belém[18]. Prevalence studies done by FREITAS et al.[14] and NASCIMENTO et al.[24] showed that the infection is widespread in Belém and Rio de Janeiro respectively.

This paper reports the results of a study evaluating the clinical and epidemiological findings presented by B19 cases attending the Infectious Diseases Department of a large University Hospital.

MATERIAL AND METHODS

Study population

From January 1994 to December 1995 a prospective study of etiologic investigation of exanthematic diseases

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was conducted at the Infectious Diseases Department of the Hospital Universitário Antonio Pedro, Niterói, RJ. A total of 148 patients were seen and 59 of them were serologically negative for measles, rubella and dengue IgM. Of these, 23 were identified as being IgM positive. Another case of B19 infection who presented arthropathy without exanthem during a family outbreak was also included in this study.

A questionnaire containing personal data, clinical and epidemiological findings was designed for the exanthematic disease study. The study population was divided in age groups and patients with ≥15 years of age were considered adults.

Blood sample collection

One blood sample for serology obtained by venepuncture was drawn from each patient. A second sample was also obtained from three patients. After centrifugation the sera were stored at -20° C until analyzed.

Laboratory tests

In order to diagnose recent B19 infection serum samples were tested for the presence of anti-B19 IgM by using an antibody capture EIA (MACEIA)[8]. Dot – blot hybridization for detection of B19 DNA was performed as described by MORI et al.[19]. Anti B19 – IgG was detected by a direct EIA[9].

RESULTS

During the study period 24 patients with recent human parvovirus infection were seen. The laboratory findings are shown in Table 1. Independently of the number of the days after the onset of the exanthema, all patients had anti-B19 IgM and IgG in their sera, even the ones with paired sera. No B19 DNA was found in any sera.

TABLE 1
Laboratory findings for 24 cases of B19 infection

	Days after exanthema onset						
Laboratory tests	1	2	3	4	5-15	16-27	Total
MACEIA +	4	3	2	5	6	5	27
IgG EIA +	4	3	2	5	6	5	27

Notes: a) For three cases a second sample was obtained.
b) Dot blot hybridization was negative for all samples.

The median age was 12.7 years (range, 2 to 36 years) and 41.7% of the cases were in children between 5-9 years of age. An analysis of B19 infection according to age and sex is given in Table 2. This shows that the infection was equally distributed between males and females in children under 15 years old. However, in the age group ≥15 years there was a clear predominance of females. The infection occcurred more frequently during the second semester of the year (87.5% – peak months: October and November). The great majority of the cases (91.7%) were seen in the first year of the study.

TABLE 2
Distribution by age and sex of 24 B19 cases investigated in the Municipality of Niterói, R.J.

Age distribution (in years)	Male	Female	Total	%
1-4	1	2	3	12.5
5-9	5	5	10	41.7
10-14	2	2	4	16.6
≥ 15	1	6	7	29.2
Total	9 (37.5%)	15 (62.5%)	24 (100.0%)	-

A possible source of infection (exposure to exanthematic disease) were identified in 14 (58.3%) patients. B19 infection was serologically confirmed in 71.4% of the contacts. The most frequently reported sites of transmission were: home – 7 cases; school – 6 cases and neighbourhood – 1 case. Four of the 7 adults studied acquired the infection from their children.

The studied cases presented an illness characterized by variable combinations of exanthema, flulike symptoms (cough, coryza, headache), arthropathy, and fever (Table 3). The classical features of erythema infectiosum (slapped cheeked syndrome) was observed in 8 (33.3%) cases of the 24 analyzed, and only in children. The other studied cases presented a clinical syndrome difficult to be recognized based only on clinical grounds. Occipital, posterior auricular, and/or cervical lymphadenopathy was detected in 4 cases (16.7%).

TABLE 3
Distribution of the most common signs and symptoms observed in the 24 cases of B19 infection

Signs and symptoms	N	%
Exanthema	23	95.8
Fever	11	45.8
Cough	7	29.2
Coryza	7	29.2
Conjunctivitis	7	29.2
Polyarthropathy	8	33.3
Lymphadenopathy	4	16.7
Headache	3	12.5

Eight patients (33.3%) (6 adults and 2 children) described a symmetrical polyarthropathy, seen more frequently in women (6 cases) . The onset was acute and the joints more affected were: small joints of the hands and feet (6 cases); knees (6 cases); shoulders (3 cases); cervical spine (3 cases). Other joints, as ankles and elbows (2 cases each), and wrists (1 case) were also affected. In 6 patients the joint pains were accompanied by stiffness and swelling and this was most pronounced in the small joints of the hands (6 cases). Arthritis was less observed in the joints of the feet (3 cases), knees (3 cases), elbows (2 cases), and wrist (1 case). One of the patients (34 years old man) had no other symptom apart from the polyarthropathy. The interval between development of the rash and onset of the joint symptoms varied between one and five days. The acute polyarthropathy completely resolved within two weeks in all patients.

