

ABNORMAL IMMUNE RESPONSE IN PATIENTS WITH MINIMAL CHANGE NEPHROPATHY IN REMISSION

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Summary

The immune response was studied in 18 patients with minimal change nephropathy in remission for two to 10 years (mean 5.6 years). The patients' antibody responses to dinitrophenyl-Ficoll (DNP), keyhole-limpet haemocyanin (KLH), and delayed cutaneous hypersensitivity to KLH were significantly reduced compared to normal subjects. These findings show that there is a generalized impairment of the immune response extending to T-independent, T-dependent humoral and cell mediated mechanisms in minimal change nephropathy in remission. Although these patients may be clinically normal, abnormalities of the immune system, demonstrable when in relapse, clearly persist into remission. If these abnormalities are not an epiphenomenon, then any explanation for the pathogenesis of minimal change nephropathy must take account of the abnormalities found in remission.

Introduction

Among the many abnormalities of the immune system found in minimal change nephropathy are hypoglobulinaemia [1-3], a diminished antibody titre to common bacterial antigens [4,5] and, in some instances, a diminished antibody response following immunization [6]. The hypoglobulinaemia in minimal change nephropathy in relapse is characterized by low serum concentrations of IgG, which may continue low in remission, but increased serum concentrations of IgM and IgE which may continue raised in remission [1,2]. Proteinuria alone does not account for the hypogammaglobulinaemia, and in vitro studies of immunoglobulin production by cell cultures from patients with minimal change nephropathy have shown depressed IgG synthesis, indicating that in vivo abnormal synthesis and possibly catabolism of IgG is occurring [7]. Sera from patients in relapse have shown diminished antibody titres to pneumococcal and streptococcal antigens, whereas immunization of patients with minimal change nephropathy using *Strep pneumoniae* has been reported to produce either impaired or normal responses [4,5,8,9].

Although patients become clinically normal when minimal change nephropathy remits, certain abnormalities of the immune response persist into remission, in particular the low serum concentrations of IgG and the raised serum concentrations of IgM, and depressed antibody titres to streptococcal antigens [5].

We therefore studied the immune response to patients with minimal change nephropathy in remission to known T-dependent and T-independent antigens, examining both humoral and cell-mediated immunity.

Patients and methods

Patients Eighteen patients were studied. All had had minimal change nephropathy proven histologically and/or a steroid-responsive nephrotic syndrome. Six patients had been treated with prednisolone alone and 12 with prednisolone plus cyclophosphamide. The patients had been in remission for two to 10 years (mean 5.6 years). Sixty-six healthy people of a similar age range were used as controls.

Immunogens Dinitrophenyl-Ficoll (DNP) was given intradermally (0.2mg) and the IgG antibody response was measured on day 0 (i.e. preceding the injection) and on day 14. The antibody was measured by haemagglutination and expressed as the change in reciprocal titres \log_{10} from days 0 to 14.

Keyhole-limpet haemocyanin (KLF) was given intradermally (0.2mg) and the IgG antibody response measured on days 0 and 14 using an ELISA technique and expressed as reciprocal titres \log_{10} . The skin reaction to intradermal KLH on day 14 (10 μ g) was measured on day 16, and recorded simply as positive or negative.

The study received approval from the Ethical Committee of Guy's Hospital.

Results

1. *IgG anti-DNP* The mean change in titres in patients (1.80 \pm 0.11 [SE]) was significantly lower than that of controls (2.44 \pm 0.06 [SE]), $p < 0.001$ (Wilcoxon). All but one of the patients responded.

2. *IgG anti-KLH* Eleven of the 18 patients mounted a response, which was not significantly different to the control population (χ^2). However, the responders in each group made significantly different amounts of antibody: patients 2.14 \pm 0.2, controls 2.67 \pm 0.09 (mean \pm SE), $p < 0.01$ (Wilcoxon).

3. *Delayed hypersensitivity to KLH* Only six of the 18 patients responded positively, compared to 52 of the 66 controls. This was significantly fewer ($p > 0.001$, χ^2).

Discussion

This study shows that patients who have been in remission for several years following minimal change nephropathy have an impaired response to T-dependent

and T-independent antigens. It has been noted previously that serum anti-streptococcal antibody titres are diminished in minimal change nephropathy in remission [5], but this study did not employ a controlled administration of antigen and assessment of the immune response at set time intervals afterwards. Our findings therefore add to the general picture that despite the absence of proteinuria, minimal change nephropathy in remission is accompanied by abnormalities of the immune system, several of which have also been demonstrated to be present during relapse [2,5].

The impaired response to T-dependent and T-independent antigens and the fact that both humoral and cell-mediated immunity were impaired strongly suggest that there is a generalized suppression of immunity in these patients. How this is mediated is not known, but a possible explanation is an abnormality of macrophage function, because of the central role played by this cell in the immune response.

Possible reasons for the impaired immune response in remission are as follows. First, previous treatment with immunosuppressive drugs may have produced long-term effects on the immune system. We have previously shown such an effect by cyclophosphamide on suppressor cell function [10], although other workers, using a different system, were not able to demonstrate long-term effects of this drug. Prednisolone alone is not recorded as having long-term effects in man following cessation, and in the patients we studied there were no differences between patients treated with prednisolone alone or prednisolone and cyclophosphamide. Second, the biochemical abnormalities accompanying the nephrotic syndrome may produce abnormal cell function which is prolonged into remission because the long-lived lymphocytes, which in man have a life span of up to 20 years, do not repair the biochemical insult. Finally, the occurrence of similar abnormalities of the immune response in remission and in relapse suggest that there is a pre-existing abnormality which may predispose to the development of a nephropathy when a suitable insult (e.g. infection or a reaginic reaction, both of which can precipitate minimal change nephropathy) occurs. At present, there is no way of differentiating between these various possibilities.

Do these abnormalities of minimal change nephropathy in relapse or remission throw any light on the pathogenesis of this disorder? Since the abnormalities are common to both proteinuric and non-proteinuric states it is not logical to incriminate them as part of a mechanism leading to proteinuria. If the impaired immune response is anything other than an epiphenomenon, then it could be seen as an expression of an effect of the immune system which is in some way directed against the mechanism(s) responsible for causing proteinuria, i.e. the patients in remission continue so because their 'abnormal' immune system is preventing relapse, while in relapse these self-same 'protective' abnormalities have been overcome or, in the very first episode have not had sufficient time to exert their effect.

References

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