SUCCESSFUL HAEMODIALYSIS AND RENAL TRANSPLANTATION IN A PATIENT WITH HAEMOPHILIA A

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Summary

A 19-year old male with severe haemophilia A (factor VIII activity less than 1%) developed terminal renal insufficiency and was subsequently dialysed via an external arteriovenous shunt for one year. To prevent bleeding he received cryoprecipitate (2000—2500 units of factor VIII) three times a week during dialysis. After one year of uneventful dialysis he received a kidney graft from a cadaver donor that was matched for the B locus antigens. During the first two weeks after transplantation his factor VIII level was kept at approximately 70% by daily cryoprecipitate infusions. Thereafter he was free from bleeding at a level of 20% with prophylactic cryoprecipitate treatment (1000 units 3 times a week). He was discharged from the hospital five weeks after transplantation with excellent renal function (ECC 75 ml/min). No rejection crisis occurred. His factor VIII requirements remained unchanged after transplantation, indicating that the human kidney does not substantially contribute to the production of clot-promoting factor VIII.

Introduction

Renal and urologic complications frequently occur in patients with haemophilia. After haemarthrosis, haematuria is the most common problem. In a study of 35 patients an abnormal pyelogram was found in 38% and a reduced creatinine clearance in 26%\textsuperscript{1}. Cases of irreversible renal failure due to obstruction, renal cortical necrosis, or retroperitoneal haematoma resulting in death have been occasionally reported\textsuperscript{2}. This paper describes the successful treatment of terminal renal insufficiency by haemodialysis and renal transplantation in a patient with classic haemophilia A. In addition, transplantation enabled us to investigate whether the kidney contributes to factor VIII production and whether renal transplantation is a useful method of correcting the bleeding disorder of haemophilia A.
Methods

Factor VIII procoagulant-activity was measured by the one-stage method. A pool of citrated plasma from 30 normal individuals was used as the standard of 100% factor VIII activity. For the correction of the bleeding tendency we used cryoprecipitated factor VIII. Amounts of cryoprecipitate administered are expressed in terms of factor VIII Units. One Unit of factor VIII is defined as the amount of factor VIII activity present in 1 ml of normal human plasma. The cryoprecipitate derived from 4 donors contained about 500 units of factor VIII activity.

Case History

The patient is a 19-year old male with severe haemophilia. His spontaneous factor VIII activity was less than 1%. He experienced the usual problems of his disorder with recurrent haemarthrosis and haematuria. At the age of 4 he had a swelling in the left abdomen with haematuria. Subsequently he developed transient anuria, possibly as a consequence of bilateral obstruction by clots following antifibrinolytic therapy with tranexamic acid. At the age of 10 the excretory urogram showed a large stone in the right renal pelvis. Seven years later he had right-sided hydronephrosis with recurrent urinary tract infections. This kidney showed relatively good function. The left kidney was enlarged, showed extreme hydronephrosis, and had a very thin cortex with only slight excretion of contrast. His bleeding frequency diminished when, at the age of 18, he was put on prophylactic treatment with cryoprecipitate (1000 units 3 times a week).

