ACQUIRED IMMUNODEFICIENCY SYNDROME IN THE CHILD OF A HAEMOPHILIAC

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Summary Oral thrush developed during the second month of life in the 5-month-old son of a patient with haemophilia A. He did not feed well, and interstitial pneumonitis, lymphadenopathy, hepatosplenomegaly, and a cellular immune defect consistent with the acquired immunodeficiency syndrome (AIDS) followed. Both parents had signs of pre-AIDS during the year before their son's illness. Transmission presumably occurred in 3 steps: parenterally, via factor VIII concentrate in the haemophiliac; heterosexually, from the haemophiliac to his wife; and vertically, from mother to infant, or via close paternal-infant or maternal-infant contact. This first report of AIDS in the child of a haemophiliac supports the theory that AIDS is caused by an infectious agent. Concentrate-treated haemophiliacs may transmit this agent to their spouses or children, resulting in pre-AIDS or AIDS.

Introduction

THE acquired immunodeficiency syndrome (AIDS) has been reported in sexual partners and infants of homosexuals, intravenous drug abusers, and Haitians.[1-9] Several studies have reported no special risk for AIDS-like immunological abnormalities in the spouses and siblings of symptom-free haemophiliacs,[10,11] but AIDS in the wife of a haemophiliac[12] and pre-AIDS in the sexual partner of a haemophiliac have been described.[13]

We report the first case of AIDS in the infant of a man with haemophilia A treated with factor VIII concentrate, who, together with his wife, has lymphadenopathy and impaired cellular immunity consistent with pre-AIDS. Our observations support the theory that pre-AIDS can be transmitted heterosexually to partners not otherwise at risk for AIDS and suggest that AIDS can be transmitted to the offspring of haemophiliacs either vertically, through the female sexual partners, or through close maternal-infant or paternal-infant contact.

Methods

A patient with haemophilia A and his wife, their 5-month-old son, and his wife's 3½-year-old daughter by a previous marriage were examined in August, 1984, at the Hemophilia Center of Western Pennsylvania and Children's Hospital of Pittsburgh. The haemophiliac had also been evaluated in May and July, 1983.[14] Complete and differential blood-counts were obtained, and T lymphocytes, including T helper cells and T suppressor cells, were counted by means of flow cytometry.[15] Serum immunoglobulins were measured with a rate nephelometer.[16] Cytomegalovirus antibody (IgG) and Epstein-Barr virus (EBV) viral-capsid antibody (VCA-IgG) were measured by means of indirect immunofluorescence. Lymphocyte responsiveness to phytohaemagglutinin (PHA) or pokeweed mitogen (PWM) was evaluated in a suspension-culture (microculture) system.[14,17,18] Specimens for isolation of cytomegalovirus (CMV) were cultured on foreskin fibroblasts. The T-colony assay was done with mononuclear cells cultured in semisolid agar in the presence of PHA and incubated for 7 days in a 5% CO_2 humidified atmosphere at 37°C.[14,17,19] Colonies (tight clusters containing at least 25 cells) were identified with an inverted microscope. The assay was repeated with interleukin-2 (Electronucleonics Laboratories, Silver Springs, MD) prepared from PHA-stimulated lymphocytes (after which PHA was removed by chromatography) at a concentration of 5%/plate. Antibody to human T-lymphotropic virus type III (HTLV-III) was measured with the western blot technique, with a human T-lymphoid-lymphoma cell-line as substrate.[20]

