mechanical stimuli: cyclooxygenase-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up-regulated by steady laminar shear stress. Proc Natl Acad Sci USA 1996; 93: 10417–10422

33. Howard AB, Alexander RW, Nerem RM, Griendling KK.

Goodpasture syndrome and end-stage renal failure — to transplant or not to transplant?

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Although an unusual condition, its association with serious morbidity and mortality confers upon this disease an importance greater than its incidence alone would allow. ... While nephrologists will continue to be satisfied by the immunopathogenetic precision of this disease, they remain challenged by the immediacy of diagnosis and the treatment it demands.

Daly et al., 1996 [1]

Introduction

Goodpasture syndrome is the most common manifestation (60%) of human anti-basement membrane diseases, characterized by the presence of autoantibodies that predominantly recognize the non-collagenous (NC1) domain of the alpha 3 chain of basement membrane (type IV) collagen. The clinical manifestation of Goodpasture syndrome is a rapidly progressive glomerulonephritis and pulmonary haemorrhage, but anti-basement membrane disease can also occur as glomerulonephritis without lung involvement (35%), or as isolated pulmonary haemorrhage (<5%). For reasons summarized in the citation above, Goodpasture syndrome, despite its low incidence, has drawn widespread attention over almost 80 years of research history.

Pathogenesis

The cause of the disease is unknown. Smoking, inhalation of gasoline or other hydrocarbon fumes, as well as viral respiratory infections have been implicated to promote the disease by causing injury to the basement membrane where the antigenic epitope resides in the type IV collagen network. It seems possible that increased quantities of the cryptic epitope thus become exposed to the immune system, triggering an autoimmune response. The disease association with HLA DR2 and DR4 haplotypes implies a genetic susceptibility [2]. There is evidence of T-cell involvement in the autoimmune response, as NC1-specific CD4 and CD8 T cells have been isolated from patients in early and late phases of Goodpasture syndrome, respectively [3,4]. The autoantibodies are predominantly of the IgG1 subtype, and in active disease they may represent up to 1% of total serum IgG [5]. Antibody deposition in the basement membrane is often, but not always accompanied by complement, promoting autoimmune inflammatory damage in those regions where alpha 3 (IV) is expressed and accessible. Serum antibody titres correlate with active disease, but not necessarily with the degree of inflammatory tissue damage and impairment of renal function, or the severity of lung hemorrhage.

Course and prognosis

If left untreated, the course of Goodpasture syndrome is usually fatal. Since the 1970s, a combined therapy with plasmapheresis and immunosuppression has led to a much improved survival. The pulmonary complications usually resolve and do not have much impact on long-term pulmonary function [6]. However, the glomerulonephritis results in terminal renal failure in ~70%. The renal outcome can be predicted from the serum creatinine and the fraction of glomeruli with crescents at the time of presentation [1,7,8]. Patients with creatinine values > 600 μmol/l or > 50% crescents at renal biopsy can rarely be expected to retain independent renal function. Early diagnosis and immediate institution of therapy are the only way to improve the dismal renal outcome in Goodpasture syndrome.
Nevertheless, treatment for isolated kidney disease should be instituted only if there is a reasonable chance for the recovery of renal function. The natural course of the disease seems to be self-limited and non-remitting in the vast majority of cases. The autoantibodies have been found to disappear spontaneously after ~1 year. In ~5% of the cases, relapses of systemic disease with pulmonary haemorrhage more frequently than glomerulonephritis have been described, sometimes occurring as late as 5 or more years after the initial disease manifestation. Cigarette smoking, and respiratory viral or bacterial infection have been postulated as risk factors. As recurrence is closely associated with anti-GBM antibody levels, determination of autoantibodies should be used to monitor suspected cases [9].

Treatment

The early concept of pre-transplantation bilateral nephrectomy as a means to reduce antibody production and the risk of disease recurrence has been abandoned in the 1980s. A recent retrospective study clearly demonstrated the practice to be of no benefit [10]. Today, treatment is based on combined plasmapheresis and immunosuppression. Plasmapheresis and steroids have proven especially effective in controlling pulmonary haemorrhage, the former serving to rapidly eliminate circulating autoantibodies [11]. Combined therapy with prednisone and cyclophosphamide suppresses further autoantibody formation. With this treatment, antibody titres usually decrease rapidly and are at or below detection limit after a median time of 2 months [8]. In general, it appears to be prudent clinical practice to discontinue immunosuppressive therapy no earlier than 3 months after anti-GBM antibody titres have become undetectable. Persistently negative antibody titres indicate remission.