In September 1975 he was involved in a motor accident that resulted in irreversible damage to his left kidney and spleen. A left nephrectomy and splenectomy were performed. Under cover of cryoprecipitate his post-operative course was uneventful and he was discharged with a normal serum creatinine of 66 μmol/L. In November 1975 he was re-admitted because of pain in the right flank. His creatinine was now raised to 360 μmol/L. Two days after admission he developed complete anuria. The right kidney was explored and the pelvis was found to be completely filled with clots. These were removed together with the pelvic stone that had been first noted 8 years before. Urinary drainage was ensured via a pyelostomy. He experienced, however, recurrent bleeding, his renal function did not improve and he developed severe hyperkalaemia. A Scribner shunt was inserted and haemodialysis was started on December 1, 1975. Meanwhile, his condition was rapidly deteriorating. He had fever, ongoing bleeding through his pyelostomy and ureter, and intermittent periods of anuria. The kidney became infected and since the bleeding could not be controlled a right nephrectomy was performed. After this operation his condition gradually improved. He was treated with haemodialysis for 5 hours 3 times a week. Initially, he was dialysed under regional heparinisation while receiving 1000 units of cryoprecipitate at the start and at the end of each dialysis. For 2 months we tried to dialyse him without any anticoagulants. Cryoprecipitate (2000–2500 units) was administered just before the end of each dialysis. However, this procedure led to
the formation of small clots in the dialysate and, therefore, we went back to regional heparinisation and substitution with 2000–2500 units of factor VIII only at the end of the dialysis. With this treatment his factor VIII level was approximately 10% before dialysis and 40% after dialysis. He did extremely well during the whole dialysis period and his bleeding tendency posed no major problem. After his condition had improved he was prepared for renal transplantation. His HLA-type was A2,A28/BW15,BW40. His blood group was A Rhesus (D) pos. Despite the many blood transfusions received in the past (more than 150) he had only formed HLA-antibodies of restricted specificity (against A1,B5, and B8). Antibodies against HB$_s$ virus antigen were also present. He had no history of clinically manifest hepatitis and his liver function tests were normal.

On December 28, 1976, one year after the start of dialysis, a cadaver kidney became available. The blood group of the donor was A Rhesus (D) pos and he had the same B locus antigens as the recipient (HLA type: A3,A29/BW15,BW40). The cross-match was negative. The transplantation was performed under cover of 2500 units of cryoprecipitate. There was immediate diuresis and dialysis was no longer required. He was treated with conventional immunosuppressive therapy. Signs of rejection did not occur.

![Plasma factor VIII activity during cryoprecipitate treatment](image)

Figure 1. Plasma factor VIII activity during cryoprecipitate treatment in the early post-operative period. Each bag of cryoprecipitate prepared from the plasma of 4 donors contains about 500 units of factor VIII activity.
Figure 1 shows the course of his factor VIII requirements in the early post-operative period. Initially, factor VIII activity was kept at approximately 70% by infusions of cryoprecipitate twice a day. The blood loss during and after the operation was negligible. During the first days he had gross haematuria. The only serious complication encountered was obstruction of the urethral catheter by a large clot on the third day after transplantation. At this time his factor VIII activity was 90% and he had a very high fibrinogen level (11,160 mg/L, normal upper limit 4,600 mg/L). To prevent further clotting after removal of the catheter on day 14, cryoprecipitate infusions were reduced to half of the original amount and his fluid intake was raised to ensure a diuresis of at least 4 L per 24 hr. The factor VIII level dropped to 20–40%. When the substitution therapy was tapered off further, the factor VIII level fell to values between 6 and 20%. This indicated that transplantation did not markedly decrease the factor VIII requirements of this patient. He was discharged in excellent condition 35 days after transplantation. His creatinine clearance was 75 ml/min and there were no signs of rejection. Blood pressure was 150/100 mmHg. His condition has since been stable. He now receives prophylactic cryoprecipitate treatment, 1000 units 3 times a week. The lowest factor VIII level recorded during this treatment is 4%. That his bleeding tendency is still present is further suggested by the occurrence of a large haematoma in the right gluteal region appearing a few weeks after his discharge, for which he had to be readmitted temporarily.

Discussion

Our experience shows that it is feasible to treat terminal renal insufficiency in patients with a severe bleeding disorder, such as haemophilia, with regular haemodialysis and renal transplantation. The first problem encountered is the construction of an arteriovenous shunt, that obviously increases the risk of bleeding. An internal arteriovenous shunt has been used in a haemophiliac to facilitate prophylactic administration of cryoprecipitate. Our patient received an external arteriovenous cannula that is still functioning after transplantation, and that is now being used for cryoprecipitate administration. Clotting of the cannula has never occurred and bleeding problems were not different from those in other dialysis patients.

