Epidemiology and clinical features of parvovirus B19 infection in the Amazon region. Brief review.

INTRODUCTION: Human parvovirus B19 was accidentally discovered by Cossart et al (7), when screening sera from blood donors for the presence of hepatitis B surface antigen. Since then several studies have assessed its role in the aetiology of distinctive clinical conditions worldwide (14). In the context of yet expanding spectrum of disease, this agent is known to induce transient aplastic crisis in patients with chronic haemolytic anaemia (36) and is the causative agent of erythema infectiosum (EI) during childhood (2). In addition to this, parvovirus B19 infection may course with arthropathy and arthralgia in adults (23), fetal loss as an outcome of non-immunologic hydrops fetalis in pregnancy (3,4), and chronic anaemia in immunocompromised individuals (17).

Several studies have assessed the worldwide distribution of B19 infection, affecting mainly children aged between 4 and 10 years. In urban settings throughout the world, seroprevalence rates have been reported to range from 2% to 15% in children 1-5 years old, 15% to 60% in those aged 5-19 years, and 30% to 60% among adults (1).

Very few studies on the occurrence of parvovirus B19 infection have been conducted in Brazil to date. The association between this agent and erythema infectiosum was first reported by Miranda et al (19), almost one decade ago. An also early finding was that from Cruz et al (8) who were able to detect this agent in a blood donor plasma in Rio de Janeiro. In order to assess the epidemiological magnitude of parvovirus B19 infection, seroprevalence studies have been carried out in Northern and Southeastern regions of Brazil, involving both urban and remote communities (12,13,30). While seroprevalence rates as low as 5% were recorded among Indian...
COMMUNITIES IN URBAN COMMUNITIES

Serum samples from 460 apparently healthy inhabitants of Belém, Brazil, collected between 1983 and 1989 were tested for the presence of parvovirus B19 antibody by a capture radioimmunoassay previously described by COHEN et al (6). The seropositivity rates by age-groups and sex are shown in Figs. 1a and 1b. Our figures indicate that at the age of 20 years nearly half of the population in Belém had been infected by B19 (12). While these data are comparable to those for several urban populations worldwide (5,22,25), they differ significantly from the prevalence rates in Rio de Janeiro, of nearly 80% by the age of 15 years (20). This latter figure is higher than those found in most studies, possibly due to the fact that sera were collected in an overcrowded environment. It is noteworthy the decrease in B19 antibody prevalence in the 20 to 40 years old group (mainly for women) in a pattern similar to that reported by NASCIMENTO et al (20) in Rio and COHEN & BUCKLEY (5) in the U.K. Also of interest is the higher overall prevalence among females in Belém (65% vs 63%), possibly reflecting a more intense contact between infected children and women than children and men. Such a sex difference has also been recorded in Germany (25) and in the United States (16).

In the 1988-1989 period additional 78 sera were obtained from patients with rashes in whom measlesvirus, rubellavirus, and arboviruses had been ruled out as aetiological agents of the illness. Of these, approximately a quarter (28%) tested positive for both B19-IgM and IgG and 8 (11.5%) were B19-IgG positive only (Fig. 2a), suggesting that B19 is a frequent cause of illness with rash in Belém, Brazil. A further, similar investigation was performed in Belém, involving 42 patients with unexplained exanthemata (other exanthemats agents than B19 ruled out as causing the infection) whose sera were collected in 1990 (13). A remarkable
difference (p < 0.001) is noted if a comparison is made between the frequency of B19-IgM positive patients in the latter investigation (5%) (Fig. 2b), with the rate of recent parvovirus infection in cases of exanthem, 28.2%, of the former study. Results from both studies also do not agree in terms of B19 IgG antibody: 11.5% in the 1988-1989 investigation vs. 26.2% in the 1990 one.

Altogether, these results support the view that B19 infection, in addition to the seasonality, has a cyclical pattern characterized by several years of high infection rates followed by a period of low infection rate (3). In fact, the number of cases clinically diagnosed as erythema infectiosum in 1988/1989 were significantly higher than in 1990 (13).

**SOROEPIDEMIOLOGY IN REMOTE COMMUNITIES**

Three Brazilian Indian communities were located in Pará state: one in the North (Tiriyo), and two in the South (Xikrin and Mekranoi). (Fig. 3). From Tiriyo tribe, Alto Paru, 212 sera collected between 1974 and 1980; from Xikrin tribe, Catete, 128 sera collected in 1976; and from Mekranoi tribe, Alto Iriri, 121 sera collected between 1977 and 1978.

