HEART-LIVER TRANSPLANTATION IN A PATIENT WITH FAMILIAL HYPERCHOLESTEROLAEMIA

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Summary A girl aged 6 years 9 months with severe heart disease secondary to homozygous familial hypercholesterolaemia underwent orthotopic cardiac transplantation and her liver was replaced with the liver of the same donor. In the first 10 weeks after transplantation serum cholesterol fell to 270 mg/dl from preoperative concentrations of more than 1000 mg/dl.

INTRODUCTION

CARDIAC transplantation for end-stage heart disease would be futile in a patient with homozygous familial hypercholesterolaemia (FH) unless the metabolic processes responsible for the rapidly progressive atherosclerosis in such patients can be counteracted. We have attempted to meet this objective by orthotopic transplantation of the liver and heart from the same donor into a recipient with severe FH.

CASE REPORT

On September 1, 1983, a girl aged 6 years and 4 months was admitted for metabolic studies to the University of Texas Southwestern Medical School in Dallas. From the age of 3 months progressive xanthomas had developed on the contact areas of her buttocks and extremities. FH had been diagnosed when she was 6 years old. Culture of cutaneous fibroblasts indicated that she had the deficiency of low density lipoprotein (LDL) receptors which is typical of FH. On admission, her plasma cholesterol was 1225 mg/dl and her plasma triglyceride was 154 mg/dl. Liver function tests were normal and she had no cardiac symptoms.

However, angina pectoris quickly developed and she required a double coronary artery bypass. A portacaval shunt was suggested, but liver transplantation was viewed as a better way of reducing cholesterol concentration (normal <195 mg/dl) was more than 1000 mg/dl and her total plasma triglycerides (normal <150 mg/dl) were less strikingly raised (see figure). Within a few days of the heart-liver transplantation, serum cholesterol concentrations had fallen to less than 10% of the pre-existing level, but as the patient recovered from the operation and began to eat, the values rose to above 300 mg/dl and then fell slowly to 268 mg/dl (fig). Triglyceride concentrations were increased in the first month but declined 300 mg/day cyclosporin and 7·5 mg/day prednisone is being continued.

RESULTS

Effects on Circulating Cholesterol and Triglycerides

Serum or plasma cholesterol concentrations were determined in the Dallas and Pittsburgh laboratories with commercial kits that were based on an enzymatic assay principle. Differences between the results in the two laboratories in analysing plasma (Dallas) or serum (Pittsburgh) averaged less than 4%. Triglyceride analyses with enzymatic methods also yielded generally comparable results in the 2 laboratories but with a 15% variation. Plasma cholesterol and triglyceride concentrations of the donor were 120 and 100 mg/dl, respectively, in the Dallas laboratory.

During her stay on the metabolic ward in Dallas in September and October, 1983, the patient was in a lipidoprotein turnover study. She was on an isocaloric formula/solid food diet containing 40% of calories as fat and less than 300 mg of cholesterol per day. The patient's average cholesterol concentration (normal <195 mg/dl) was more than 1000 mg/dl and her total plasma triglycerides (normal <150 mg/dl) were less strikingly raised (see figure). Within a few days of the heart-liver transplantation, serum cholesterol concentrations had fallen to less than a fourth of the pre-existing level, but as the patient recovered from the operation and began to eat, the values rose to above 300 mg/dl and then fell slowly to 268 mg/dl (fig). Triglyceride concentrations were increased in the first month but declined (figure) as the postoperative prednisone doses were decreased from 30 mg/day toward the present level of 7·5 mg/day.

The visible tendinocutaneous xanthomas have undergone a dramatic regression during the 10 weeks of follow-up. The lesions have flattened and have changed from yellow to pink.

DISCUSSION

FH is caused by a defect in the gene for the LDL receptor. Although the abnormality is common to all cells, the liver has weighed 16.2 kg. There was a total donor/recipient mismatch at the HLA A, B, and D<sub>R</sub> loci. The technical details of this 16-hour operation will be reported separately (B. W. Shaw, Jr, personal communication). The removed heart had advanced atherosclerotic and valvular disease. The excised liver was normal by gross and microscopic examination.

Good cardiac and hepatic function were achieved from the grafts. Cyclosporin and steroids were used as immunosuppressants. A persistent increase in serum bilirubin concentration 5 days after surgery suggested rejection but this subsided without an increase in immunosuppression. Standard liver function tests have been normal since the second postoperative week. Immunosuppression with 300 mg/day cyclosporin and 7·5 mg/day prednisone is being continued.
a central role in the resulting hypercholesterolaemia,\(^5\)\(^7\) and the possibility has been raised of treating the disease with liver transplantation.\(^6\) The paucity of LDL receptors in the hepatocytes of patients with FH has been thought to be the most important factor in the sluggish catabolism as well as in the heightened total body synthesis of LDL and cholesterol.\(^5\)\(^7\) If this were true, provision of a normal liver would correct FH because transplanted hepatocytes retain their original metabolic specificity.\(^2\)

In our patient, the degree of correction has been substantial, at least as judged by serum cholesterol concentrations, but it has not been complete. Serum cholesterol is now about 270 mg/dl. Absorption of cholesterol from rapidly involuting xanthomatous deposits may be most important factor in the sluggish catabolism as well as in the heightened total body synthesis of LDL and cholesterol of patients with FH has been thought to be the original metabolic specificity.\(^2\)

ADDENDUM

June 12, 1984: After 6 more weeks of follow-up (total now, 4 months) the patient remains well with normal cardiac and liver function. Plasma cholesterol and triglyceride concentrations remain the same as at the time of the report.

