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REVIEW ARTICLE

Hemolytic Uremic Syndrome after Renal Transplantation

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Abstract

Hemolytic Uremic Syndrom after kidney transplantation affects an increasing number of patients. It is characterized as recurrent and de novo. Older age at onset of HUS, shorter mean interval between HUS and transplantation or ESRD, living related donor and treatment with CNI have been associated with an increased risk of recurrence. Patients who lost the first transplant because of HUS recurrence should not receive a second transplant. The outcome of recurring HUS after transplantation is worse in familial forms leading invariably to graft loss and for this reason doctors should discourage the use of living related donors in this setting.

De novo HUS is not a rare complication after kidney transplantation and may be associated with infection, CNI or mTOR inhibitor toxicity, antibody use (OKT3), or acute vascular rejection. The clinical picture is obscure and treatment rests on removal of inciting factor with or without plasma exchange / FFP infusion. *Hippokratia 2006; 10 (3): 99-104*

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Thrombotic microngiopahty (TMA) is a well recognized serious complication of renal transplantation. The term has been applied to a diverse group of conditions that share the common pathomechanism of endothelial damage (Table 1). Histopathologically, TMA in the kidney is characterized by subendothelial accumulation of amorphous material in glomeruli, with narrowing or occlusion of the capillaries, fibrinoid or mucoid change in the intimal of small arteries, glomerular and/or arterial fibrin thrombi and fragmented red blood cells in the vascular wall, glomeruli or interstitium. The majority of cases represent de novo TMA, which occurs in 2.8%-3.5% of renal transplant recipients and is associated with 22% rate of graft loss[1]. The clinical presentation of TMA is variable. TMA may present systematically as hemolytic uremic syndrome (HUS) with the classic findings of renal failure, hemolytic anemia, schistocytes and thrombocytopenia or may be localized in the allograft only with worsening of renal function or delayed graft function (DGF) but few or no systemic manifestations of HUS. It is not known whether patients with localized or systemic TMA have different characteristics and clinical courses. The optimal management of post-transplantation TMA also remains controversial.

HUS and thrombotic thrombocytopenic purpura (TTP) are in fact a single entity[2]. They are two different expressions of the same disease and this is consistent with the reports of familial cases that, despite the same genetic abnormality were classified as HUS or TTP in different members of the same family[3]. More convincing are the reports of different episodes of recurrent disease in the same patient that were in some occasions defined as HUS and in others as TTP in spite the fact that they were associated with the same genetic defect[4]. *The term HUS tends to be preferred in children with renal insufficiency* and *the term TTP in adults with predominantly neurologic involvement*. However, some evidence suggests that the two entities may be distinguished based upon the presence and/or activity of the von Willebrand factor cleaving protease (ADAMST13).

HUS is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal failure. It affects 1 in 100,000 adults and leads to end stage renal failure (ESRF) in 50% of them. In children the average frequency is 2 every 100,000, with peak incidence in Argentina (20 in 100,000). The prognosis in children is much better with only 2% to 4% of them progressing in ESRF in Western Countries[5-7]. The prognosis difference of HUS between adult and children is mainly due to the largely benign Shiga – toxin (STX) – associated HUS that affects children in almost 80% of cases while in adults the incidence is only 5%.

Pathogenetically, the activation of microvascular endothelium leads to endothelium–blood cell interaction and platelet thrombosis and furthermore to occlusion of capillaries and small vessels of target organ.

Classification of post-transplant HUS

HUS after kidney transplantation appears to affect an increasing number of patients. The frequency of HUS

Table 1. *Causes of thrombotic microangiopathy*

Shiga toxin – associated HUS
E. Coli
S. dysenteriae
Non – Shiga toxin associated HUS/TTP
Familial relapsing
Genetically determined
Neuroaminidase – associated
Sporadic, idiopathic
Secondary
Pregnancy
TTP
Severe pre – eclampsia/HELL Syndrome
Post partum HUS
Transplantation
Drugs
Cancer
HIV infection
Systemic diseases
Antiphospholipid syndrome
Malignant hypertension
SLE, Scleroderma

is higher in transplant patients compared to general population. After transplantation, HUS may be characterized recurrent or de novo HUS (Table 2).

