Various Associations of Human Parvovirus B19 Infection

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Abstract

A variety of diseases encountered in association with human parvovirus 1319 infection seen at Paediatric clinic during 6 months is presented and their relation to parvovirus B19 is discussed. We conclude that investigation of parvavirus 819 in variable diseases by using the newly developed methods of molecular biology will enlighten many etiopathogenetic mechanisms (JPMA 46:235, 1996).

Introduction

Human parvovinis B19 (B 19) was accidentally discovered in 1975 in human serum while evaluating screening tests for hepatitis B virus. The newly foundvirus was named B19 as a reference to the batch in which it was initially found[1,2]. Subsequent studies of its effects inhumans have identified this virus as being able to induce aplastic crises in sickle cell disease and to be the causative agent of erythema infectiosum. The virus is known to induce aplastic crises in patients with hereditary spherocytosis and other chronic haemolytic anemias. The most common manifestation of human parvovirus infection, however, is eiythema infectiosum (fifth disease). Many clinical characteristics of B 19 infections have been defined since 1975, especially during the last 10 years many well-defined clinical syndromes have been added to the list of diseases caused by this virus, but others are still unclear[3,4]. B 19 is ubiquitous and may occur year-round, but outbreaks of erythema infectiosum (El) are most common in spring. Most infections occur among school-age children. Prevalence of IgG antibodies against the virus is high (30% to 60%) in adulthood[5]. B 19 DNA is found in respiratory secretion of viremic patients and outbreaks of erythema infectiosuni in schools may be prolonged over months, suggesting close contact rather than aerosol transmission. Patient-to-patient transmission of B 19 associated aplastic crisis has occurred. Vertical and parenteral transmission may occur[6-8]. Although, it is rare and the classical clinical picture is arthropathy in adults, erythema infectiosum in children and asyrnptomatic infection in all age groups. The diseases caused by this virus are divided into three main categories: 1) diseases found among normal hosts (asymptomatic disease, El, arthropathy, hydrops fetalis); 2) Haematologic diseases (aplastic crisis, chronic anaemia, idiopathic thrombocytopenic purpura-ITp, transient eiythroblastopenia of childhood, Diamond-Blackfan anaemia); 3) Heterogenous group of diseases, in which the etiologic role of parvovirus is less clear and sometimes putative (neurologic disease, rheumatologic disease, vasculitic and myocarditic syndromes). In particular, El, hydrops fetalis and the hematologic diseases may be paediatric concern[1,7]. Here we studied the diseases associated with serologically proven B19 infection during a six month period at a paediatric clinic.

Materials and Methods

The diagnosis of the viral infection was based mainly on clinical and serological criteria (detection of specific 1gM, then lgG, antibodies by ELISA technique) Identification of specific 1gM and igG antibodies to B i 9 is a reliable method in the diagnosis of B19 infection[9,10]. Acute 819 infection was considered to be present if the anti-B 19 1gM index was >1.2 (sensitivity 89%, specificity 98%)[11].

Specific 1gM and IgG antibodies to B 19 were investigated by using ELISA method (IDEIA TM-Parvovirus 819 IgM/JgG-DAKO AIS, Denmark) in patients referred to the clinic between March-October 1993 with different complaints, in whom one or more of the following laboratory findings were identified: anaemia, reticulocytopenia, thrombocytopenia and ezythroid hypoplasia or aplasia on bone marrow aspiration. Patients in whomspecific IgM antibodies (serologically suggesting acute orjust convalesced B19 infection) were identified and entered the study. Test principle: The reaction wells were specifically coated for IgG and IgM- test with different recombinant surface proteins of the B 19. IgG antibodies were detected by the VP I protein, whereas the 1gM immune response was measured by the VP2 protein.