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**ISOLATION OF HUMAN T-LYMPHTROPIC RETROVIRUS (LAV) FROM ZAIRAIN MARRIED COUPLE, ONE WITH AIDS, ONE WITH PRODROMES**

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**Summary**

A Zairian married couple had been living in France since 1981. The man had acquired immunodeficiency syndrome (AIDS) and his wife had prodromes of the disorder. Infection with a human T-lymphotropic retrovirus (lymphadenopathy-associated virus) was demonstrated in both by isolation of the virus from their cultured lymphocytes and the detection of specific antibodies in serum samples. Since this virus has been isolated from patients in other AIDS risk categories, the finding of the virus in AIDS patients from the African group adds further support to the hypothesis that this human retrovirus is the AIDS aetiological agent.

**INTRODUCTION**

Evidence of a role for retroviruses in acquired immunodeficiency syndrome (AIDS) has been supported by the isolation of a new human T-lymphotropic retrovirus (lymphadenopathy-associated virus; LAV) from high-risk populations such as homosexual men with lymphadenopathy syndrome\(^8\)\(^10\) and from AIDS patients\(^9\)\(^11\) such as a young haemophiliac.\(^3\) LAV affects in particular the OKT4-positive helper T-lymphocyte subpopulation\(^1\) (and D. Klatzmann et al, unpublished) that is involved in the cellular immune deficiency.\(^3\)\(^6\) Epidemiological surveys on serum antibodies to LAV\(^8\)\(^9\) also suggest that this virus may have a role in the pathogenesis of AIDS. Many cases of this disorder reported in Europe since 1983 have been in Black patients from central and equatorial Africa\(^10\)\(^14\) or Whites who have travelled in this area.\(^11\)\(^15\) They have none of the usual risk factors. Clearly, the isolation of LAV in AIDS patients from the African group, which has geographical, ethnic, and epidemiological characteristics distinct from those of the other AIDS risk categories, would be strong support for its role in the disease. We report here the isolation of an LAV-related virus from cultured lymphocytes of a Zairian couple living in France. The man had AIDS and prodomal symptoms were recognised in his wife.

**CASE-REPORTS**

**Patient 1**

A 26-year-old Black Zairian man was admitted to the Bicêtre hospital in November, 1982, with fever, weight loss, meningeal syndrome, hepatomegaly, splenomegaly, and lymphadenopathy. He had previously been healthy and denied homosexuality and drug abuse. He had never received any blood product transfusion. He and his wife had come from Zaire to France in 1981 and had not returned to Africa since. They had never travelled in the Caribbean or in the USA. The patient had oral thrush and condyloma acuminata. A herpes simplex homini virus was isolated in cultures from a genital ulcer. Severe disseminated cryptococcosis was diagnosed on direct examination and cultures of the cerebrospinal fluid, lymph-node and bone-marrow aspirates, urine, and liver biopsy samples. Examination of faecal samples revealed no parasite. He had serum antibodies to herpes simplex virus, cytomegalovirus, and Epstein-Barr virus, and markers of hepatitis B infection were present (table I). His lymphocytes expressed the HLA DR5 phenotype. The cryptococcosis was controlled by antifungal agents, and the patient was discharged in April, 1983, on oral flucytosine and ketoconazole. Recently *Mycobacterium kansasi* tenosynovitis of the hand developed and he remains chronically ill.

**Patient 2**

Patient 1 and his wife, a 23-year-old Black Zairian, had been living together since 1980 and had discontinued sexual relations from November, 1982, until April, 1983. They parted a month later. In 1983, after 6 more weeks of follow-up (total now, 4 months) the patient remains well with normal cardiac and liver function. Plasma cholesterol and triglyceride concentrations remain the same as at the time of the report.

**REFERENCES**

Virus.

OK admission gradually falling to seven antigens (tetanus, diphtheria, streptococcus, cells (helper/inducer γδ) lymphopenia with a profound reduction in OKT4-positive lymphocytes. 16 Blastogenic responses were determined with phytohaemagglutinin and concanavalin A were very low.

**Results**

Each patient's lymphocytes to concanavalin A was greatly impaired. The blastogenic response of peripheral blood lymphocytes to concanavalin A was greatly impaired. She had oral thrush and chronic herpetic ulcers that had developed before June, 1982. Both were confirmed by culture. She had prurigo, confirmed by a skin biopsy. No parasites were detected in the stools. She had serum antibodies against herpes simplex virus, cytomegalovirus, and Epstein-Barr virus (table I). Cervical lymphadenopathy developed in February, 1984. She refused further investigation.

