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# APLASTIC CRISIS DUE TO HUMAN PARVOVIRUS B19 INFECTION IN HEREDITARY HEMOLYTIC ANAEMIA

R. C. N. CUBEL(1); M. C. VALADÃO(2); W. V. PEREIRA(2); M. C. MAGALHÃES(3) & J. P. NASCIMENTO(1).

## SUMMARY

Specific anti-B19 IgM was demonstrated in sera from three children showing transient aplastic crisis. A two years-old boy living in Rio de Janeiro suffering from sickle-cell anaemia showed the crisis during August, 1990. Two siblings living in Santa Maria, RS, developed aplastic crisis during May, 1991, when they were also diagnosed for hereditary spherocytosis. For a third child from this same family, who first developed aplastic crisis no IgM anti-B19 was detected in her sera.

**KEYWORDS:** Human parvovirus B19; Transient aplastic crisis; Hereditary spherocytosis; Sickle-cell disease

## INTRODUCTION

Transient aplastic crisis in sickle-cell patients was actually the first disease associated with B19 parvovirus infections [16, 18]. Case reports have amply documented that B19 parvovirus can also induce transient aplastic crisis in patients with a variety of other underlying hemolytic process like hereditary spherocytosis, thalassemias, erythrocyte enzyme deficiency, autoimmune hemolytic anaemia [1, 5, 8, 9, 17, 19] and possibly also with hemorrhage induced erythropoietic stress[7].

In Brazil, infections by parvovirus B19 were first diagnosed in fifth disease patients living in Belém [10] and in a healthy blood donnor in Rio de Janeiro[2]. The infection is widespread in cities like Rio de Janeiro[13] and Belém[6] where antibody prevalence studies were done. Other common outcome of B19 infection like hydrops fetalis, that occcurs when pregnant women become infected, was also described in Rio de Janeiro[14].

These three cases reported now are the first laboratory based notification of aplastic crisis in patients with underlying hemolytic diseases in Brazil.

## PATIENTS AND METHODS

### Case 1

A two years old boy of mixed African origin, who had being diagnosed for sickle-cell anaemia since six months ago, received medical attention in an outpatient pediatric department at Hospital Universitário Gafrée-Guinle. Major symptoms were fever (39 C), and generalized pain, that it was stronger in the right arm. On the examination, he was found to be pale and the spleen and liver were enlarged.

The patient was then reffered to pediatric ward in the same hospital. Clinical diagnosis was pneumonia and osteomyelites leading to treatment with antibiotics and vitamins. He was maintained at the ward during fifty seven days. Packed red blood cells were transfused twice. Bone marrow smears was done on 14 of September showing no erythrocytes and very few erythroblasts. Peripherical blood was then collected and reffered for B19 diagnosis.

1- Departamento de Virologia, Instituto Oswaldo Cruz, FIOCRUZ, RJ
2- Serviço de Hematologia, Hosp. Universitário, UFSM, RS
3- Serviço de Hematologia, Hosp. Gafrée-Guinle, UNIRIO, RJ
**Correspondence to:** R. C. N. Cubel, Dept. Virologia, FIOCRUZ, Av. Brasil 4365, 21045, Rio de Janeiro, Brasil.

### Case 2

Three siblings were admitted during May, 1991 to Hospital Universitário - UFSM, RS. The patients were a 3 years old girl (patient A), a 8 years old boy (patient B) and a 10 years old girl (patient C). The index case was patient C whose looked pale showing fever and vomiting since one week before. Patient B did not show any symptom of acute disease but there was a report of anaemia, malaise, pain in the legs, and anorexy since 18 months ago. Patient A had upper respiratory tract symptoms five days before and previous anaemia was also reffered. Figure 2 summarises the laboratory findings during the two months follow up of these 3 patients. Microespherocytes were detected on blood smears from all three siblings. All three children were receiving ferrous sulfate previously since 2 years before this occurence.

### B19 diagnosis

Sera collected in the dates showed in figure 1 and 2 were processed for IgM and IgG specific anti-B19 antibodies by an enzymeimmunoassay developed by us[3]. Each serum was also submitted to B19 DNA detection by "dot-blot" hybridization using biotinylated B19/pGEM1 recombinant plasmide as molecular probe[11].

## DISCUSSION

Although human parvovirus B19 seems to be able to infect platelets and leukocytes in the peripheral blood, efficient cytolytic replication occurs in erythroid progenitors like the late erythroid progenitor cell or even the pronormoblass [4, 12]. This leads predominantly to the partial or complete disappearance of reticulocytes from the peripheral blood and to the subsequent fall in blood hemoglobin which is so characteristic for illness associated with B19 virus infections. Low reticulocytes counts observed between 23 of August and 11 of September for case 1 and in 6 of May for patient C and in 14 of May for patient B (Case 2) indicate depression of erythropoiesis in bone marrow, even when bone marrow aspirate was not performed. In hematologically normal individuals with high hemoglobin concentrations and red blood cells with an average life span of 120 days, the effect on peripheral blood hemoglobin is small and there are no clinical consequences. In those with chronic hemolytic anaemia, the hemoglobin is already low and the red blood cells have a short life span (15 - 20 days), so that arrest of erythropoiesis in the marrow leads to a sharp fall in hemoglobin and symptoms of anaemia[15]. In contrast to the situation in fifty disease in normal individuals where viremia is usually absent at the time of clinical