The specific proteins, which are immobilized on the testplate, bind to the corresponding antibodies in the sample. Plates were incubated at room temperature for60 minutes. The complex reacts with the enzyme conjugate and afteradding the substrate a yellow colour is produced by enzymatical cleavage. Unbound reactants are removed by washings. The resultant colour change was quantified by spectrophotometry at a wavelength of 450 nm. Optical density was directly proportional to the amount of antigen-specific IgM or IgG present in the sample. To report test results ma numerical form relative to the cut-off, the patients' optical density values were divided by the mean of the cut-off calibrator absorbance values. The quotient was referred to as the index result of every case, In order to eliminate false positive results caused by rheumatoid factors aRF-Absorbent was used which is in eluded in the kit. Patient sera were mixed with this solution and then assayed. After B19-specific IgM antibodies were demonstrated, haematologic studies, including haemography, reticulocyte count and (when indicated) bone marrow aspiration were conducted. Specific Iaboratoiy investigations necessitated by the clinical condition of each patient were carried out. In all but one patient, serological tests for B 19 were repeated in the succeeding 8-16 weeks after the first investigation. The possibility of acute infection due to the following agents was excluded by the indicated serological analyses: Toxoplasma and rubella virus (microparticle enzyme-immunoassay, Abbott, Chicago, USA); cytomegalovirus, herpes simplex virus and measles virus (EIA, Enzignost, Bebring, Marburg, Germany); and Epstein-Barr virus (indirect immunofluorescence IgM anti-VCA, Gull Laboratories, Salt Lake City).

Results

Of 9 patients included in the study, 5 were girls and 4 boys. The age range was 1 month to 8 years. Complaints on referral, physical examination and laboratory investigations are summarized in Table I.

Table I. Clinical and laboratory findings of patients.

Sex-Age	Symptoms/clinical picture	Physical examination	Hb	WBC	PLT	Rtc	BMA* findings
F-3y	Abdominal distention	Growth retardation, hepatomegaly (2 cm) splenomegaly (4 cm)	106	10.6	323	5	Erythroid hypoplasia
F-6y	Pallor, fever	Generalized microlymphadenopathy, hepatomegaly (4 cm)	26	3.6	243	10	Erythroid hypoplasia, megaloblastic changes, lymphocytosis
F-6y	Pain on the extremities, pallor, swelling of the knees in the past	Sternal pain, generalized microlymphadenopathy	41	6.5	259	ND	Erythroid hypoplasia megaloblastic changes, increase in the number of plasmocytes
M-8y	Fatique,pallor,paresthesia on the lower extremities	Splenomegaly (3 cm), clubbing of the fingers	41	11.5	98	17	Overt megaloblastic changes, erythroid hypoplasia
M-2y	Dark urine, jaundice, fever	Icterus, splenomegaly (2 cm) Generalized microlymphadenopathy	43	15.2	160	9	ND
M-8y	Cutaneous rash, mucosal swelling	Diffuse petechia, generalized microlymph-adenopathy	118	22.7	15	ND	Increase in the number of the young elements of megaloblastic cell line
F-2y	Cutaneous rash	Diffuse petechia	96	17.2	17	ND	Increased megakaryocytes
F-6mo	Pallor	Hepatomegaly (3cm) splenomegaly (2cm)	50	7.4	599	6	Hypo-aplasia in the erythroid cell line
M-1mo	Hydrops, prematurity	Ascites, hepato-splenomegaly (2cm)	185	10.6	175	12	ND

Abbreviations:
Y: Year, mo: month, F: Female, M: Male, Hb (G/L): Hemoglobin, WBC($x10^9$/L): White cell Count, PLT ($x10^9$/L): Platelet count, Rtc($x10^9$/L): Reticulocytes, ND: Not done.
*: Initial bone marrow examination.

Anaemia was identified in six cases, reticulocytopcnia in one and thronthoc\\ topenia (ITP) in three cases. Variable degrees of crythroid hypo-aplasia was seen on bone marrow aspiration in all five patients excluding patient 6 and 7 in whom idiopathic thrombocytopenic purpura was diagnosed and patient 5 and 9 on whom bone marrow aspi ration was not performed. During initial investigations, all nine patients had specific IgM antibodies to B 19. 1gM antibodies disappeared in six patients, both IgM and IgG posiUvitv persisted in one patient who had been diagnosed as leukocytociastic vasculitis. In patient 8 with pure red cell anemia (possibly chronically infected case), IgG antibody production were absent but 1gM antibodies had become negative and in patient 9 with hydrops fetalis, 1gM antibodies persisted for 6 months, but IgG antibodies were negative. The diagnoses in our patients were as follows: Celiac disease+iron deficiency, megaloblastic anemia due to vitamin B 12 deficiency, acute lymphoblastic leukemia (ALL), leukocytoclastic vasculitis + iron deficiency, hemolytic anemia, ITP, fetal hydrops and pure red cell anemia. Serological tests for B 19 were performed while the signs and symptoms of disease appeared in the patients with ALL and 1W, after the disease signs and symptoms had established in the others (Table II).