Twenty-three (95.8%) patients reported a maculopapular rash, most frequently generalized. The rash started on the face in 14 (60.9%) cases and it was pruritic in only 3 (13%) cases. The rash initially lasted from 3 to 7 days, but it was recrudescent, mainly precipitated by heat or exercises, in 6 (26.1%) cases (Table 4). The total duration of the exanthema did not last more than 10 days. The reticular aspect was observed in 9 (39.1%) patients, mostly when the rash was clearing.

TABLE 4
Pattern of the exanthema presented by the 23 cases of B19 infection

Exanthema	N	%
Maculopapular	23	100.0
Generalized	21	91.3
Onset of the rash		
Face	14	60.9
Limbs	6	26.1
Trunk	3	13.0
Reticular aspect	9	39.1
"Slapped – cheek" appearance	8	34.8
Recrudescent with exercises/heat	6	26.1
Pruritus	3	13.0

FAMILY OUTBREAK

A six-year-old girl was seen on 24 October 1994 with a low fever (37.5° C) and a symmetrical painful polyarthropathy affecting the small joints of the hands and feet, shoulders and cervical spine. Stiffness and swelling were described on her hands and feet. The next day she developed an itchy maculopapular exanthema that had started on her legs and spread to her trunk and arms. On her extremities the rash presented reticular aspect. At first, her disease was diagnosed as an early form of rheumatoid arthritis. Ten days later, while the laboratory tests were being performed, her parents and her brother developed episodes of rash and arthropathy: Father (34 years old) – joint pains involving his shoulders, cervical spine and small joints of the feet and hands associated with stiffness and swelling of the latter; Mother (31 years old) – symmetrical arthritis of her knees, ankles and small joints of the feet associated with maculopapular rash only on her legs; Brother (7 years old) – flulike symptoms (cough, coryza and conjuctivitis) followed by a bright red cheek rash and lacelike maculopapular rash over his body. None of the secondary cases had fever. Laboratory studies were negative for rheumathoid arthritis in the first case and IgM human parvovirus antibodies were detected in blood samples drawn from the whole family.

DISCUSSION

Although widely reported in the literature, clinical and epidemiological aspects of human parvovirus B19 infections are still scarcely described in Brazil[10,12,13,17,18]. This report presents a detailed description of these characteristics in 24 cases of erythema infectiosum and/or polyarthropathy.

According to COHEN[5] outbreaks of erythema infectiosum usually occur in winter or spring, though cases may be recorded in any month. In our study 87.5% of the cases were also seen during this period, October and November being the peak months. Our results are different from the findings of MIRANDA et al.[18]. These authors, studying "fifth disease" cases (based on clinical evidence) in the Amazon region, verified higher incidence of the disease during the first half of the year, period when the highest rainfall and humidity are registered.

COHEN[5], based on studies carried out in Britain, also suggests B19 epidemic may occur in intervals of two years. Such fact seems to have happened along the period of this study since the great majority of the cases (91.7%) were seen in the first year of the research. Nevertheless as B19 infection epidemiology is not well known in our country more studies must be done to confirm this fact.

Some studies[2,11,32] have shown that children aged six to ten years are the most affected age group by fifth disease. Another peak of the infection, smaller than the first, occurs in adults, especially in women[4], probably due to a high exposure to children of that age[4,14]. Another explanation for the female excess in adult cases may be related to a superior immune response in the women, since the exanthema and the joint lesions appear to be antibody

mediated[4,27]. We have found similar results since the most affected age groups were children aged five to nine years old (41.7%), and adults (29.2%). In addition, among the adults there was a clear predominance of female patients. Also, contact with their infected children was an important source of infection for the adults.