An overall seropositivity rate of 7.8% (36 persons out of 461 individuals tested for presence of IgG antibodies to Parovirus B19) was recorded among these three communities (Table 1). The lowest prevalence rate was of 4.7% among the Xikrin Indians, and the highest was of 10.7%, among the Mekranoi. In the group of Amerindians aged <10 years, the overall seroprevalence rate was 4.2%, ranging from 0% to 12.5% among the Xikrin and Tiriyo tribes, respectively. In the next age-group (10-19 years), 5.8% were seropositive, the rates ranging from 0% to 13.0%, among the Xikrin and Mekranoi, respectively. Among the oldest groups (20 years or older), we found an overall seroprevalence rate of 18.9%, ranging from 13.7% in the Mekranoi to 25.3% in the Xicrin.

In general, the seropositivity rates for B19 among three communities were rather lower than those found in previous serosurveys carried out in urban populations throughout the world. For instance, in England (5), Japan (22), and Brazil (20), antibody rates ranging from 60% to 80%, at least 7 times higher than those recorded for Amerindians. In addition, the prevalence rates obtained from the three tribes living in remote areas of the Amazon region are strikingly different from those obtained in Belém, Pará with seroprevalence rate of 42.6% in the urban population (12).

**CLINICAL FEATURES**

A broad spectrum of clinical pictures are seen in parovirus B19 infected humans, which can be summarized as follows (14):
(1) **Infections in the normal host:**
   - Erythema infectiosum

**(EI) or fifth disease**
- Arthropathy
- Hydrops fetalis

(2) **Haematologic manifestations:**
- Aplastic crisis
- Chronic anaemia
- Other haematologic diseases

(3) **Other diseases:**
- Neurologic disease
- Rheumatologic disease
- Other diseases

EI has been by far the commonest manifestation of the infection in our patients, which comprised nearly two hundred serologically confirmed cases, most of them in children, during a two-year period outbreak (1988-89) detected in Belém and neighbouring areas. However, few sporadic typical cases had been clinically diagnosed among us since 1984, when no specific laboratorial facilities were available (19).

In the normal host, early and usually vague symptoms appear after an incubation period of about one week and correspond to viremia - namely low fever, malaise, myalgia, and nausea. Erythroblastopenia, occurring in bone marrow during this period, doesn’t produce any threat to these subjects because their erythrocytes have a normal life-span. In many cases prodromes are not present at all. In children an erythematous rash appears by about the beginning of the second or third week of infection, manifested itself typically as a “slapped-cheek” facies and a lacelike pattern on trunk and limbs, which may lasts for a week or more leaving no scalling or pigment disturbance. In adults, however, these aspects are only seldom seen, and a picture of arthralgia and/or arthritis predominates, in which mainly small joints are symmetrically affected, leading eventually to some degree of labor incapacity, and may occur as the sole manifestation of infection (27,14,15). Joint disease occurs predominantly in women, and may exceptionally last for months or even years, mainly in HLA-DR4 phenotypes (14,24). Both EI and arthropathy are immuno-complex mediated, thus representing late events in the course of infection. It hasn’t been a major feature in our series, even in adult patients. A 13-year-old girl was examined by one of us (MFRM - unpublished data), who had been hospitalized presenting with fever of five days duration, an erythematous rash, joint pain, lumbar pain,

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**Tabela** Seroprevalence of parvovirus B19 specif IgG antibodies in three Amerindian communities in the Amazon region, Brazil

<table>
<thead>
<tr>
<th>Age(years) and sex</th>
<th>Tiriyo</th>
<th>N. Positive/N. Tested</th>
<th>Meikrautoil</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALE</td>
<td>0/1 (0)</td>
<td>0/15 (0)</td>
<td>0/16 (0)</td>
</tr>
<tr>
<td>FEMALE</td>
<td>1/4 (25.0)</td>
<td>0/23 (0)</td>
<td>0/16 (0)</td>
</tr>
<tr>
<td>10-19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALE</td>
<td>0/43 (7.0)</td>
<td>0/15 (0)</td>
<td>2/11 (18.2)</td>
</tr>
<tr>
<td>FEMALE</td>
<td>1/43 (2.0)</td>
<td>0/08 (0)</td>
<td>1/13 (7.7)</td>
</tr>
<tr>
<td>20-29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALE</td>
<td>0/2/30 (7.0)</td>
<td>0/17 (0)</td>
<td>2/21 (9.5)</td>
</tr>
<tr>
<td>FEMALE</td>
<td>2/29 (6.9)</td>
<td>0/17 (0)</td>
<td>4/18 (22.2)</td>
</tr>
<tr>
<td>30-39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALE</td>
<td>0/21 (0)</td>
<td>1/15 (6.7)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>FEMALE</td>
<td>1/27 (3.7)</td>
<td>3/12 (25.0)</td>
<td>2/12 (16.7)</td>
</tr>
<tr>
<td>&gt;40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALE</td>
<td>6/11 (54.5)</td>
<td>1/1 (100.0)</td>
<td>0/6 (0)</td>
</tr>
<tr>
<td>FEMALE</td>
<td>1/3 (33.3)</td>
<td>1/1 (100.0)</td>
<td>2/6 (33.3)</td>
</tr>
<tr>
<td>SUB-TOTAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MALE</td>
<td>11/106 (10.4)</td>
<td>2/63 (3.2)</td>
<td>4/56 (7.2)</td>
</tr>
<tr>
<td>FEMALE</td>
<td>6/106 (5.7)</td>
<td>4/65 (6.2)</td>
<td>9/65 (13.8)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>17/212 (8.0)</td>
<td>6/128 (4.7)</td>
<td>13/121 (10.7)</td>
</tr>
</tbody>
</table>

