ACQUIRED IMMUNODEFICIENCY IN AN INFANT: POSSIBLE TRANSMISSION BY MEANS OF BLOOD PRODUCTS

ARTHUR J. AMMANN MORTON J. COWAN
DIANE W. WARA PEGGY WEINTRUB
SELMA DRITZ HOWARD GOLDMAN
HERBERT A. PERKINS

Pediatric Immunology/Rheumatology Division of the University of California San Francisco Medical Center; City and County Public Health Department of San Francisco; and the Irwin Memorial Blood Bank, San Francisco, California, USA

Summary An infant who received multiple transfusions during the first few days of life for rhesus disease became ill with recurrent infections when 6 months old. Hepatitis, thrush, *Candida* dermatitis, otitis media, and disseminated *Mycobacterium avium intracellulare* infection occurred by ,14 months of age. Immunological studies showed raised immunoglobulin levels, decreased mononuclear-cell responses to allogeneic cells and mitogen, and a decreased helper/suppressor cell ratio. It was determined that one of the blood donors, who was well at the time of blood donation, had died 17 months later with multiple opportunistic infections and acquired immunodeficiency. The clinical and laboratory findings in our patient suggest that he acquired a transmissible infectious agent from a blood transfusion, resulting in acquired immunodeficiency, and that this agent was not cytomegalovirus, Epstein-Barr virus, or hepatitis B virus.

Introduction

ACQUISITION of subclinical and clinical infection after the administration of blood products has been reported for hepatitis B virus and cytomegalovirus.[1-3] Patients receiving large volumes of blood, immunosuppressed patients, and newborn infants appear particularly susceptible to severe post-transfusion syndromes.[4,5] Concern has arisen about the possible role of a transmissible infectious agent in the aetiology of an acquired immunodeficiency syndrome (AIDS) in patients with haemophilia A repeatedly receiving blood products.[6] AIDS has been found primarily in young homosexual men but also in intravenous-drug users and Haitian refugees.[7,8] Although the aetiology of AIDS is unknown, an infectious agent is likely. The widespread occurrence of AIDS suggests that a transmissible infectious agent may inadvertently be inoculated into patients by means of blood-product administration. We report a 20-month-old male infant with clinical and laboratory features of AIDS and *Mycobacterium avium intracellulare* infection who received multiple blood products during the first 2 weeks of life.

Case-report

The patient was born to a 29-year-old G_2P_2 woman with a history of rhesus sensitisation. The infant weighed 2850 g at 33 weeks' gestational age and was delivered by caesarean section. No intrauterine transfusions were given. He was jaundiced at birth and the first two-volume exchange transfusion was carried out within the first 24 h of life. Over the next 4 days five more two-volume exchange transfusions were carried out. After the first day the infant required intubation, which was maintained for 16 days. There were no complications of the exchanges except transient thrombocytopenia. During 8 weeks in hospital, the infant received blood products from eighteen donors; six two-volume exchange transfusions, five platelet transfusions, and seven partial transfusions for correction of anaemia. All blood was irradiated with 30 Gy before administration. Calibration of the radiation source indicated that the administered dose was within 2 Gy of the calculated dose.

After discharge from the hospital at 2 months of age, the baby remained well until at 4 months hepatosplenomegaly was observed and at 6 months recurrent draining otitis media, thrush, and *Candida* dermatitis developed. The episodes of otitis were not controlled by oral antibiotics, and bilateral myringotomy and intravenous antibiotics were required. His growth and development were normal until he was 6 months old, when weight loss and developmental retardation were first observed. At 10 months intermittent vomiting and diarrhoea began. Hepatitis was diagnosed on the basis of high liver enzyme levels. There was no antibody to hepatitis A or B, cytomegalovirus, or Epstein-Barr virus. The total white-cell count, total lymphocyte count, platelet count, α_1-antitrypsin, and sweat electrolytes were normal. Immunoglobulins were normal for age.

When the baby was 13 months old jaundice was noted. Intermittent vomiting and diarrhoea continued. A month later he

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IMMUNOLOGICAL EVALUATION

Age (mo)	Immunoglobulin (g/l)*			%T cells	%OKT4	%OKT8	OKT4/8	PHA (cpm)	MLC (cpm)
	IgG	IgM	IgA						
10	7·8	0·8	0·4	ND	ND	ND	ND	ND	ND
14	18·7	3·2	8·9	23	ND	ND	ND	6800	900
18	ND	ND	ND	7	40	34	1·2	11 230	480
Normal range	..	..	..	>65	51±7	29±8	1·9±0·7	>15 000	>5000

*Values are normal at 10 months and increased at 14 months.
OKT4 = helper/inducer cells; OKT8 = suppressor/cytotoxic cells; PHA = phytohaemagglutinin stimulation of peripheral-blood lymphocytes; MLC = mixed lymphocyte culture; ND = not done.

was admitted to the University of California San Francisco hospital. He had oral thrush, lymphadenopathy, and hepatosplenomegaly. Laboratory studies showed a white-cell count of $7{\cdot}2\times10^9$/l with 49% polymorphonuclear cells and 42% lymphocytes, platelet count 283×10^9/l, total bilirubin 8 mg/dl (137 μmol/l) with a direct fraction of 6 mg/dl (103 μmol/l), and alkaline phosphatase 3850 U/l (King-Armstrong). Liver biopsy showed periportal fibrosis with some giant cells. There was no evidence of active hepatitis. Serum was negative for hepatitis e antigen, hepatitis B surface antigen, and hepatitis A and B antibody. Immunological studies (see table) showed raised levels of IgG, IgM, and IgA, no antibody to blood group B (patient was group A), and no antibody response to tetanus antigen. The percentage of T cells, phytohaemagglutinin response of peripheral-blood lymphocytes, and mixed-lymphocyte-culture response were lower than normal.

