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**A.-M.W. van Elsacker-Niele · H.T. Weiland**
**A.C.M. Kroes · M.C. Kappers-Klunne**

# Parvovirus B19 infection and idiopathic thrombocytopenic purpura*

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**Abstract** The potential association of human parvovirus B19 infection with idiopathic thrombocytopenic purpura (ITP) was studied. All 60 adult patients presenting with ITP at the University Hospital Rotterdam – Dijkzigt during a 12-year period (41 with acute ITP, 19 with chronic ITP) were included. Patient files were retrospectively analyzed. Stored serum samples were tested for parvovirus B19-specific IgG and IgM antibodies, and for parvovirus B19 DNA. In only one patient (1.7%) was evidence of recent B19 infection found. Parvovirus B19 is not a frequent cause of adult ITP and should be tested for only when there are other indications of possible parvovirus B19 involvement.

**Key words** Idiopathic thrombocytopenic purpura · ITP · Human parvovirus B19

A.-M.W. van Elsacker-Niele[1] · H.T. Weiland
Department of Virology, University Hospital and Faculty of Medicine, Leiden, The Netherlands

A.C.M. Kroes[2]
Department of Virology, University Hospital Rotterdam Dijkzigt, Rotterdam, The Netherlands

M.C. Kappers-Klunne (✉)
Department of Hematology, Room L434, University Hospital Rotterdam/Erasmus University, Dr. Molewaterplein 40, 3015 GD-Rotterdam, The Netherlands

[1]*Present address:*
Public Health Laboratory, Leeuwarden, The Netherlands

[2]*Present address:*
Department of Virology, University Hospital and Faculty of Medicine, Leiden, The Netherlands

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## Introduction

The human parvovirus B19 replicates in erythroid precursor cells in the bone marrow. This causes lysis of infected cells and, in the immunologically normal host, a temporary arrest in erythropoiesis. Viral replication in granulocytes, thrombocytes, and their precursors has not been demonstrated, but there is transcription of the viral genome [18]. The granulocytopenia and thrombocytopenia that can occur with parvovirus B19 infection are most probably due to the cytotoxic effect of the NS1 protein of the virus [18].

In recent years, there have been reports of an association between parvovirus B19 infection and idiopathic thrombocytopenic purpura (ITP) [10, 12]. However, due to the small number of patients studied, the frequency and clinical relevance of this association have remained questionable. In one study, the results of parvovirus B19 serology on 61 serum samples from patients with recent ITP were described [10]. No nucleic acid detection technique was used. Recent parvovirus B19 infection was demonstrated in 5% of these serum samples, which led to the conclusion that parvovirus B19 serology should be included in virological investigations in ITP. Here we report the results of a study on parvovirus B19 infection among 60 adult patients with ITP. Both serology and B19 DNA detection methods were used.

## Patients and methods

All patients presenting between March 1980 and August 1993 at the Department of Hematology of the University Hospital Rotterdam with a diagnosis of idiopathic thrombocytopenic purpura (ITP) were retrospectively analyzed. The diagnosis of ITP was based on the following criteria: isolated thrombocytopenia, normal or increased numbers of bone marrow megakaryocytes, and absence of splenomegaly. When patients presented within 6 months after the first symptoms of ITP they were considered to have acute ITP, those who presented after 6 months were assigned to the group of chronic ITP.

Blood samples were drawn from each patient at admission, and sometimes one or more additional samples were obtained. All patients were tested for anti-platelet antibodies, using an immunofluorescence technique as described previously [19]. In 22 cases the mean platelet life span was determined using indium 111-labeled autologous platelets [19]. Sera were kept frozen at –20 °C. They were initially tested for recent infection with cytomegalovirus, Epstein-Barr virus, and hepatitis B virus as possible causes of thrombocytopenia. Now they were tested for parvovirus B19-specific IgG and IgM antibodies using an immunofluorescence assay [3] or an ELISA [16]. These tests appear to be of comparable diagnostic value (unpublished data).