Recurrent HUS

The first case of recurrent HUS was reported in 1976. Since then an extremely variable rate of recurrence ranging from 9% to 54% has been reported in different series[8]. Differentiation of recurrent HUS from other conditions largely accounts for these findings. A recent meta–analysis showed that the recurrence rate is 27%[8]. Older age at onset of HUS, shorter mean interval between HUS and transplantation or ESRD, living related transplant and treatment with calcinurin inhibitors have been associated with an increased risk of recurrence. Conceivably, older age at onset and faster progression to ESRD both reflect non-STX – associated HUS, whereas the increased risk associated with living related transplantation most likely disclosed a genetic (familial) predisposition to the disease. Later on, it was suggested that the progression to ESRD was associated with the type of HUS and not the patient age.

Recurrent disease occurs in most patients with familial HUS which is usually due to mutations in the gene for complement factor H[9] and the gene for complement factor I[10,11]. Recurrence is independent of the source of the transplant (CD or LD) or the immunosuppressive regimen[12]. Reports of children with end stage renal disease who underwent continued kidney and liver transplantation, the latter to normalize factor H concentration and function are not encouraging [13,14]. Patients with mutations in the gene for membrane cofactor protein (MCP), a membrane protein highly expressed in the kidney have successful transplantations with no disease recurrence[15,16].

Today we know that STX-associated HUS does not recur after transplantation (0.8% recurrence in children)[17]. There is evidence that anti-STX-neutralizing antibodies persist over the long term in the circulation of these patients and render extremely unlikely the possibility of HUS recurrence[18]. Even adult patients with STX–related HUS are virtually without risk of post-transplant recurrence.

Non-STX HUS presents a substantial risk of recurrence and graft loss after renal transplantation both in children and in adults. Children present a recurrence rate ranging from 50% to 90%[19-21]. In all series the most recurrences occurred within the first two months after transplantation. Graft outcome was poor with graft loss occurring two or three weeks after HUS recurrence and ranging from 80% to 90%. In adults, recurrence of non-STX HUS is frequent and happens early after transplantation. The risk of recurrence is lower in patients with pre-transplant bilateral nephrectomy compared to non-nephrectomized patients[21]. Overall graft success may be diminished in patients with recurrent HUS, the one and five year graft survival estimated to be 33% and 19% respectively in one series compared to 57% for patients without recurrent HUS. The outcome of recurring HUS after transplantation is worse in familial forms of HUS leading invariably to graft loss and for this reason doctors should discourage the use of living related donors in this setting.

Screening for complement factor H, factor I and membrane cofactor protein genotype could be useful in patients with ESRD due to no-STX HUS who wish to have a kidney transplant.

Management

Prophylaxis: The use of low dose aspirin and dipyridamole has been reported after transplantation with inconsistent results[22,23]. CsA and antilymphocyte globulin should be used with caution. Heavy inadequacy of the specific protease cleaving the vWillebrand factor must be treated with FFP infusion every 15 days after kidney transplantation[17,24]. Landau has proposed high dose FFP infusion in patients with Factor H deficiency to prevent

Table 2. *Causes of HUS after kidney transplantation*

Recurrent HUS
Shiga toxin related HUS
Non – Shiga toxin HUS
Genetically determined
Non – genetically determined
De novo HUS
Viruses: Influenza, Parvovirus B19, Cytomegalovirus
Drugs: CsA, Tacrolimus, OKT3, ATG, Rapamycin, Everolimus
Anticardiolipin antibodies in HCV + recipients
Acute rejection

post-transplant HUS in children[25] but it is uncertain if this approach has any success.

Treatment: It consists of plasma exchange with FFP or FFP infusion with reduction or discontinuation of cyclosporine at the first sign of recurrence with limited success[22,26-28]. Fulminant recurrence of haemolytic uremic syndrome has been noticed in children during a CNI free immunosuppression [29]. Nephrectomy of native kidneys has been performed with limited success. Combined kidney – liver transplantation has been performed in cases with factor H with discouraging results.

De novo postransplant HUS

De novo HUS is not a rare complication after kidney transplantation and frequently is associated with CNI / mTOR inhibitor toxicity or acute vascular rejection.

Viral infections

Influenza A viruses[30], parvoviruses and cytomegalovirus have been implicated in the pathogenesis of de novo HUS. Parvoviruses can infect the endothelial cell through a specific binding to the P-antigen on the cell surface. The consequent endothelial injury can then sustain the microangiopathic process. Similar mechanisms have been involved in the setting of infection with cytomegalovirus, which, in addition to directly damaging the endothelial cells, can sustain the platelet adhesion to the microvascular wall by inducing the expression of adhesion molecules and the release of vWF[31-33].

