Hassan Hussein
Dr.med

Complement activation during acute graft rejection after renal transplantation

Geboren am 27.11.1967 in kamichli/ Syrien
Studiengang der Fachrichtung Medizin von 1984 bis 1992
Staatsexamen am 22.04.1992 an der Universität Tishreen/ Lattakia/ Syrien

Promotionfach: Immunologie
Doktorvater: Prof. Dr.med. vet. M. Kirschfink

Complement has been implicated in various forms of renal tissue damage, including nephritis and renal transplantation rejection. Complement activation is induced after binding of antibodies to renal tissue, but may also occur in non-immunological situations such as ischemia/ reperfusion. There is increasing evidence that complement plays a role not only in hyperacute but also in acute renal graft rejection. Previous clinical studies observed substantial deposits of various complement components in renal allografts tissues during rejection process. Other studies demonstrated the elevation of complement activation products in the circulation of patients with renal rejection.
Aim of the current study was to investigate a possible correlation of complement activation with the development of acute rejection after renal transplantation and to evaluate complement as a new diagnostic parameter that may be useful to detect patients at risk for graft rejection.
In collaboration with the Department of Urology at the Clinic of Surgery, University of Heidelberg Medical School, 316 patients undergoing renal transplantation between 1995 and 1998 were included in the study. 30 patients were diagnosed to have experienced an acute renal graft rejection. 30 patients with stable graft function during one month period post-transplantation were taken as control group. From each patient EDTA-

plasma and urine were collected every 3-4 days and stored at –70 °C for complement analysis. Complement measurements were performed in plasma by using sandwich ELISAs for C1rsC1inh complex (classical pathway), C3b(Bb)P complex (alternative pathway), SC5b-9 (terminal sequence) and factor D. In addition, complement activation products C3a and C4d were quantified by two commercially available ELISA. C3a and SC5b-9 were also measured in urine.

A possible pathogenic role of complement activation in renal allograft rejection is evidenced by three remarkable results presented:

-Plasma levels of C1rsC1inh, C3a and factor D posttransplantation and during rejection crisis were clearly higher in patients with acute rejection than in those with stable graft function at corresponding time points.

-In patients with biopsy-proven rejection, plasma levels of all investigated complement parameters were elevated (above the normal levels of healthy controls) from the early days after transplantation until the end of monitoring period.

-Plasma levels of C1rsC1inh, C3a and factor D were significantly different ($p< 0.05$) between time points before and after the clinical recognition of rejection. While C1rsC1inh and factor D rose already 5-8 days before rejection, C3a increased close to the date of rejection (1-4 days before rejection). In contrast to the rejection group, corresponding values of patients with stable graft function did not show any considerable variations.

Measurements of complement activation markers appear to correlate with some complications often associated with kidney transplantation. All investigated complement parameters in both groups of patients showed high levels early after transplantation interpreted to be due to ischemia/ reperfusion injury. Only factor D of patients with stable graft function correlated with impaired renal function, as judged from creatinine analysis.

Analysing each parameter for different cut-off levels and considering the ROC curves, high diagnostic values of C1rsC1inh were observed for cut-off level of 300 U/ml (sensitivity=78%, specificity=73%), and of C3a for a cut-off level of 300 ng/ml (sensitivity=73%, specificity=65%) during acute renal rejection. Our data also confirm that creatinine still represents a reliable parameter in detecting acute renal rejection, with a sensitivity of 71 % and a high specificity of 78% for cut-off value 2.5 mg/dl.

Finally, the results of the present study clearly implicate complement in the pathogenesis of acute renal allograft rejection. Elevation of plasma concentrations of C1rsC1inh, C4d, C3a and factor D, with differences in time of appearance, reflects involvement of both the classical and alternative pathways of complement. With respect to the kinetics of the complement cascade reaction and the accelerated turnover of complement components, short intervals between the determinations seem to be essential to confirm these results. Because of the restricted number of patients included in this retrospective study, larger studies are needed to confirm the value of complement activation products in early recognition of patients at risk for acute rejection.