A parvovirus B19-specific polymerase chain reaction (PCR) [15] was also performed on the sera. Spiking with parvovirus B19 containing serum was used to detect inhibition of the PCR by test samples. This test can detect as few as 100 parvovirus B19 genome copies. In chronically infected immunocompromised patients, viremia with parvovirus B19 has a waxing and waning course and can easily reach levels of $10^7$ virus particles per milliliter serum, whereas in the immunologically normal host viremia generally lasts for 2 months after primary infection, and up to $10^{14}$ virus particles per milliliter serum can be found [5, 7, 9, 14].

## Results

There were 41 patients with acute ITP (14 male, 27 female), and 19 with chronic ITP (7 male, 12 female). The mean age was 37.9 years (range 16–75 years) for patients with acute ITP and 39.3 years (range 16–78 years) for patients with chronic ITP.

In 28 of the 41 patients with acute ITP, bleeding tendency was the presenting symptom. Six of these 41 complained of fatigue and seven had had fever, sore throat, or a "cold" prior to diagnosis of ITP.

Data on platelet number and life span and on anti-platelet antibody testing are presented in Table 1. Mean platelet life span was shortened in all 22 patients tested, supporting the diagnosis of ITP. None of the patients had serologic evidence of recent infection with cytomegalovirus, Epstein-Barr virus, or hepatitis B virus.

We tested 86 serum samples from all 60 patients for B19-specific antibodies. On average, the period between first symptoms of acute ITP and the first serum sample was 14.8 days (range 0–105 days, median 3 days). In 32 of the 60 patients (55%) parvovirus B19-specific IgG without specific IgM was detected in the initial serum sample, generally indicating past parvovirus B19 infection (more than 3 months earlier). There was no significant difference in the results of parvovirus B19 serology between the patients with acute ITP and those with chronic ITP (22/41 vs. 10/19 positive for specific IgG). Parvovirus B19-specific PCR was negative in all sera, while none of them proved to inhibit the PCR.

In one patient (2.4%) with acute ITP both specific IgG and IgM were present in the initial serum sample. A sample obtained 2 weeks later contained detectable specific IgG, but not IgM. These findings indicate recent parvovirus B19 infection. This 68-year-old female patient presented with a 2-day history of bruises. She had no other symptoms, and the family history was unremarkable. Physical examination revealed petechiae and ecchymosis on the extremities, without other abnormalities. Laboratory studies revealed marked thrombocytopenia ($4 \times 10^9$/l), a shortened mean platelet life span (1.9 days; normal 8–10 days), and an increased number of megakaryocytes in the bone marrow. All other hematologic values were within the normal range. Tests for platelet-associated and circulating anti-platelet antibodies were negative. The patient was treated with prednisone and recovered completely within 3 months.

**Table 1** Platelet numbers, platelet life span, and anti-platelet antibodies[a] in patients with acute and chronic ITP

| | Patients with acute ITP ($n=41$) | Patients with chronic ITP ($n=19$) |
|---|---|---|
| Mean platelet number (range) | $11.61 \times 10^9$/l (1.00–42.00) | $33.05 \times 10^9$/l (3.00–89.00) |
| Mean platelet life span (range) {number tested} | 0.8 days (0.05–1.9) {18} | 1.4 days (0.35–3.3) {4} |
| Platelet-associated antibodies | 18/30 | 6/16 |
| Circulating anti-platelet antibodies | 14/41 | 3/19 |

[a] IgG and/or IgM antibodies; data on anti-platelet antibodies are presented as number positive/number tested

## Discussion

The human parvovirus B19 is the cause of erythema infectiosum, also known as fifth disease. Acute parvovirus B19 infection can also cause arthralgia or arthritis in adults (mainly women), aplastic crisis in chronic hemolytic anemia, intrauterine fetal death, and various other conditions. Chronic parvovirus B19 infection occurs in patients with impaired humoral immunity, and may lead to chronic anemia [7, 9].