* Percentages in parenthesis.
locomotion troubles, and some altered laboratory test results including an ESR of 92 mm/1st hour, an ASO titre of 500 units Todd, a positive RCP test, and a 1:500 positive FAN with speckled and nucleolar patterns. A CBC showed only an eosinophilia of 17%. One month later, an Elisa B19-IgM was positive, while the patient showed a second cutaneous flare with typical features of EI.

We also have followed two cases – a five-year-old boy and his mother – who almost simultaneously presented with fever, cervical lymph node swelling, lymphocytosis and atypical lymphocytes in peripheral blood smears. Ten days later, a rash suggestive of EI developed in both of them, together with positive B19-IgM and negative mononucleosis serologies (18). Such a “mononucleosis-like syndrome” is mentioned elsewhere (14).

B19 may contaminate the fetus through transplacental route in up to 10% of cases. In Germany the number of abortions per year may reach as many as 300-500 (24). On the other hand, in most of the reported infections occurring during pregnancy the fetus has not been adversely affected (27). One of the most hazardous outcomes may be fetal death due to hydrops fetalis, which develops as a consequence of fetal chronic anaemia and hypoxia. IgM-positive pregnant women presenting with symptoms compatible with B19 infection must undergo repeated echographies to search for fetal subcutaneous edema, which is considered to be a marker of anaemia, as well as regular a-FP dosages (15). A study to assess the outcome of B19 effects during pregnancy is under way in Belém, involving Instituto Evandro Chagas, Universidade Federal do Pará, Universidade do Estado do Pará and Fundação Santa Casa de Misericórdia do Pará. To date, we have no records on the occurrence of B19-related hydrops fetalis.

Transient aplastic crisis (TAC) relates to an alternative mode of the disease’s presentation, which affects recipients presenting with either diminished red cell production or elevated destruction or loss. Iron deficiency and congenital dyserythropoietic anaemia are examples of the first group, while hemolytic and autoimmune anaemias, malaria and blood loss conditions belong to the second one. Although otherwise and immunologically healthy, these patients are unable to compensate the interruption in erythrocyte supply produced by viral-induced lysis of pronormoblasts at bone marrow level. An acute life-threatening anaemia subsides that needs immediate red cell replacement. To the best of our knowledge, no documented TAC cases have been seen among us, nevertheless attention must be paid as regard to the possibility of such a picture occur in the Amazon, where iron-defficiency conditions and malaria are highly prevalent.

Immunocompromised hosts, such as leukemia and AIDS patients, develop anaemia of chronic course, as a result of continuous destruction of red progenitor cells in the bone marrow by parvovirus B19. This is a condition in which intravenous immunoglobulin is formally indicated.

An expanding number of conditions has recently been attributed to the virus and included into its pathologic spectrum. Of recent observation, cases of the so called papular-purpuric “gloves and socks” syndrome, in which pruritic edematous purpuric papules develop on hands and feet, together with fever, mucous membrane involvement (cheilitis, perlèche,
erosions) and adenopathy. The disease heals spontaneously within one or two weeks and affects mainly young adults (14,15,24). Also cases of idiopathic thrombocytopenic purpura, transient erythroleukemia of childhood, Diamond-Blackfan anaemia, encephalitis, meningitis, plexus brachialis neuropathy, systemic vasculitis, polyarteritis nodosa, Schönlein-Henoch purpura, Kawasaki's disease and systemic lupus erythematosus, among others, have also been reported as conditions in which parvovirus B19 might play a role. In view of the high sensitivity of PCR detection of B19-DNA can be made even up to 70 days after the onset of symptoms, relationships between a given clinical condition and B19 infection might be fortuitous (24).

BRIEF FIND COMMENTS

We have recently the opportunity of establishing in the General Virology Service of Evandro Chagas Institute two highly sensitive molecular biology techniques: the polymerase chain reaction (PCR) and nested PCR, which allow the detection of minute amounts of viral nucleic acid of parvovirus B19 in different biological specimens. This will enable us to perform molecular epidemiological studies. With these techniques we are intending to study the association between parvovirus B19 and fetal damage (cases of spontaneous abortion, stillbirth and hydrops fetalis), as well as to assess the role of B19 in the aetiology of erythema multiforme and purpura, aplastic crisis in patients suffering from chronic haemolytic anaemias and other clinical conditions.

REFERENCES