High Prevalence of Parvovirus B19 IgG Antibodies among Dutch Hemophilia Patients

Abstract

Background and Objectives: Human parvovirus B19 is a potential risk to hemophilic patients receiving blood products. Materials and Methods: To determine the prevalence of the corresponding antibody in patients with hemophilia A or B or von Willebrand’s disease, we tested 326 hemophilia patients for anti-B19 IgG. The results were compared with those of 203 age-matched controls (male blood donors and children). Results: The overall prevalence of B19 IgG in the hemophilia patients was 302/326, and in the controls 123/203. Below the age of 10, hemophilia patients had a higher prevalence of B19 IgG (76% vs. 23%, 11/48; p<0.00001). In those below the age of 5 who had been treated exclusively with monoclonally purified concentrate, it made no difference whether the product was or solvent-detergent treated. There was a significantly lower incidence in patients who were rarely treated. Conclusion: Parvovirus B19 is frequently transmitted in blood products. Existing virus-inactivating methods do not prevent transmission.

Introduction

Human parvovirus B19 (B19) is a single-stranded, non-enveloped DNA virus which belongs to the family Paroviridae [1]. B19 was first detected in 1975 in England [2]. B19 is the causative agent of erythema infectiosum [3] and it is the primary cause of transient aplastic crises in patients with chronic hemolytic anemia [4]. Parvo B19 has also been related with acute arthralgia and arthritis [5, 6], fetal death [7] and chronic anemia [8, 9]. In some cases life threatening infections have been described [10]. B19 is mostly transmitted via the respiratory tract [3]. In the production of blood products, current virus-inactivating steps seem to be ineffective to prevent transmission of Parvo B19 [11–14]. In particular, hemophilia patients receiving blood products on a regular basis are at risk of acquiring B19 infection [15–18].
with recombinant factor VIII [H.M. van den Berg, pers. commun.]. Before that time, hemophilia A patients were mainly treated with a Dutch dry-heat-treated (60°C, 72 h) intermediate-purified clotting factor concentrate or cryoprecipitate (period 1985–1990) and a Dutch pasteurized intermediate-purified product (period 1990–1992). Hemophilia B patients were mainly treated with a Dutch prothrombin complex concentrate which after 1985 and before 1992 was virus inactivated by dry-heat treatment (60°C, 72 h and since 1992 by the solvent-detergent method).

Before 1985, Dutch clotting products were not virus inactivated. Since 1993 most hemophilia B patients are treated with an imported monoclonally purified solvent-detergent-treated factor IX concentrate.

In the Netherlands recombinant factor VIII products were introduced in 1994. For all patients the product they had received was registered. None of the patients eligible for this study have been exclusively treated with recombinant clotting factor concentrates.

According to the amount of clotting factor product used, patients were placed into three treatment groups. No treatment—patients who received no treatment at all or less than 5 infusions; little treatment—patients who were treated on demand and received less than 10 infusions per year, and heavily treated—patients who were treated on a prophylactic basis or who received more than 10 infusions per year.

**Assays**

Parvovirus B19-specific IgG (B19 IgG) was determined using an ELISA test based on a recombinant VP2 protein (Biotrin, Dublin, Ireland). All samples were analyzed at the Viral Diagnostic Laboratory of the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands.

**Statistical Analysis**

We used the $\chi^2$ test to determine the difference in prevalence of B19 IgG among the different patient populations and the control groups.

**Results**

Table 1 shows the prevalence of B19 IgG in relation to age among hemophilia patients and controls. Particularly in the younger age groups, significant differences in prevalence of anti-Parvo B19 IgG were found between hemophilia patients and controls. In children of 0–10 years, 42/55 (76%) of the hemophilia patients and 11/48 (23%) of the controls were positive (p < 0.00001). We did not observe significant differences between patients with hemophilia A, B or von Willebrand’s disease (table 2).

Table 3 shows the prevalence of B19 IgG in the various treatment groups. Patients who had received little treatment had a significantly lower risk as compared to the heavily treated group (p < 0.002). It was striking that all children with severe hemophilia A who had been treated on a prophylactic basis with clotting factor concentrates were positive. No difference was seen between patients who were treated with solvent-detergent or with pasteurized products.

**Discussion**

The significant difference in prevalence of B19 IgG between hemophiliacs and healthy persons demonstrates that there is a high risk of transmission of Parvo B19 through plasma-derived clotting products. This indicates that the current purification methods and virus-inactivating steps are not able to inactivate this virus completely and thus do not prevent transmission of non-enveloped viruses.
McOrnish et al. [19] studied the prevalence of Parvo B19 viremia in blood donors. They found that 1:3,300 donors was B19 DNA PCR positive whereas during the seasonal outbreaks 1:260 was viremic. During the B19 antibody-negative period Parvo B19 levels can be as high as 10^8 genome equivalents/ml [20]. Lefrère et al. [21] detected B19 DNA in 6/20 batches of plasma-derived, large-pool clotting factor concentrate inactivated with an organic solvent-detergent method.

Zakrzewska et al. [22] reported in her study of 25 clotting products to be B19 DNA positive by PCR. She found B19 DNA in low-purity non-inactivated product as well as in solvent-detergent, steam- and dry-heat-treated products and also in mononclogically purified clotting factor concentrates. She did not detect B19 DNA in seven concentrates inactivated by pasteurization techniques. In another study, transmission of B19 through the infusion of factor VIII concentrate dry heat treated at 100°C for 30 min was reported [14]. Saldanha and Minor [23] tested plasma products for Parvo B19 DNA by PCR and found 100% of 7 batches of factor VIII concentrate and 85% of 5 plasma pools to be PCR positive with levels of 10^6-10^9 genome equivalents/ml [23]. The viral reduction of the solvent-detergent affinity-purified factor VIII process is not sufficient to eliminate such high levels. In our study 5 patients with severe hemophilia A (2–7 years old), which had been exclusively treated with mononclogically purified pasteurized factor VIII concentrate, were all B19 antibody positive, indicating the presence of B19 DNA in this clotting factor concentrate.

In rare cases B19 may cause severe disease or become chronic, especially in immunocompromised patients, e.g., HIV-positive hemophilia patients or patients with leukemia [8, 24]. Therefore, measures should be taken to reduce the risk of transmission of B19 in clotting products. Elimination of B19 virus by nanofiltration of factor IX concentrates looks promising [25]. Unfortunately, this method cannot be applied to the high-molecular-weight factor VIII molecule.

References


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