TABLE 1
LABORATORY DATA OF THE SICKLE-CELL PATIENT

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ht (%) | 24 | 28 | 15 | 10 | 18 | 25 | 21 | 24 | 26 |
| Hb (g/dl) | 7.9 | 8.7 | 4.0 | 3.7 | 5.9 | 7.3 | 6.5 | 7.0 | 8.2 |
| Retic (%) | | | 1.4 | | | | 0.3 | 5.6 | |
| Leuk (x10⁹/l) | 10.9 | 8.8 | 9.3 | | 14.3 | 11.2 | 4.8 | 10.5 | 5.7 |
| Anti-B19 Antibodies | | | | | | | | IgM+ IgG- | |
| B19 DNA | | | | | | | | Neg | |
| Days after onset | 8 | | | | | | | | |
| | 11 | 18 | 23 | 24 | 28 | 9 | 11 | 18 | 24 |
| | | August | | | | | | September | |
| | | | | ↑ | | | ↑ | | |
| | | | | Packed red blood cells transfusion | | | Packed red blood cells transfusion | | |

TABLE 2:
LABORATORY DATA OF HEREDITARY SPHEROCYTOSIS SIBLINGS

Patient A (3 years old girl)

| | | | | |
|---|---|---|---|---|
| Ht (%) | 21 | | 28 | 23 |
| Hb(g/dl) | 6.9 | | 9.9 | 8.6 |
| Retic (%) | 20 | | 18 | 15 |
| Leuk(x10$^9$/l) | 17.3 | | 6.1 | 5.9 |
| Anti-B19 | | | IgM+ | IgM- |
| Antibodies | | | IgG+ | IgG+ |
| B19 DNA | | | Neg | Neg |
| Days after onset | 5 | | | |

5 6 8 14 3 July
May

Patient B (8 years old boy)

| | | | |
|---|---|---|---|
| Ht (%) | 31 | 17 | 28 |
| Hb (g/dl) | 11 | 5.9 | 10.6 |
| Retic (%) | 11 | 1.2 | 16 |
| Leuk (x10$^9$/l) | 5.9 | 5.6 | 7.7 |
| Anti-B19 | | | IgM+ |
| Antibodies | | | IgG+ |
| B19 DNA | | | Neg |
| Days after onset | | | |

5 6 8 14 3 July
May

Patient C (10 years old girl)

| | | | | |
|---|---|---|---|---|
| Ht (%) | 10 | 12 | 21 | 23 |
| Hb (g/dl) | 4.1 | 4.7 | 6.9 | 8.6 |
| Retic (%) | | 0.2 | 27 | 15 |
| Leuk (x10$^9$/l) | 3.1 | 2.9 | 6.2 | 5.9 |
| Anti-B19 | | | | IgM- |
| Antibodies | | | | IgG- |
| B19 DNA | | | | Neg |
| Days after onset | 7 | | | |

5 6 8 14 3 July
May

Whole blood transfusion

presentation, very high concentrations of B19 human parvovirus (more than $10^8$ particles/ml blood) are found in patients presenting with aplastic crisis [20].

However the period of viremia is short (about 2-4 days) and can be overlooked, as happened with patients A and B. Case 1 was the one where we could have detected B19 DNA in blood if a serum specimen collected on 23 August was available; as also was for patient C if we had a serum specimen collected on 5 of May. In all our patients B19 DNA was not detected which might be explained by the fact that these examinations were carried out more than a week after the onset of symptoms.

Bone marrows hypoplasis is frequent in homozygous sickle-cell (SS) disease during systemic infection with **Streptococcus pneumoniae, Salmonella and Mycoplasma pneumoniae**[18]. However, the classic aplastic crisis characterized by a self limited total erythropoietic arrest lasting 5 to 10 days (as occured in Case 1) is always caused by human parvovirus B19[15].

Clinical manifestations accompanying B19 infections vary considerably. Some patients with transient aplastic crisis have no other symptoms of a viral infection, while others have fever, signs of respiratory infection, headache, gastrointestinal complaints, or a flu-like disease. Patient C had fever and other symptoms suggestive of viral infection. Patient A had upper respiratory tract symptoms. The occurence of aplastic crisis in siblings within a few days interval as occured in Case 2 is almost pathognomonic of B19 infection.

Investigation revealed that the siblings suffered from spherocytosis, apparently hereditary and not known before. The persistence of erythroblastopenia during the first day of patient C in hospital entailed a relative ineffectiveness of the blood transfusion.

## RESUMO

**Crise aplástica devido à infecção por parvovirus humano B19 em anemia hemolítica hereditária**

IgM específica anti-B19 foi demonstrada nos soros de três crianças apresentando aplasia transitória de medula. Um menino de dois anos de idade vivendo no Rio de Janeiro e sendo portador de anemia falciforme, apresentou a crise durante Agosto de 1990. Dois irmãos vivendo em Santa Maria - RS, desenvolveram crise de aplasia em Maio de 1991, quando foram também diagnosticados como portadores de microesferocitose. IgM anti-B19 não foi detectada no soro de uma terceira

criança, desta mesma família, a qual primeiramente apresentou crise de aplasia.

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