Recurrence of HUS following live related renal transplantation associated with subsequent de-novo disease in the donor.

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Short title: Live-related renal transplantation in (D-) HUS

Abstract

There is a significant risk of disease recurrence in patients with non-diarrheal (D-) hemolytic uremic syndrome (HUS) undergoing renal transplantation. Recent studies have shown that approximately 20% of sporadic cases of HUS have mutations in the gene for the complement regulatory protein factor H. We report here two families; in each of which a family member initially presented with sporadic HUS and subsequently received a live related renal transplant, one from a sib and the other from the father. Subsequently both recipients suffered recurrent HUS in the allograft and both donors developed HUS within a year of the transplant. Neither family have a factor H mutation. This report underlines the risk of disease recurrence in recipients associated with live related renal transplantation in HUS and also suggests that the donors may be at risk.

Index words: HUS, renal transplant

Introduction

Hemolytic uremic syndrome (HUS) is characterized by the triad of microangiopathic hemolytic anaemia, thrombocytopenia and acute renal failure. It can be classified as diarrheal-associated (D+) and non-diarrheal (D-). The latter in turn is further classified as sporadic (which may be recurrent), or if more than one member of a family is affected, familial. Both autosomal dominant and recessive forms of inheritance have been described in familial HUS [1]. Sporadic HUS can be associated with pregnancy, systemic lupus erythematosus (SLE) human immunodeficiency virus (HIV) and various drugs including the oral contraceptive and cyclosporine .

A primary genetic defect in (D-) HUS was first described in 1998 [2]. In one family and one sporadic case mutations were found in the gene for complement factor H which is an important down-regulator of the alternative complement pathway. Subsequently factor H mutations have been found in approximately 20% of patients with familial and sporadic HUS [3]. These mutations cluster in the C-terminal end of the protein [3;4;4;5;5]. These studies have shown that a significant proportion of patients who present with sporadic HUS have an underlying genetic defect which can frequently be detected in unaffected family members. In families with HUS carriers of

the gene defect may be unaffected for many years. Recovery of renal function is rare in familial and sporadic HUS. Several studies have shown that there is a high risk of disease recurrence in (D-) HUS patients who undergo renal transplantation.[6-8]. The meta-analysis of Ducloux et al showed that in those patients who suffered recurrent HUS post transplant that 52% had received a live-related transplant compared to 22% ($p<0.001$) in those patients who did not suffer a recurrence. The cases presented here extend these observations to show that there is not only a significant risk of recurrent HUS following live related transplantation but also that the donor may present later with HUS thus making the diagnosis of the familial form.

Case Histories

Patient 1 was admitted at the age of 4 months with a short history of nausea, vomiting and blood in the stool. She was the first child of healthy parents. The pregnancy and birth weight were unremarkable and her development was normal. Investigations demonstrated anaemia, thrombocytopenia and evidence of haemolysis on the peripheral blood film. Hypertension and rapidly progressive, irreversible renal failure were treated with peritoneal dialysis 18 days after admission. A renal biopsy showed changes compatible with HUS. During the following 16 months she was treated with

peritoneal dialysis and had two further episodes of acute thrombocytopenia and anaemia associated with infection. Seventeen months after the onset of the disease and 4 months after the last hemolytic recurrence, she received a live related transplant from her father. Immunosuppression was with cyclosporin, azathioprine and prednisolone. . The initial course was uncomplicated with immediate graft function. A urinary tract infection after two weeks and a rotavirus gastroenteritis two weeks later were accompanied by decreased haemoglobin and platelet levels, but there was no evidence of haemolysis. Seven weeks after transplantation, the patient's condition rapidly deteriorated with declining graft function, hemolytic anaemia and thrombocytopenia. Biopsy of the allograft showed recurrent HUS. Immediately after the biopsy the patient became hypotensive and the transplant was re-explored. No haemorrhage was found but she later developed diffuse bleeding from the surgical wounds. A diagnosis of severe HUS with superimposed disseminated intravascular coagulation was made. During the following weeks the patient's general condition fluctuated with recurrent hemolytic episodes. Three months after the transplant, at 24 months of age, the patient died. Post mortem examination showed haemorrhage and micro thrombi in the lungs, gastrointestinal tract and the kidneys.

Patient 2 is the 30-year old father of patient 1. He was referred ten months after the live related transplant because of hemolytic anaemia, thrombocytopenia, hypertension and acute renal failure. His previous history and the donor evaluation one year earlier were unremarkable. Plasmapheresis with fresh frozen plasma as substitution fluid was started immediately without any improvement in renal function. Plasmapheresis was discontinued after the 12th exchange because the patient developed transfusion related pulmonary oedema which necessitated ventilatory support in the intensive care unit. Haemodialysis was commenced and the haemolysis and thrombocytopaenia resolved spontaneously. During the following four years there were no further episodes of haemolysis. Subsequently he received a live unrelated kidney transplant from his stepfather. The initial course was uncomplicated with immediate function of the kidney. Initial immunosuppression was with cyclosporin, azathioprine and prednisolone. One month after the transplant there was evidence of recurrent HUS which was treated with plasmapheresis and subsequently nephrectomy of the remaining native kidney. This resulted in a temporary improvement in graft function; subsequently cyclosporin was replaced with tacrolimus. Despite this it was necessary

to recommence haemodialysis three months post-transplantation. Throughout this period of time C3 levels were normal.