Thrombocytopenia can occur in acute parvovirus B19 infection. It has been attributed to the cytotoxic effect of its protein NS1 [18]. Chronic thrombocytopenia as a result of chronic parvovirus B19 seems a logical possibility in this condition, where NS1 is likely to be continuously produced within the bone marrow. In a recent case report, parvovirus B19 associated thrombocytopenia lasting for about 1 month was described in an elderly woman with a deficient immunological response to parvovirus B19 [13]. Therefore, both acute and chronic ITP might be caused by parvovirus B19 infection.

In the immunologically normal host, acute parvovirus B19 infection can be detected by the presence of viral DNA and of specific IgM antibodies. These antibodies last approximately 3 months after the infection. In the immunocompromised host, antibodies may not

**Table 2** Review of the recent literature on adult patients with purpura associated with human parvovirus B19 infection

| Reference | Patient sex (age in years) | Symptoms | Platelets ($\times 10^9$/l) |
|---|---|---|---|
| 1 | ♀ (?) | Acute dermatosis with erythematous and purpuric lesions on hands and feet ("gloves and socks"), fatigue, adenopathy, during B19 viremia | 105 |
| 6 | ♀ (26) | Purpuric plaques on buttocks, preceded by symmetric arthralgia in upper and lower limbs, and followed by more widespread petechiae, mainly on palms and soles; subsequently, Koplik spots in the mouth and a diffuse morbiliform rash. Initially, only B19-specific IgM detectable; later also specific IgG (no serologic evidence of recent measles) | 238 |
| 2 | ♀ (29) | Fever up to 40 °C, myalgias, and purpura during B19 viremia in an HIV-seropositive woman; full recovery with production of specific antibodies | 5 |
| 17 | ♂ (33) | Purpura, myalgia, arthralgia, arthritis, and fever (38.2 °C) during B19 viremia | 193 |
| 8 | ♀ (36) | Itching, pain, and swelling of hands and feet, followed by petechiae on soft palate and on hands and feet ("glove and socks" distribution), followed by desquamation; probably beginning during B19 viremia | 315–192 |
| 13 | ♀ (73) | Fever, arthralgia, and diarrhea, followed by petechiae and overt bleeding in a previously healthy woman with persistent B19 infection, without production of lasting specific antibodies | 10 |

be produced in detectable quantities, and diagnosis relies on the detection of parvovirus B19 DNA. In the present series, the available techniques for demonstrating a recent parvovirus B19 infection in retrospectively analyzed cases of ITP provided negative results in all but a single case. In this patient, parvovirus B19 infection apparently presented as isolated thrombocytopenia. This frequency of one case in 60 analyzable ITP patients, 41 of them with acute ITP, is even lower than that found in another recent report [10].

Furthermore, the prevalence of B19-specific IgG in this study group is not higher than in the general population [4], and there was no difference in this respect between patients with acute and those with chronic ITP. This, in itself, suggests that there is no important correlation between parvovirus B19 infection and ITP, be it acute or chronic, in adult patients. In pediatric ITP there may well be a correlation, especially since infection with the human parvovirus B19 usually occurs in childhood [4]. Unfortunately, we had no access to sera from cases of ITP in children. However, in one publication on acute ITP in childhood recent infection with human parvovirus B19 was suggested in 17 of 35 children studied [11].

In order to assess the clinical presentation of (thrombocytopenic) purpura associated with adult parvovirus B19 infection, a literature search was done. Table 2 presents an overview of six recently published cases of petechiae or purpura associated with proven B19 infection. It is apparent from this overview that in most patients the petechiae or purpura occurred during B19 viremia, when specific DNA or IgM are readily detectable. Also, the clinical presentation varies widely. In five of the six patients other signs indicative of B19 infection were present, such as arthralgia, myalgia, and erythematous rash. Of the six patients, three do not fit our definition of ITP because they were not thrombocytopenic.

The human parvovirus B19 seems to be at best a minor causative factor in adult ITP, but it may be important in pediatric ITP. It stands to reason that in adult patients with ITP, parvovirus B19 infection need be considered only in cases where other symptoms suggestive of this infection are present in the patients or their household contacts.

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