ACQUIRED-IMMUNODEFICIENCY-LIKE SYNDROME IN TWO HAEMOPHILIACS

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Summary The immunological status of two multiply transfused patients with severe haemophilia A and diffuse lymphadenopathy was evaluated. Both patients appeared clinically well and denied homosexuality or intravenous drug abuse. Immunological studies revealed depressed cellular immune function with anergy, relative lymphopenia, decreased T helper cells, and increased T suppressor cells in both patients and an altered T-helper-cell/T-suppressor-cell ratio in one. Hyperresponsiveness of the humoral immune system was demonstrated by elevated IgG and IgM. Lymph-node biopsy revealed benign non-specific hyperplasia in both patients. The lymphadenopathy and immunological features in these two haemophiliacs bear a striking resemblance to the acquired immunodeficiency syndrome (AIDS) of homosexuals, intravenous drug abusers, and Haitian immigrants. These findings may represent a prodromal phase or a forme fruste of AIDS. Transmission of an infectious agent in blood products seems likely.

Introduction

ACQUIRED dysfunction of the cellular immune system has been recognised in homosexuals,[1-11] intravenous drug abusers,[12] Haitian refugees,[13] and haemophiliacs.[14] This syndrome, characterised by lymphopenia, defective T-lymphocyte function, and a reversal of the T-helper-cell/T-suppressor-cell ratio, has been associated with an increased risk of opportunistic infections and malignant neoplasms in otherwise healthy people. The causative agent(s) of this acquired immunodeficiency syndrome (AIDS) have not yet been identified. We now report a strikingly similar disorder in two symptom-free haemophiliacs with diffuse lymphadenopathy.

Methods

Two patients with severe haemophilia A and diffuse lymphadenopathy were evaluated in September, 1982, at the Hemophilia Center of Western Pennsylvania and Presbyterian University Hospital. Complete and differential blood counts were obtained on both patients. Serum immunoglobulins were measured with nephelometry,[15] and serum proteins and immune complexes were measured with agarose-gel electrophoresis.[16,17] T cells, including T helper cells and T suppressor cells, were measured with flow cytometry and monoclonal antibody (Becton Dickinson).[18] Lymphocyte responsiveness to phytohaemagglutinin was determined by incubation of Ficoll 'Hypaque'-separated lymphocytes with phytohaemagglutinin and tritiated ^{3}H-thymidine.[19] Specimens for isolation of cytomegalovirus (CMV) were cultured on foreskin fibroblasts. Lymph-node biopsy specimens were examined by the department of pathology.

Case-reports

Patient 1

This 32-year-old White man with severe haemophilia A has a factor-VIII level of <0·01 U/ml and is on home treatment with factor-VIII concentrate. In 1980–81 he used 5680 units of factor-VIII concentrate from a single lot. He was noted to have lymphadenopathy at his 6-month evaluation April 8, 1982. The nodes had been present for several months, but he felt well. He denied malaise or systemic symptoms (weight loss, night sweats, fever, pruritus). Although he carries anti-HBs and anti-HBc, he has had no clinical hepatitis. He denied a history of intravenous drug abuse, foreign travel, or homosexuality. Specifically, there was no known bisexuality, promiscuity, or contact with known AIDS cases. He is employed as a welder. Physical examination showed bilateral non-tender adenopathy in the cervical, posterior auricular, occipital, supraclavicular, axillary, and inguinal areas and no hepatosplenomegaly. A 'Monospot' test was negative, and IgG-CMV titres were 1:16 (seronegative) on April 13, 1982, and May 11, 1982.

A right axillary lymph-node biopsy, carried out on Sept. 3, 1982, under cover of factor-VIII concentrate, revealed benign non-specific hyperplasia. Aerobic, anaerobic, and CMV cultures of the node, as well as smears stained for *Mycobacterium*, both typical and atypical, were negative. Urine, buffy-coat, and throat cultures were negative for CMV, and he was anergic to the following skin-test antigens: *Candida*, histoplasmosis, mumps, and PPD. A baseline chest X-ray was unremarkable. The results of immunological studies are shown in the accompanying table. When evaluated on Oct. 5, 1982, he had lost 5 lb in weight but remains well.

Patient 2

This 18-year-old White man with severe haemophilia A has a factor-VIII level of <0·01 U/ml and is on clinic treatment with factor-VIII concentrate. In 1978–79, the year before development of adenopathy, he used 33 308 units of factor-VIII concentrate from