Case-reports

Patient 1.—This 5-month-old white male was born to a 23-year-old gravida-2 para-2 white woman with insulin-dependent diabetes mellitus after a 36-week gestation. The antenatal course was complicated by vulvovaginal candidiasis refractory to topical antifungal agents and an episode of ketoacidosis during the 2nd trimester. Delivery was by caesarean section before rupture of membranes. Perinatal problems included hypoglycaemia and hyperbilirubinaemia, which responded to phototherapy. The boy was breastfed for 2½ months. During the 2nd month oral thrush, resistant to nystatin and gentian violet, developed. He did not feed well, and after 3 months tachypnoea and perioral cyanosis developed. A chest X-ray showed diffuse bilateral infiltrates. Arterial-blood gas on 51 supplementary oxygen was pH 7·35, pCO_2 30·5, bicarbonate 22, and pO_2 145. The white-cell count was 20 500/μl, with 48% polymorphonuclear leucocytes, 4% bands, 1% monocytes, and 45% lymphocytes. Although blood-cultures were sterile and a spinal tap showed 7 lymphocytes/μl, the patient was given ampicillin. Because of progressive respiratory deterioration he was intubated. Chest X-ray showed pulmonary congestion and a raised cardiac-thoracic ratio. He required mechanical ventilation, dopamine, dobutamine, nitroprusside, 5% albumin, and packed red blood-cells. Nafcillin, cephazolin, and gentamicin were also given. Bronchoscopy showed no structural defect, and open lung biopsy demonstrated pulmonary interstitial fibrosis and no viral inclusions. Bacterial and fungal cultures were negative, as was the stain for acid-fast bacilli. His pulmonary oedema responded to digoxin, frusemide, and fluid restriction. Cardiac catheterisation showed elevated left ventricular end-diastolic pressure without intercardiac shunt or anatomical defect. This was consistent with myocarditis. Although the course was complicated by an episode of otitis media, which responded to intravenous ampicillin, the infant continued to improve and was extubated 3 weeks later. Further examination revealed oral thrush, hepatosplenomegaly, and lymphadenopathy in the cervical, axillary, and inguinal areas. Many of the nodes were 2 × 2 cm in diameter. A chest X-ray showed hyperexpansion with streaking infiltrates; no thymic shadow was noted. Antibiotic therapy was discontinued. Electrocardiogram showed 1st-degree atrioventricular block, extreme right-axis deviation, and right ventricular hypertrophy greater than expected for his age. An echocardiogram showed a thickened left ventricle but no left ventricular dysfunction. Digoxin and diuretics were discontinued without difficulty. Tests for legionella antigen, pneumocystis antigen, herpes simplex IgG, and toxoplasma IgG were negative. Initial antibodies to Epstein-Barr virus early antigen (EA IgG), nuclear antigen (EBNA-IgG), and viral-capsid antigen (VCA-IgG, VCA-IgM) were all negative. CMV was isolated from the urine and throat, and his initial CMV-IgG titre was >120. Immune complexes were positive and the antinuclear antibody was negative. Skin testing revealed non-reactivity to candida and purified protein derivative. Results of other immunological studies are shown in the table. The infant gained weight on a 24 calorie/ounce formula and was discharged. Hepatosplenomegaly, lymphadenopathy, and oral thrush persist but the chest infiltrates have resolved. His only current medication is oral nystatin.

Patient 2.—The father of the infant is a 26-year-old white man with severe haemophilia A, with factor VIII <0·01 U/ml. He has

IMMUNOLOGICAL DATA

Test	Normal range	Patient and date tested: 1 September, 1984	2 September, 1983	2 September, 1984	3 September, 1984	4 September, 1984
White-cell count (cells/μl)	4100–10 700	12 800	5500	5200	5700	9800
Lymphocyte count (cells/μl):	20–40% (1500–4000)	59% (7552)	26% (1450)	29% (1508)	52% (2964)	54% (5292)
T lymphocyte	70% (1050–2800)	85% (6419)	76% (1109)	91% (1372)	96% (2845)	92% (4869)
T helper	50% (750–2000)	15% (1133)	30% (431)	17% (256)	35% (1037)	64% (3387)
T suppressor	20% (300–800)	69% (5211)	46% (662)	70% (1056)	58% (1719)	28% (1482)
H/S ratio	(1·0–3·0)	0·22	0·65	0·24	0·60	2·29
*Immunoglobulins (mg/dl):**						
IgG	774–1176	1380	ND	2060	2070	739
IgA	119–285	15	ND	710	296	151
IgM	63–123	262	ND	210	233	149
IgE	0–122	<2·4	ND	18·2	281	97·8
Suspension cultures:†						
With PHA	18 518±3590	47 836	21 803	22 899	39 142	37 843
With PWM	12 139±1742	3367	4173	2214	2824	22 479
T-colony assay‡	3964±395	0	1800	0	0	480
T-colony assay after interleukin-2	7383±624	2220	6100	3180	2600	6700
Platelets (cells/μl)	(150–450 × 10^3)	351	186	138	260	297
CMV-IgG titre	<4	>120	4	>120	75	<16
EBV-VCA-IgG titre	<5	100	80	⩾1000	⩾1000	300
HTLV-III titre	-	-	+	+	+	-