The coagulation disorder made us try to dialyse the patient without heparinisation but this was not successful, since small clots formed in the artificial kidney. Apparently, a factor VIII level of 10% before dialysis was not low enough to prevent these clots. Best results were obtained with regional heparinisation followed by substitution therapy with cryoprecipitate at the end of each dialysis.

Several animal transplantation experiments have been done to discover the sites of synthesis of antihaemophilic factor. These studies have been reviewed by Webster et al. It has been convincingly shown that the liver is the major site of synthesis, since liver transplantation does correct the defect. However, these studies also suggest that 20% of factor VIII activity is synthesised at extrahepatic sites. The spleen might represent such a location, although most investigators believe that it serves only as a storage site. This is based on the observation that plenic grafts only raise the factor VIII level in the immediate post-operative
period. Antihaemophilic activity has also been found in renal perfusates\(^6\) and in tissue cultures of kidney sections\(^7\). From these findings one might expect renal transplantation to correct the coagulation disorder. Webster et al\(^8\), however, failed to find such a correction in a short term experiment, where a kidney was grafted from a normal to a haemophilic dog. Our experience with a human haemophilic confirms the findings of this animal experiment and shows that the bleeding disorder does not disappear after long-term follow-up. Since the patient has received continuous substitution therapy since transplantation we cannot exclude the possibility that the graft produces minor amounts of factor VIII activity, but if so the production is too low to be of great practical importance. This is also suggested by the fact that the patient experienced one major bleeding episode after transplantation. These results are in apparent contradiction with the finding that autotransplantation of kidneys in normal dogs resulted in a transient post-operative rise in factor VIII levels\(^8\), suggesting that the kidney nevertheless plays some role in factor VIII production. This has been clarified by the elegant studies of Jaffe\(^9\) who has shown that the functional antihaemophilic protein consists of three subcomponents: an antigen, von Willebrand factor, and a clot-promoting factor. The first two components are present on molecules synthesised by endothelial cells. These are also produced in the kidney. The precursor molecule has no clotting activity and is converted to clot-promoting antihaemophilic globulin at another site, possibly the liver. The defect in haemophilia A seems to be located in this terminal conversion step, since haemophilic endothelial cells produce a precursor molecule that is probably identical with that of normal subjects\(^9\).

Although our experience demonstrates that kidney transplantation provides no solution to the problem of haemophilia itself, it is clear that the presence of this disease in a patient with renal failure cannot be regarded as a contraindication to treatment with regular haemodialysis or renal transplantation.

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Open Discussion

KURUVILA (Bombay) Firstly, did your patient require less heparin than your other patients? Secondly, vasopressin has been recently used as a substitute for cryoprecipitate. Have you any experience of this? Thirdly, are you aware of any liver transplantation in haemophiliacs and whether this has corrected the abnormality?

KOENE We did not try to change our original heparinisation schedule and did not try lower doses of heparin in this patient, but it might well be that you can use much lower doses. We have no experience of treatment with vasopressin. The drug seems to be only useful in patients who are partially deficient in factor VIII. The only experiments with liver transplants have been done in haemophiliac dogs, and there it has been shown that these transplants can correct the deficiency.

CHAIRMAN (GELIN, Gottenburg) This boy had multiple blood transfusions, but you had no rejection whatsoever. Do you see any relationship between the lack of factor VIII and rejection?

KOENE I do not think one can conclude anything about the influence of factor VIII deficiency from this single case. Our results are compatible with the findings of others that transplants in patients who do not form polyspecific antibodies after so many blood transfusions, do have a better prognosis. Furthermore kidney grafts matched for the B locus antigens also have better prognosis in patients who have antibodies.

CHAIRMAN But you do not put any emphasis on factor VIII being one of the rejection mechanisms?

KOENE No, and I do not think you can do that because especially in the initial period, we were very intensively replacing factor VIII by cryoprecipitate infusions.