IMMUNOLOGICAL DATA

Test		Normal range	Patient 1	Patient 2
White-cell count	(cells/μl)	4100–10 700	4600	4400
Lymphocyte count	(cells/μl)	20–40% (1500–4000)	19% (874)	26% (1144)
T lymphocytes		70% (1050–2800)	74% (646)	70% (801)
T helper cells		50% (750–2000)	32% (280)	35% (400)
T suppressor cells		20% (300–800)	34% (297)	30% (343)
T helper/suppressor ratio		1·0–3·0	0·9	1·2
Immunoglobulins:				
IgG	(mg/dl)	975±201	1810	4560
IgA	(mg/dl)	202±83	172	191
IgM	(mg/dl)	93±30	127	241
Serum-protein electrophoresis				
Total protein	(g/dl)	6·0–8·3	7·80	8·60
Albumin	(g/dl)	3·2–5·2	4·20	3·29
α_1	(g/dl)	0·1–0·4	0·45	0·31
α_2	(g/dl)	0·6–1·0	0·59	0·70
β	(g/dl)	0·6–1·4	0·84	0·81
γ	(g/dl)	0·7–1·6	1·69	3·49
			+	+
Immune complexes		0	+ (biclonal pattern)	+ (biclonal pattern)
PHA stimulation index				
Autologous plasma	(cpm)	>150	1006·2	931·6
AB plasma	(cpm)	>150	914·0	510·6
CMV (IgG) titre		<20 seronegative >30 seropositive	125	49

PHA = phytohaemagglutinin.

G. M. ANABWANI AND OTHERS: REFERENCES—*continued*

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twelve different lots. In December, 1979, he was first noted to have adenopathy in the posterior cervical and occipital areas. The adenopathy progressed to involve the supraclavicular area in August, 1980, and the anterior cervical, posterior auricular, axillary, and inguinal areas in August, 1982. He denies malaise or symptoms of weight loss, fever, sweats, or pruritus. There is no history of intravenous drug abuse or recent foreign travel. There was no history of homosexuality, or contact with known AIDS cases. Though a carrier of anti-HBs and anti-HBc, he has not had clinical hepatitis. Physical examination showed bilateral non-tender adenopathy in the anterior and posterior cervical, posterior auricular, occipital, supraclavicular, axillary, and inguinal areas and no hepatosplenomegaly. Preliminary laboratory data from December, 1979, revealed a negative monospot test and seronegative toxoplasmosis and CMV titres. Serum IgG and IgM levels were elevated at that time to 2960 mg/dl and 228 mg/dl, respectively. His only other medical problem was short stature and pubertal delay, for which he was treated with sublingual testosterone proprionate between February, 1979, and November, 1980, with improvement in both height and weight.

A right posterior cervical lymph-node biopsy, carried out on Sept. 29, 1982, under cover of factor-VIII concentrate, revealed benign non-specific hyperplasia. Cultures of the lymph node for aerobic and anaerobic bacteria and CMV were negative, as were smears for *Mycobacterium*, both typical and atypical. In addition, his buffy coat was negative for CMV. He was anergic to *Candida*, histoplasmosis, mumps, and PPD skin-test antigens. A baseline chest X-ray was unremarkable. Immunological data are shown in the table.

Discussion

Because of the reports of acquired immunodeficiency syndrome in several groups of people with a high frequency of hepatitis-B exposure, inlcuding three haemophiliacs with opportunistic infections,[1,4] we studied two sympton-free patients with severe haemophilia A and lymphadenopathy. Both haemophiliacs are treated with factor-VIII concentrate and have evidence of chronic hepatitis-B exposure, by serological markers.

The detection of (1) a defective cellular immune system with anergy, absolute lymphopenia, and reversal of the T-helper-cell/T-suppressor-cell ratio in one of these two haemophiliacs and (2) an intact but hyperfunctioning humoral immune system with hypergammaglobulinaemia and benign non-specific lymph-node hyperplasia in both is consistent with the diagnosis of AIDS. In the absence of opportunistic infection or malignant tumour, their presentation with asymptomatic diffuse lymphadenopathy may represent a prodromal phase or a forme fruste of AIDS. Some homosexuals have been observed to have a similar prodromal phase.[1,2]

Although viruses (such as hepatitis B, CMV, and herpes simplex 2) and drugs (such as amyl and isobutyl nitrates and marijuana) have been implicated, the aetiology of this syndrome remains unknown. The presence of this AIDS-like syndrome in haemophiliacs suggests the possibility of transmission by an infectious agent through blood products.

This study suggests that haemophiliacs may be at increased risk for the acquired immunodeficiency syndrome and associated infectious or malignant complications. Careful observation of these and other haemophiliacs for appearance of symptoms will be necessary to further our understanding of this disorder.

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References continued at foot of next column

Preliminary Communication

INCREASED SEROTONIN-2 BINDING SITES IN FRONTAL CORTEX OF SUICIDE VICTIMS

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Summary Differences in serotonin-2 (5-HT_2) receptor properties were studied in frontal cortex from suicide victims and controls. The number of 5-HT_2 receptors was significantly higher (44%) in the suicide group. The postsynaptic receptor changes were consistent with previous findings of a reduced number of presynaptic serotonin receptors in the same post-mortem series. The combined findings of both studies support the decreased use of serotonin in suicide victims and may also throw light on the mechanism of action of antidepressant drugs.

INTRODUCTION

ALTERED functioning of the serotoninergic system is implicated in depression and suicide.[1] Post-mortem studies of suicide victims and depressives have revealed below-normal levels of serotonin (5-hydroxytryptamine [5-HT]) and its principal metabolite 5-hydroxyindoleacetic acid (5-HIAA) in various brain regions.[2-6] In-vivo studies of

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