Table II. Serological tests and the diagnosis of patients.

B19 Serology				Diagnosis	Time of the serological Test for B19*
Initial		Final			
IgM	IgG	IgM	IgG		
+	+	-	+	Celiac disease+ Iron deficiency	After
+	+	-	+	ALL	Concomitant
+	-	+	+	Leucocytoklastic vasculitis+ Iron deficiency	After
+	ND	ND	ND	Megaloblastic anaemia+ Vitamin B12 deficiency	After
+	+	-	+	Hemolytic anemia**	After
+	+	-	+	Acute ITP	Concomitant
+	+	-	+	Acute ITP	Concomitant
+	-	-	-	Pure red cell aplasia	After
+	+	+	-	Hydrops fetalis	After

*Temporal relationship of the serological test for B19 and the diagnosis.
**The cause of the hemolytic anemia was not detected.
ND: Not done.

Discussion

Although the major target cell population of 819 in human is eiythroid cell lines, it can invade and cause a variety of infections in different types of cells. It is reported that B19 uses eiythrocyte P antigen(globoside) as a receptor for entrance to the cell and this antigen is expressed in cells other than erythroid cells lines[6,8,12]. Rarely individuals lack P antigen (The P negative phenotypes: PiK and p) and, remarkably, are not susceptible to B19 infection[1,8,12]. Knowledge of a parvovirus receptor has implications for the understanding of the pathogenesisofB 19 infectionandforthepossibie use of parvovimses in gene therapy[1]. In all of the diseases defined in relation with 819 infection until now, patients' immunological response to the virus and heniatological status played a major role in the development of the symptoms of clinical disease.In particular, itis interesting that the clinical disease observed in the patients in whom the humoral immune system, which builds up the strongest defence mechanism against B 19 cannot provide an effective viral neutralization both qualitatively and quantitatively[13-15]. Varying clinical manifestations are due to a combination of the erythroid aplasia and the immunological status of the infected host. In normal host; infection results in a self-limiting subclinical eiythroid aplasia, followed by a presumably immunologically mediated rash or arthralgia[1]. Since the subjects with unstable haematological processes such as iron deficiency and vitamin B12 deficiency anaemia and haemolytic anaemia with hyperplasia presents a favourable environment for B 19 infection, it is not a surprise to encounter B19 infection in these patients. Among the patients with iron deficiency anaemia, no etiological association has been defmed between Celiac disease and B19. However, in, our patients with vasculitis in whom iron deficiency developed due to chronic blood loss, 1319 might have an etiopathological role as mentioned above, It is possible that an underlying immune disorder predisposed our patients to both chronic B19 infection and vasculitis. Various immune abnormalities have been reported in patients with systemic vasculitis[16]. B 19 associated vasculitis brought new insights to the spectrum of this virus[17-19]. The foetus has a rapidly expanding red cell volume, diminished red cell survival (45-70 days) and decreased capacity for clearing infections.