The patient was readmitted for evaluation of bloody stools and malabsorption when 15 months old. During this hospital stay Coombs-positive haemolytic anaemia, thrombocytopenia with antiplatelet antibodies, and neutropenia were found. Bone-marrow aspirate showed hypoplastic marrow with immature myeloid elements; megakaryocytes were present. The bone marrow was cultured for viruses, bacteria, and fungi. Because of life-threatening bleeding secondary to thrombocytopenia and anaemia secondary to the haemolysis, prednisone therapy (2 mg/kg) was started but failed to correct bleeding and haemolysis. When the prednisone dose was increased to 30 mg/kg for 5 days the platelet count rose, haemolysis was reduced, and bleeding was controlled. The patient was discharged from hospital on tapering doses of prednisone.

When the patient was 18 months old he was readmitted for treatment of *M avium* infection. A bone-marrow sample taken when he was 15 months old, before steroid therapy, was reported positive for *M avium*. Cultures of gastric aspirate, urine, and repeat bone marrow were positive for acid-fast organisms on smear, and *M avium* was cultured. Treatment with isoniazid, amikacin, rifampicin, and ethambutol was started, and later ansamycin was substituted for rifampicin and paraminosalicylic acid was added. During the next 2 months the patient had intermittent thrombocytopenia and anaemia. Hyperalimentation was used to maintain nutrition and administer antibiotics. Bone-marrow aspirates were still positive for *M avium* after 10 weeks of treatment. Immunological studies showed a further rise in immunoglobulin levels and decline in the percentage of T cells; the proportion of OKT4 cells was lower than normal and that of OKT8 cells normal with a low ratio (table).

Viral cultures on blood, bone marrow, urine, and nasopharyngeal swabs were negative on all occasions except for a single isolate of cytomegalovirus from the nasopharynx. Two subsequent cultures of the nasopharynx and all cultures of liver-biopsy material were negative for cytomegalovirus. There was still no antibody to hepatitis B core and surface antigens, Epstein-Barr virus, or cytomegalovirus. Peripheral-blood lymphocytes did not show spontaneous transformation in culture.

There was no family history of immunodeficiency. A 4-year-old brother is well, showing normal growth and development. The parents are heterosexual, non-Haitian, and have no history of intravenous-drug abuse. Studies of T-cell numbers and function on the mother, father, and brother showed normal numbers of T cells, helper/inducer cells (OKT4), suppressor/cytotoxic cells (OKT8), and normal mononuclear-cell response to phytohaemagglutinin and in mixed lymphocyte culture.

The identification of the organism growing in the patient's marrow, gastric aspirate, and urine as *M avium* and the suspicion that he had AIDS led to an investigation to determine the health status of the donors of blood transfused to the patient before the initial bone-marrow aspirate positive for *M avium*. The list of donors was compared with a list of known AIDS patients in the San Francisco area. One of the platelet donors was identified as a patient with AIDS who had died 17 months after the blood donation. At that time he had appeared healthy, but 7 months later he became ill and deteriorated progressively with cytomegalovirus pneumonia, lymphadenopathy, herpes simplex II infection, *Pneumocystis carinii* pneumonia, *Salmonella* sepsis, and encephalitis of unknown aetiology, and he died 10 months later.

Discussion

Transfusion of blood products is known to be associated with a risk of viral transmission. The severity of the disease appears to be related to the number of transfusions as well as the underlying disorder. Particularly severe post-transfusion syndromes occur in immunosuppressed patients, patients with splenectomy, and newborn infants.[4,5,9] Despite the known association of administration of blood products and transmission of infectious agents, there have been no reports of AIDS in transfused patients except for patients with haemophilia A.[6]

Our patient had several features of AIDS. The clinical infection appeared 6–7 months after multiple blood-product administration. Our studies in a family with vertically transmitted AIDS suggest that the period before the appearance of T-cell abnormalities is approximately 2–6 months in infants (M. J. Cowan et al, unpublished), whereas it may be as long as 12–14 months in adults with AIDS. Hepatitis, chronic *Candida* infection, *M avium* infection, lymphadenopathy, hepatosplenomegaly, and chronic malabsorption are other features of AIDS.[7,10] The immunological profile of our patient was consistent with AIDS.[7,11]