Anticardiolipinic antibodies and de novo HUS

Patients with hepatitis C and anticardiolipinic antibodies may present HUS after kidney transplantation[34]

Use of calcinurin inhibitors

Association of CsA with HUS was reported initially in bone marrow transplantation (BMT), later in liver transplantation and finally in kidney and heart transplantation[35]. Today treatment with calcinurin inhibitors is a well-established risk factor for the development of de novo TMA[36].

The frequency after kidney transplantation was higher in patients treated with Neoral and its increased bioavailability. The use of tacrolimus (FK506) in kidney transplantation was accompanied by reports of its successful use in transplant recipient with CsA-associated HUS. Later on it was proved that tacrolimus could induce HUS after renal transplantation[37].

Both CsA and tacrolimus – associated HUS can present with a spectrum of clinical signs ranging from variable degrees of haematologic or renal abnormalities to the full blown pentad of microangiopathic haemolytic anaemia, thrombocytopenia, neurological signs, fever and renal failure. The haematological changes can precede or follow the signs of target organ dysfunction that occasionally can be the only sign of the disease.

The diagnosis of HUS due to CsA or tacrolimus can be done on the basis of graft biopsies performed to determine the cause of delayed graft function or to rule out acute allograft rejection. Every organ may present vascular lesions due to CsA or tacrolimus HUS. Pulmonary, dermatologic, musculoskeletal, hepatic and gastrointestinal involvement has been described in CsA – associated HUS[34].

The pathogenesis of calcinurin inhibitors associated HUS is not completely understood. They cause endothelial injury and reduction of both prostacyclin synthesis and the prostacyclin to thromboxane A2 ratio. These changes lead to vasoconstriction, platelet aggregation and thrombus formation[38,39]. Calcinurin inhibitors have direct and indirect preglomerular constricting properties, the latter through a stimulatory effect on endothelin secretion[40], which cause increased vascular sear stress, abnormal vWF fragmentation and platelet activation and further amplification of the microangiopathic process.

A recent analysis of the United States Renal Data System (USRDS) and Medicare claims identified multiple additional risk factors including younger recipient age, female gender of the recipient, longer duration of dialysis before transplantation, previous renal transplant, delayed graft function, allograft rejection, increased peak panel – reactive antibody and treatment with sirolimus[41].

Use of mTOR inhibitors

Initially it was thought that sirolimus (rapamycin, SRL) did not induce HUS and would be a solution to the problem of patients with HUS due to CsA or FK506. Recently it has been reported de novo HUS after rapamycin use[42]. Recent evidence suggests that treatment with SRL may be followed by the development of TMA. First, TMA has been noticed in patients on protocols containing SRL in conjunction with CNIs[43,44]. Secondly, a recent analysis of the USRDS identified SRL use post-transplantation as a risk factor for TMA[41] at least at the same level as CsA. Thirdly, there are recent reports describing patients who developed TMA on a regimen containing SRL in the absence of CNIs[41,45]. Recently, it was estimated that the relative risk of developing TMA after kidney transplantation is 16.1 (incidence 20.7%) for the combination of CsA+SRL and 4.7 (incidence 6.1%) for FK+SRL[46].

The pathomechanism by which sirolimus causes de novo HUS is obscure. A working hypothesis is that SRL acts to inhibit endothelial cell proliferation[47]. In the transplant setting endothelial cell may be injured by a variety o mechanisms including direct drug toxicity, infection, immune processes or OKT3 use. In response to injury endothelial cell may be repopulated by recipient derived endothelial cells[48]. The antiproliferative effect of SRL may prevent repopulation of the allograft vasculature by reparative endothelial proliferation, thereby promoting local activation of the clotting cascade, consumption of platelets and red blood cell destruction. This hypothesis is supported by the observation that the majority of de novo TMA is renal-limited. SRL has also been shown

to cause platelet aggregation[49] thus providing another potential mechanism by which SRL could promote TMA. Another scenario is the clotting of vasculature in cases of reperfusion injury or acute rejection because of high expression of tissue factor in patients taking SRL[50].

Antibodies

OKT3 antibodies administration has been shown to cause HUS rarely. This complication is most likely to occur with high-dose OKT3 (10 mg/d than the current dose of 5 mg/d). The pathogenesis of OKT3-HUS is due to a four-fold to six-fold increase of prothrombin activity, complement activation and increased TNF-a release[51,52].