In contrast to the situation of sickle-cell patients with fifth disease, where very high concentrations of B19 parvovirus (more than 10^8 particles/ml blood) are found, in normal individuals viremia is usually absent at the time of clinical manifestations[10,34]. The appearance of specific symptoms (rash, arthralgia) coincides with the presence of antibodies in the circulation and seldom is associated with the presence of virus in serum[16]. An immune-mediated mechanism may be the possible cause of these symptoms[30]. According to this fact, in none of our cases B19 DNA was found by dot-blot hybridization whereas IgG and IgM antibodies were detected in all of them from one to 27 days after the onset of the clinical manifestations. Studies using DNA amplification by polymerase chain reaction (PCR) have shown that B19 DNA can be detected in the blood up to six months after acute infection[21].

Although outbreaks of fifth disease may be recognized on clinical or epidemiological grounds, sporadic cases of the disease do not always present classical features[20]. Frequently this infection is mistaken for rubella, measles or another exanthema. Thus, laboratory confirmation is therefore important for exanthematic diseases surveillance and to establish an accurate diagnosis of the range of diseases caused by B19 infection[5].

As described in literature[15,28,33], in this report the majority of the cases studied developed a clinical syndrome, characterized by variable combinations of exanthema, flulike symptoms and arthropathy, difficult to be recognized based only on clinical grounds. The characteristic cheek rash of fifth disease (slapped cheek syndrome) and other typical patterns of the exanthema as reticular aspect and recrudescence with exercises or heat were seen only in children, and even so only in some of them.

Acute arthropathy is a common presentation of B19 infection in adults, especially in women[5,28,33]. Despite the frequent involvement of the joints, as many as 80% of the cases[1,2], they are not often recognized. Occasionally the arthropathy may occur in the absence of other symptoms or just with a non-specific rash, as found in this report, which makes the etiologic diagnosis still more difficult. According to COHEN[5] B19 arthropathy usually resolves in a few weeks, but 10% of women with B19 infection develop joint symptoms lasting more than two months. In some cases these symptoms may persist for more than four years[33].

The pathogenesis of this chronic arthritis is not completely understood since histologically no inflammatory response has been detected in the joints[22,33]. Moreover, evidence that B19 virus may persist in the synovium causing chronic lesion[29] has not been confirmed[25]. As it was seen in this report, some cases may be wrongly diagnosed as rheumatoid arthritis since some patients with B19 arthropathy fulfill the diagnostic criteria for this disease[33]. Thus, B19 infection should be considered in the differential diagnosis of early onset rheumatoid arthritis[5].

In general B19 arthropathy is symmetrical, affecting preferentially the same joints of the hands and feet, knees, wrists, elbows, shoulders, and cervical spine[5,23,33]. Frequently, joint pain is accompanied by stiffness and swelling and in many cases the arthritis may be severe enough to cause absence from work[15]. Our results are similar to those related by these authors. The patients presented a symmetrical polyarthropathy seen more commonly in female adults. The joints more affected were small joints of the hands and feet, knees, shoulders, wrists, and cervical spine. Although there are some reports about the persistence of joint symptoms[5,28], in some cases for months or years, in our cases the acute polyarthropathy completely resolved within two weeks in all patients.

B19 infection diagnosis is difficult when the disease does not present the classical fifth disease features. The family story presented here illustrates these difficulties and shows the importance of looking for more adult cases in families of children with fifth disease. Moreover, although B19 acute arthropathy is more frequently seen in adults, it may affect children and make the diagnosis still more difficult.

RESUMO

Parvovirose humana: estudo clínico e epidemiológico de 24 casos

No período de maio / 94 a novembro / 95, 24 casos de parvovirose humana foram atendidos no Serviço de Doenças Infecciosas e Parasitárias do Hospital Universitário Antonio Pedro, Niterói – RJ. Amostras sangüíneas para a detecção de IgM (ensaio imunoenzimático por captura) foram positivas do 1º ao 27º dia após o início do exantema. Os sinais e sintomas clássicos do eritema infeccioso foram observados em 8 (33,3%) dos casos e apenas em crianças. Oito pacientes (6 adultos e 2 crianças) apresentaram poliartropatia simétrica, vista mais freqüentemente em mulheres.

Os resultados deste trabalho demonstram que o diagnóstico da parvovirose humana é difícil quando a doença não apresenta quadro clínico clássico e, devido ao freqüente envolvimento das articulações, tal infecção deve ser considerada no diagnóstico diferencial da artrite reumatóide na sua fase inicial.

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