Patient 3 is a man who presented at the age of 30 with a short history of intermittent diarrhoea and vomiting. Investigations showed acute renal failure with thrombocytopaenia and evidence of haemolysis on a peripheral blood film. Renal biopsy showed features typical of HUS. Despite treatment with steroids and plasmapheresis there was no recovery of renal function and peritoneal dialysis was commenced. One year later the patient received a cadaveric renal transplant. Immunosuppression included prednisolone, azathioprine and cyclosporin. There was immediate function of the graft and there were no problems in the postoperative period. For the next 20 months there was excellent graft function but a deterioration in the plasma creatinine following this led to a biopsy of the allograft. This was initially reported as showing features compatible with type 1 mesangiocapillary glomerulonephritis. However, a subsequent biopsy three months later showed recurrent HUS and within two months dialysis had been recommenced.

One year later the patient received an HLA identical live related transplant from his 31year old sister. There was immediate graft function and immunosuppression was

with prednisolone, cyclosporin and azathioprine. Six months later a rise in plasma creatinine from 1.1 mg/dL (100 μmol/L) 1.6 mg/dL (145 μmol/L) associated with nephrotic range proteinuria resulted in a biopsy which showed recurrent HUS. Cyclosporin was replaced with tacrolimus and plasmapheresis was undertaken. Despite this graft function continued to decline and dialysis was recommenced six months later. Throughout this period the C3 levels were low but factor H levels were normal.

Patient 4 is the sister of patient 3. Prior to donating a kidney to her brother the patient had been well. The only thing of note in the past medical history was pre-eclampsia in her third pregnancy. The post operative course after donor nephrectomy was complicated by pneumonia. Three months later she presented with a short history of general malaise and malignant hypertension. She had laboratory evidence of microangiopathic hemolytic anaemia and plasma creatinine was 2.5 mg/dL (224 μmol/L). Renal biopsy showed acute thrombotic microangiopathy, consistent with HUS. Despite treatment with plasma exchange renal function deteriorated rapidly and she became dialysis dependent within one month. After 6 years of haemodialysis she received a cadaveric renal transplant. She was immunosuppressed with

mycophenylate mofetil and sirolimus. Graft function, which was good in the initial post-transplant period, began to deteriorate after 10 days, with features of intravascular haemolysis. Transplant biopsy confirmed recurrence of HUS and she subsequently underwent graft nephrectomy. Throughout her illness she had a persistently low C3 level but factor H levels were normal.

Screening for mutations in the factor H gene was undertaken in Patients 2, 3 and 4 using previously described methods [3] and no abnormalities were detected.

Discussion

Recent studies have documented the high rate of recurrence of HUS in patients undergoing renal transplantation [6-9] . From these reports it is apparent that the risk of recurrence ranges from 10 to 50% and that the risk is greatest in patients receiving a live related transplant. Interestingly 3 of the 4 cases described here also developed recurrent HUS after either a cadaver or unrelated live transplant as well. That the donor may later develop HUS is not so well appreciated although it has been described twice before, once in a 21 year old female who develop HUS 3 weeks after nephrectomy[10] and the other time in a 24 year old man who developed HUS six months after surgery [11]. Because (D-) HUS may be familial it is not surprising that a

donor in this situation might develop HUS at a later stage. But it is remarkable that in all of the four reported cases HUS developed in the donor within such a short period of time after donation. This would appear to be more than a coincidence and strengthens the case for a true biological relationship. We have proposed previously a "two hit hypothesis" for the development of HUS in patients with factor H abnormalities whereby any factor causing endothelial cell activation may lead to a thrombotic microangiopathy if activation of the alternative pathway is not regulated. Although neither of these families have factor H mutations it is tempting to speculate that hyperfiltration in the remnant kidney decreases the threshold for the first "hit" necessary to initiate the thrombotic microangiopathy. That a similar percent of patients with both sporadic and familial HUS have factor H mutations suggests that a significant proportion of patients with sporadic HUS will have a primary genetic abnormality. Although we have not found a factor H mutation in either of these families we presume that both the donor and recipient carry the same, as of yet unknown, genetic defect. Thus, the cases we describe here not only underline the high risk of recurrence of HUS following transplantation but also suggest that there may be a significant risk to the donor should he or she carry the same genetic defect. Both

these risks clearly need to be explained to potential donors and recipients. Despite this a patient with an exon 20 factor H mutation whom we recently described [3] received a live related transplant from the parent not carrying the mutation but still developed recurrent HUS. This would suggest that the local renal synthesis of wild type factor H is not sufficient to overcome activation of the alternative pathway.

There is now enough evidence to suggest that all patients with sporadic and familial HUS should undergo screening for factor H mutations. What recommendations can be made with regard to transplantation in those patients who are found to have a factor H mutation? In our series of families recurrence of HUS resistant to plasmapheresis is frequently seen post transplant and we would currently not recommend transplantation in these patients. There have recently been two reports of liver transplantation in HUS patients with FH mutations (FH being synthesised by the liver), in one this was combined with a renal transplant [12;13]. In both cases there was evidence of a clinical improvement in the short term. Whether liver transplantation is a viable therapeutic option will depend upon long term results. The possibility of using complement inhibitors in FH related HUS is an alternative therapeutic option which has yet to be explored. In those patients who are not found to have a FH

mutation disease recurrence can still occur post transplant and patients should be aware of this. We are therefore reluctant to recommend live related transplantation in any form of (D-) HUS at present. However, if families do wish to pursue live related transplantation they should be fully informed of the risks.