Antibodies against the von Willebrant factor-cleaving metalloprotease DAMTS13 are responsible for most cases of idiopathic TTP[53].

Acute rejection and HUS

The procedure of rejection with its detrimental effect on endothelium could be a triggering factor to TMA in patients predisposed to develop HUS. Some investigators have suggested an association of acute vascular rejection with HUS[54]. Patients with HUS as primary renal disease present more and heavier rejection episodes compared to patients without HUS and higher frequency of CAN has been reported in patients with HUS as primary renal disease who did not develop HUS after kidney transplantation. In fact this relationship, if there is any, has to be clarified in the future.

HUS is the result of a primary non-inflammatory toxic lesion of the endothelium followed by a secondary local intravascular coagulation, fibrin formation and platelet activation. On the other hand acute vascular rejection is the result of an inflammatory reaction of the immune system due to complement classical pathway activation and antibody action. Recent evidence suggests that the only clue for differential diagnosis is C4d deposits in the peritubular capillaries in cases of acute vascular rejection[55]. Follow up biopsies would be informative in patients who have been treated successfully for HUS.

Clinical Picture

The clinical picture of post – transplant HUS is obscure. Anemia is usually mild and thrombocytopenia is reported in no more than 50% of patients. Renal dysfunction can be the only non – specific sign of post – transplant HUS. However, since concomitant complications such as acute rejection, CsA or tacrolimus nephrotoxicity or cytomegalovirus infection can confound the clinical picture, the definite diagnosis almost invariably rests on biopsy findings[56]. Typical changes include glomerular and arterial thrombosis, endothelial cell swelling and detachment from the basement membrane, glomerular ischemia and in the healing phase, onion skin hypertrophy of the arteriolar walls. These changes, however, can reflect an acute vascular rejection that should always be considered in the differential diagnosis with HUS, in particular when tubulitis and interstitial infiltration are accompanied by severe endovasculitic lessons affecting the entire vascular tree of the graft[36].

Patients with parvovirus infection may present fever, fatigue, athralgia, aplastic anemia and thrombocytopenia followed by deterioration of renal function

Management

Treatment of post-transplant HUS rests on removal of the inciting factor, relief of symptoms and plasma infusion or exchange. Drug withdrawal is first line therapy for de-novo CsA or FK506 associated HUS but is effective in less than 50% of cases. A significantly higher success rate has been reported with drug withdrawal plus plasma infusion or exchange[26,58]. In adults the suggested dose of FFP is 20 mg/kg/d initially every day and later every second day according to the evolution of haemolysis, thrombocytopenia and decrease in serum creatinine level[58]. In cases with anuria, cardiac overload or hypertension, plasma exchange was given every 48 hours between hemodialysis sessions and 2 lt of plasma volume was exchanged with 1200-600 ml FFP + 500 ml albumin or macromolecular solutions[58].

Plasma exchange has been suggested as a first line therapy in heavy cases and as secondary in cases with no response to treatment with FFP infusion. It has been reported the use of steroids (1 mg/kg/d) as well as the use of anti-platelet agents concomitantly with the plasma exchange. A similar response has been noticed with intravenous infusion of IgG (0.4 g/kg) alone or in combination with plasma exchange. The rational of this therapy is the neutralization of circulating cytotoxic or platelet agglutinating factors[33].

After remission is achieved it is better to switch from one drug to another or treat with mycophenolate mofetil[59,60]. Monoclonal anti IL-2 receptor antibodies also can be a valid option for maintaining adequate immunosuppression and avoiding the toxic effects of calcinurin inhibitors. The outcome of de novo forms occurring in the setting of viral infection parallels the response to treatment of the underlying disease[30,31,33].

In spite of the above, we must have in mind that the complication rate of plasma exchange may be as high as 30% some of which may be fatal[61]. Patients with localized TMA respond to decreasing, changing or temporarily discontinuing NCIs and do not routinely require plasma exchange for graft salvage[1].

Having in mind these data, renal transplantation should be considered an effective and safe treatment of ESRD for patients with STX-associated HUS[17,55,62] and patients who lost the first kidney graft for recurrence should not receive another transplant. Living related renal transplant in familial forms should be avoided because it has the risk, among the others, to precipitate the disease onset on the donor[63].

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