Transplantation

Since the patients are usually young, a major fraction of them will eventually be eligible for renal transplantation. In the current EDTA–ERA registry report for 1982–1990, 0.47% of all renal transplantations were performed in Goodpasture patients. Given the immunological basis of the disease, transplantation of a kidney and subsequent activation of the immune system raise some important questions which are discussed below.

Time point

A majority of studies, though uncontrolled, show improved outcome and decreased risk of recurrence if transplantation is performed after autoantibodies have become undetectable. It is therefore recommended practice to delay transplantation for 9–12 months after antibody production has ceased.

Recurrence in the graft

The recurrence rate of the original disease in the graft is low, although not negligible. Reports from the 1970s had noted a recurrence rate of >30%, which has decreased to <5% in the 1990s (range 0–12%) [1,12–17]. This is probably due to improved immunosuppressive therapy regimes, as well as the delay of transplantation until autoantibody production has ceased. Not every recurrence of autoantibodies leads to glomerulonephritis and subsequent graft loss; in fact, graft loss seems to occur in about half of the published cases. It has been suggested that the isoform of recurrent autoantibodies is of crucial importance, with IgG1 (but not IgG4) fixing complement and binding macrophages, thereby causing further inflammatory damage and glomerulonephritis in the graft [18]. On the other hand, complement fixation has been observed only in 2/3 of primary disease cases, and histology of C3-positive and C3-negative cases does not differ significantly [19], indicating the existence of other pathways to induce tissue damage. These mechanisms deserve further investigation.

Overall outcome in the registry

The registry report confirms the rather good outcome of transplantations in Goodpasture patients in comparison to other causes of end-stage renal disease. This is in line with more recent reports in the literature. There is, however, a trend towards lower graft survival in the registry data. Among the reasons for graft failure, recurrence of the underlying disease accounts for 14%, corresponding to a total incidence of post-transplant recurrence of 2.6%. The proportion of recurrent antibodies without graft loss is not known, but even if it were twice as high, the numbers would be well in the range reported in the literature.

Immunosuppression

It is conceivable that form and dosage of immunosuppressive therapy play important roles in controlling the underlying disease and relapses in the graft. For instance, discontinuation of immunosuppressive treatment for various reasons has been associated with subsequent relapses. Interestingly, relapses seem to be rare under immunosuppression with cyclosporine, which has also been used successfully to treat otherwise refractory Goodpasture syndrome prior to transplantation [20]. Cyclosporine may therefore have some advantages in preventing the reactivation of this T cell and B cell-dependent disease. In view of these observations, cyclosporine may deserve further attention in the immunosuppressive therapy of Goodpasture syndrome.

Conclusion

The delay of transplantation until antibody production has ceased, as well as improved immunosuppressive...
therapies have increased the rate of successful transplantations in Goodpasture syndrome. Although there are no controlled studies, accumulated knowledge today indicates that the outcome of kidney transplantation in patients with Goodpasture syndrome is as good as in other causes of end-stage renal disease. The challenge will always be to identify the rare relapses early enough to save the graft by using adequate treatment. Screening for autoantibodies to type IV collagen NC1 with modern ELISAs based on highly purified native or recombinant antigen provide adequate means to do so. In suspected cases, one should not hesitate to perform a graft biopsy in order to verify tissue damage and glomerulonephritis. Intensified immunosuppressive therapy with cyclophosphamide and possibly plasmapheresis is usually sufficient to control relapses.

References

Why are mutations in COL4A5 not detectable in all patients with Alport's syndrome?

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Alport's syndrome is an inherited nephritis which causes chronic renal failure, high-tone sensorineural deafness, characteristic eye signs (anterior lenticonus and macular flecks), and is associated with characteristic abnormalities of the glomerular basement membrane when a renal biopsy is viewed under the electron microscope [1]. Until about 10 years ago, the eponym was used rather widely for a variety of inherited nephritides, which meant that genetic analysis of this clinically heterogeneous group of families was difficult. Once clear clinical diagnostic criteria were described [2], a much more homogeneous group of families was