*Normal values are for adult males. Values for normal adult females are 777–1351, 100–248, 68–150, and 0–122 mg/dl, respectively; infants are 242–612, 10–46, 26–60, and 0–16·3 mg/dl, respectively; and 3-year-old children are 680–1128, 51–155, 55–133, and 0–16·9 mg/dl, respectively.
†Mean ±SEM tritiated thymidine uptake in counts/min. There were 9 controls of both sexes.
‡Mean ±SEM colonies per 7·5 × 10^3 cells plated. There were 24 controls of both sexes.
ND = not done.

been receiving factor VIII concentrate for 9 years. In May, 1983,[15] splenomegaly and a low T-helper/suppressor ratio (0·65) were noted. Both CMV-IgG and EBV-VCA-IgG titres were positive. In January, 1984, diffuse lymphadenopathy was noted in the anterior and posterior cervical, axillary, and inguinal areas. Although he has chronically positive hepatitis-B antibodies (anti-HBs, anti-HBc), he has no clinical hepatitis. He denied intravenous drug abuse and had monogamous sexual contact with his wife for the 2 years before his son's illness. He is employed as a nurse's aid at a mental hospital and has had surgery on the right knee only. There has been no weight-loss, fever, or malaise, but he has had diarrhoea intermittently for 2 years. Physical examination showed small, whitish plaques on the tongue (confirmed as *Candida albicans*), bilateral non-tender adenopathy in the anterior and posterior cervical, axillary, and inguinal areas, splenomegaly 3 cm below the left costal margin, onychomycoses of all toes, contact dermatitis of the scrotum and anus, and an erythematous, non-pruritic rash over the dorsum of the arms. A rectal swab and stool culture showed no enteric pathogens, and no ova or parasites, including cryptosporidia, were present in his stool. There was no evidence of vasculitis or Kaposi's sarcoma. A monotest was negative, and he was nonreactive to an anergy panel of candida, mumps, trichophyton, and purified protein derivative. The results of immunological studies are shown in the table.

Patient 3.—The mother of patient 1 and wife of patient 2 is a 23-year-old white woman with a 4-year history of insulin-dependent diabetes. She works as a nurse at the mental hospital where her husband is employed. She assists with the infusion of her husband's factor VIII concentrate but denies contact with the product or needles. She has been well, except for recurrent vaginal candidiasis, which has responded to antifungal creams. As a child, she had a number of allergies. During the 2nd trimester of her pregnancy the vulvovaginal candidiasis became refractory to topical antifungals, and she had ketoacidosis, which resolved. During the month before birth she noted asymptomatic cervical and inguinal lymphadenopathy, and for 2 days before and 10 days after delivery she had fevers (>101°F), chills, and sweats, which resolved spontaneously 3 weeks later. She denied intravenous drug abuse and had monogamous sexual contact with her husband for 2 years before her son's illness. Her only foreign travel was a 1-week trip to Mexico in 1981. There has been no weight-loss, fever, or malaise. Physical examination showed bilateral, non-tender lymphadenopathy in the anterior and posterior cervical, axillary, and inguinal areas, and no hepatosplenomegaly. There was evidence of neovascularisation in both eyegrounds but no haemorrhages or exudates. A monotest was negative, and she was non-reactive to an anergy panel of candida, mumps, trichophyton, and purified protein derivative. The results of immunological studies are shown in the table.

Patient 4.—The half-sister of patient 1 and the 3½-year-old daughter of patient 3 by a former husband. She has been healthy since birth and has always lived with her mother and, for the last 2 years, her stepfather. Her natural father is a healthy white male with no history of intravenous drug abuse or homosexuality. Physical examination showed 0·5 × 0·5 cm anterior and posterior cervical lymphadenopathy bilaterally. The results of immunological studies are shown in the table.