**IMMUNOLOGICAL EVALUATION**

T-cell helper or suppressor-cytotoxic phenotype was determined by indirect immunofluorescence with monoclonal antibodies (Ortho Pharmaceuticals) and goat anti-mouse immunoglobulin (Cappel). B cells were counted by a fluorescence method with goat anti-human immunoglobin (Dr De The, Lyon). Moreover, an enzyme-linked immunosorbent assay showed that sequential serum samples from patient 1 (from November, 1982, to November, 1983) contained antibodies to LAV but not to HTLV-I p19. No antibody to HTLV-I p24 or HTLV-associated membrane antigens could be detected in patient 1's serum (L. Schaffar). Moreover, an enzyme-linked immunosorbent assay showed that sequential serum samples from patient 1 (from November, 1982, to November, 1983) contained antibodies to LAV but not to HTLV-I. These results were confirmed by radioimmunoprecipitation assay; LAV p25 was immunoprecipitated by patient 1's serum (fig 2A). In February, 1984, a similar pattern of virus production in patient 1's peripheral blood culture was as previously described. Maximum virus production was obtained on day 15 (fig 1) as measured by reverse transcriptase activity in the cell-free supernatant. The virus was propagated on T lymphocytes from a normal donor, and a similar pattern of virus production was observed. In both cases, the reverse transcriptase peak was followed by a fall in cell growth. The virus was characterised as LAV by indirect immunofluorescence assay; the virus-producing cells were recognised by the serum of the first patient from whom LAV was isolated (positive reference serum), but not by specific antibodies to human T-cell leukaemia virus (HTLV-I) p24 or to HTLV-I p19. No antibody to HTLV-I p24 or HTLV-associated membrane antigens could be detected in patient 1's serum (L. Schaffar). Moreover, an enzyme-linked immunosorbent assay showed that sequential serum samples from patient 1 (from November, 1982, to November, 1983) contained antibodies to LAV but not to HTLV-I. These results were confirmed by radioimmunoprecipitation assay; LAV p25 was immunoprecipitated by patient 1's serum (fig 2A).

**April, 1983.** The blastogenic response of peripheral blood lymphocytes to concanavalin A was greatly impaired. Patient 2 had cutaneous anergy to tuberculin and the multistest antigens. Her serum IgG and IgA levels were also high. Her absolute lymphocyte count was normal but she had 0.027 x 10^9/1. OKT4-positive cells and the OKT4/OKT8 ratio was 0.02. In October, 1983, this ratio was 0.15. The blastogenic responses to phytohaemagglutinin and concanavalin A were very low.

**Virus Isolation**

In November, 1983, T lymphocytes from patient 1's peripheral blood culture were as previously described. Maximum virus production was obtained on day 15 (fig 1) as measured by reverse transcriptase activity in the cell-free supernatant. The virus was propagated on T lymphocytes from a normal donor, and a similar pattern of virus production was observed. In both cases, the reverse transcriptase peak was followed by a fall in cell growth. The virus was characterised as LAV by indirect immunofluorescence assay; the virus-producing cells were recognised by the serum of the first patient from whom LAV was isolated (positive reference serum), but not by specific antibodies to human T-cell leukaemia virus (HTLV-I) p24 or to HTLV-I p19. No antibody to HTLV-I p24 or HTLV-associated membrane antigens could be detected in patient 1's serum (L. Schaffar). Moreover, an enzyme-linked immunosorbent assay showed that sequential serum samples from patient 1 (from November, 1982, to November, 1983) contained antibodies to LAV but not to HTLV-I. These results were confirmed by radioimmunoprecipitation assay; LAV p25 was immunoprecipitated by patient 1's serum (fig 2A). In February, 1984, a similar pattern of virus production in patient 1's peripheral blood culture was as previously described. Maximum virus production was obtained on day 15 (fig 1) as measured by reverse transcriptase activity in the cell-free supernatant. The virus was propagated on T lymphocytes from a normal donor, and a similar pattern of virus production was observed. In both cases, the reverse transcriptase peak was followed by a fall in cell growth. The virus was characterised as LAV by indirect immunofluorescence assay; the virus-producing cells were recognised by the serum of the first patient from whom LAV was isolated (positive reference serum), but not by specific antibodies to human T-cell leukaemia virus (HTLV-I) p24 or to HTLV-I p19. No antibody to HTLV-I p24 or HTLV-associated membrane antigens could be detected in patient 1's serum (L. Schaffar). Moreover, an enzyme-linked immunosorbent assay showed that sequential serum samples from patient 1 (from November, 1982, to November, 1983) contained antibodies to LAV but not to HTLV-I. These results were confirmed by radioimmunoprecipitation assay; LAV p25 was immunoprecipitated by patient 1's serum (fig 2A).