We believe that AIDS developed in this patient as a result of an infectious agent being transmitted by blood-product administration; it is possible, however, that he was born with a primary immunodeficiency disorder which did not show clinical signs until 6 months of age. The clinical and laboratory features of the patient are not consistent with readily diagnosable inherited disorders such as ataxia-telangiectasia, Wiskott-Aldrich syndrome, or severe combined immunodeficiency disease.[12] Normal or elevated immunoglobulins and depressed T-cell immunity may be observed in association with purine nucleoside phosphorylase or adenosine deaminase deficiency or combined immunodeficiency disease (Nezelof's syndrome).[12] Our patient had normal adenosine deaminase and purine nucleoside phosphorylase activity, but combined immunodeficiency disease cannot be excluded. However, this disorder encompasses a phenotype that is usually

sporadic and of uncertain aetiology. One possible aetiology of combined immunodeficiency disease is a transmissible infectious agent resulting in AIDS.

T-cell immunodeficiency has been observed in post-transfusion and congenital cytomegalovirus infection, but it is transient and associated with a specific unresponsiveness of peripheral-blood lymphocytes to stimulation with cytomegalovirus antigen rather than the broadly based T-cell deficiencies. The antibody response to cytomegalovirus is normal or enhanced.[13,14] Our patient had no evidence of cytomegalovirus, hepatitis B virus, or Epstein-Barr virus infection. Thus, if his AIDS was a result of a transmissible infectious agent, it must be an infectious agent not tested for or a new unidentified agent. All blood products given to the infant were irradiated with 30 Gy, so the postulated infectious agent must be resistant to such radiation doses.

M avium infection has not previously been reported in infants nor in patients with congenital T-cell deficiency. Most infections occur in immunocompromised patients, many of whom are homosexual men with AIDS. It is possible that patients with AIDS have a unique susceptibility to *M avium* infection. Therapy is usually ineffective in spite of the use of multiple drugs for long periods,[15] and was so in our patient.

Although AIDS as a consequence of a transmissible infectious agent cannot be definitely proven in this patient, the evidence strongly suggests such a possibility. Future prospective studies should attempt to determine the incidence of AIDS in transfused patients, especially newborn and premature infants, immunosuppressed patients, and patients receiving multiple blood products. As no diagnostic test is available for AIDS, serious consideration should be given to avoiding the use of blood products obtained from individuals with the potential to transmit AIDS. A disturbing observation in this report is that the platelet donor was healthy and did not become ill with AIDS until 7 months after donation.

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Correspondence should be addressed to A. J. A., Pediatric Immunology and Rheumatology, Pediatric Research Center, University of California San Francisco, San Francisco, California 94143, USA.

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Addendum

The patient died aged 2 years with *Pneumocystis carinii* pneumonia. Cultures remained positive for *M avium*.

Preliminary Communication

FORSKOLIN LOWERS INTRAOCULAR PRESSURE IN RABBITS, MONKEYS, AND MAN

JOSEPH CAPRIOLI MARVIN SEARS

Department of Ophthalmology and Visual Science, Yale University School of Medicine, New Haven, Connecticut 06510, USA

Summary Topical ocular application of forskolin, a diterpene that increases intracellular cyclic adenosine monophosphate by stimulating adenylate cyclase directly without cell surface mediation, lowered intraocular pressure (IOP) in rabbits, monkeys, and volunteers who were free from eye disease. In man 50 μl of a topical suspension of 1% forskolin significantly lowered IOP in 1 h, the effect reaching a peak at 2 h but remaining significant for at least 5 h. Outflow pressure fell by 70% on average. Forskolin and its analogues represent a new class of drugs active against glaucoma which differ in their molecular actions from any previously used drug.

INTRODUCTION

STIMULATION of beta-adrenergic receptors in the ciliary epithelium of the eye lowers intraocular pressure (IOP) by reducing net aqueous humour inflow. Cell surface receptors functionally coupled to adenylate cyclase can be activated by beta-adrenergic agonists, cholera toxin, and certain gonadotropic hormones.[1-4] Timolol, a non-selective beta-blocker, also lowers IOP, by a mechanism which has not been elucidated.[5] Forskolin, a diterpene (fig 1), acts directly on adenylate cyclase without cell surface mediation to increase intracellular levels of cyclic adenosine monophosphate (cAMP).[6] We have demonstrated the reduction of IOP in rabbits, monkeys, and man by topical forskolin.

MATERIALS AND METHODS

Forskolin was obtained from Calbiochem Behring Corporation, La Jolla, California. The studies were done on male New Zealand white rabbits weighing 2·0–2·5 kg, *Macaca arctoides* monkeys weighing 10–15 kg, and healthy volunteers with no evidence of eye disease.

IOP was measured by applanation tonometry after a drop of topical proparacaine in the awake rabbit, in monkeys under ketamine anaesthesia (10 mg/kg intramuscularly), and in the volunteers.

Forskolin was suspended in an isotonic solution containing 0·5% methylcellulose. 50 μl was applied topically to the right eye while the left eye received the vehicle only. Topical suspensions of 0·1%, 1·0%, and 4·0% were each tested in twenty rabbits. A 1·0% topical suspension was used in ten monkeys and in ten volunteers.