Discussion

AIDS has been reported in 56 children so far.[1] The putative agent (HTLV-III/lymphadenopathy virus?) may be transmitted through blood transfusions[8] or from parent to child at birth or during the neonatal period.[1-3,6,7] This is the first report of AIDS in the child of a haemophiliac, and this case fits the Centers for Disease control criteria for paediatric AIDS.[1] The child's raised lymphocyte and T-lymphocyte counts, normal or elevated immunoglobulin levels, and ability to produce both CMV and EBV antibodies do not indicate severe combined immune deficiency or Nezelof's syndrome, and the lack of lymphopenia is typical of children with AIDS.[6] The route of transmission may have been placental, through breast-milk, or by close maternal or paternal contact in the early neonatal period. Transmission is unlikely to have occurred at birth, because, in the absence of premature rupture of membranes, caesarean section would have precluded exposure to cervical secretions.

The presence of lymphadenopathy and cellular immune defects in both parents is compatible with an AIDS-related syndrome or pre-AIDS. Lymphadenopathy in the sexual partners of haemophiliacs has been previously reported,[12,13] but in this case the wife assisted in concentrate infusion, and,

therefore, her exposure to the putative AIDS agent could have been heterosexual or through concentrates.

The presence of antibodies to CMV and EBV in the infant and family members is consistent with past or current CMV and EBV infection and is typical of groups at risk for AIDS.[3,6,21-23] However, the absence of past or current EBV infection in the infant at 4 months of age, when symptoms of AIDS were developing, suggests that infection with EBV may arise from infection with the AIDS agent or is a result of immune dysfunction in AIDS. Furthermore, CMV and EBV infections have been associated with low T-helper/suppressor (H/S) ratios.[24,25] The H/S ratio in the haemophiliac has continued to fall despite serological evidence of CMV and EBV 16 months earlier, and this suggests that his current H/S ratio may not be related to CMV or EBV infection.

Both parents had serological evidence of past or current infection with HTLV-III, which is implicated in the aetiology of AIDS.[26] The presence of the antibody in the father is consistent with the detection of HTLV-III isolates and antibodies in haemophiliacs with lymphadenopathy.[26-28] The identification of the antibody in the mother, together with development of lymphadenopathy and peripartum influenza-like illness, may represent recent HTLV-III infection, and this could have been transmitted to her child.[29] The absence of HTLV-III antibody in the infant accords with the identification of HTLV-III isolates or antibodies in only 33–36% of AIDS victims[28,30] and may be due to isolated abnormalities in B-cell function.[31-32]

The depressed T-colony growth, elevated IgM, IgE, and antibodies to CMV and EBV in the symptom-free 3½-year-old stepsister (patient 4) may indicate AIDS-like immunological abnormalities, but this needs to be confirmed.

Addendum

Pneumocystis pneumonia and AIDS have recently developed in patient 2.

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"*Education of rural girls:* The most crucial population segment from the point of view of family welfare, nutrition and health is constituted by the young unmarried girls of age 10 and above in rural areas. Girls in rural areas are generally married off when they are barely 12 or 13 years of age, and once they are so married they are 'lost'. By the time the girls reach their 25th year they have generally already had their five children and all family planning programmes addressed to rural women in their late twenties are largely futile. What is generally not appreciated is that the 'potential' fertility of undernourished women is actually very low in comparison to their well-nourished counterparts. Their reproductive span is low; they attain menarche later and menopause much earlier than the well-nourished women. What is more, there is now evidence that for nearly 10 years before they attain their menopause the undernourished women are actually infertile, the menstrual cycles being presumably anovulatory. I am, therefore, afraid that our family planning programmes addressed to poor rural women in late twenties is akin to bolting the door after the horse has escaped. The most important single step that will reduce birth rates, is the raising of the age of girls at marriage. Girls are married off early because unlike boys, they are now considered 'economic liabilities' by their poor parents. The real key to the success of our family planning programme lies in our finding a way by which poor rural parents will find it rewarding not to marry off their daughters till they are at least 20 years of age."—DR C. GOPALAN: The "Population Problem"—the Qualitative Dimension. Inaugural address at the Indian Association for the Study of Population. New Delhi, Sept 27, 1982. In: Nutrition and Health Care, Problems and Policies (a collection of recent addresses by C. Gopalan), Nutrition Foundation of India, B-37 Gulmohar Park, New Delhi-110049.