Consequently, the foctus has greater susceptibility to the ill effects of certain viruses, e.g., B 191. It has been postulated that fetal infections represent the clinical manifestations of the first phase of B 19 infection. Among pregnant women with a confirmed primary Bl9 infection, it is believed that the risk of an abnormal outcome is approximately 5-10% and the risk is highest if the infection occurs during the first 20 weeks of gestation. Fetal parvovirus infection may manifest itself as non-immunologic hydrops fetalis, fetal or congenital anaemia, abortion, stillbirth, oras an asymptornatic self-limiting episode. 819 infects the erythroid progenitors of the fetus leading to severe anaemia and hypoxia. Anaemia may provoke high output cardiac failure, causing fluid to accumulate in the body cavities, resulting in generalized edema and possible death. Because of decreased capacity for clearing infections, in our patient 9 with hydrops fetalis, (probably chronically infected patients), IgM antibodies persisted for a minimum of 6 months, but IgG antibodies appeared only after the 7th month. The persistence of specific 1gM antibody for a minimum of 2 years and possibly 4 years has been reported[2,3,11]. B19 infection can cause thrombocytopenia[20-22]. Longevity of B19 in mcgakaiyoblastic cell cultures in the presence of erythropoletin suggested that the virus can infect the megakaryocytes[23]. In addition, B 19 is proposed to slow the megakaryocytic colony formation[9]. However, it is not clear whether viral invasion has a direct suppressive effect on the megakaryocytes or the immune response against the virus leads to the development of thrombocytopenia. Identification of specific 1gM antibodies while the findings of ITP developed in our patient suggests B 19 can be an etiological agent in ITP. Since the thrombocytes also carry the erythrocyte P antigen, it can be suggested that the thrombocytes altered by the viral invasion can be exposed to immune attack or the thrombocytic destruction occurs when immune response against the virus is directed to P antigen on the thrombocytes by anti-idiotypic mechanism. On the other hand, rnegakaiyocytic cell line which is activated in the bone marrow because of thrombocytopenia caused by a different mechanism and entered mitosis with increased numbers of the young elements, will provide a favourable environment for B19 infection which needs the S phase factors; therefore, 1319 infection in ITP may be an incidental association. Development of ALL after a case of 1319 infection leading to bone marrow hecmsis has been reported[24]. In our case of ALL, specific 1gM antibodies to B19 were identified during the period when the findings of disease developed; and it was shown by serial bone marrow aspirations that the bone marrow findings of ALL progressed slowly. Though it is somewhat early, it may be discussed that B19 participates directly or indirectly in the development of some of the hematological clonal diseases. Alternatively, it is possible that some leukemia cells can be a favourable target for B19. Sometimes B 19 provokes a decrease in the levels of CD4 and CD8 positive T-lymphocytes, 8-16 days after inoculation. There is usually no. change in the number or morphology of monocytic, basophilic or eosinophilic granulocytes and only infrequently, atypical lymphocytes are observed1. The relation of B19 infection and pure red cell anaemia in subjects with inadequate immune response to B 19 has been reported[14]. Many investigators have also reported cases in which patients were unable to mouni an efficient antibody response due to an underlying immuno-deficiency. In our case, though an initial IgM antibody response had been developed to 1319, an IgG response was not detected later. It must be remembered that investigation of the viral DNA will contribute to the explanation of this process. These findings may suggest that IgG antibodies playing a major role in the viral neutralization especially in the long-term, cannot develop and the infection can not be controlled. Chronic B19 infection is associated with defective or delayed antibody formation to viral antigens. In some chronically infected patients, igG antibody production is absent. Other such patients might suffer quantitative and qualitative IgG defects[1]. Some immunocomponent patients have been reported not to mount a detectable IgM response[5] and 15-20% do not produce specific IgG[25]. Alternatively, negative or equivocal serology could indicate immunodeficiency. Equivocal IgG and IgM titers is a phenomenon typical for persistent infections in patients with immunodeficiency25. Several patients have been described with chronic B19 infection accompanying subtle forms of immune dysfunction, characterized

by qualitatively abnormal immune responses rather than absolute immunodeficiency. Identification of specific IgM and IgG antibodies to B 19 is a rather reliable method in the diagnosis of B19 infection[9]. Very often, search for B19 DNA alone, or in combination for specific antibodies, will prove beneficial. However, when the investigations of viral DNA in the body fluids and at the tissue level is combined with the results of the serological tests, the evaluation can be much more significant. Particularly in cases involving those suffering from like persistent congenital red cell aplasia, the clinician shouLd, when looking for a possible B19 infection, always continue the search using the PCR technique, even if the antibody tests are negative[1]. Next step will be to reveal that the identified virus has caused cellular changes (apoptosis etc.) which lçad to the disease process, because, B 19 probably causes the pathologic changes by varying types of infection (productive, persistent, etc.) in different cells. 819, whose relation with many diseases has been defined at present, seems to keep on being a subject of interest. In this context, it will be important to differentiate the coincidental associations from the etiopathogenetic relations.

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