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TONSILLECTOMY DECREASES THE SYNTHESIS OF POLYMERIC IgA BY BLOOD LYMPHOCYTES AND CLINICAL ACTIVITY IN PATIENTS WITH IgA NEPHROPATHY

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Summary

Polymeric IgA seems to play an important role in the pathogenesis of IgA nephropathy. As patients with this disease often present recurrent macrohaematuria following upper respiratory tract infections we undertook tonsillectomy in eight patients. Two years later the percentage of lymphocytes producing polymeric-IgA significantly decreased. Simultaneously the number of episodes of macrohaematuria and the microhaematuria diminished. Since tonsil lymphocytes from these patients produce high amounts of polymeric IgA, our results suggest that tonsillectomy may be useful for patients with IgA nephropathy and recurrent macrohaematuria associated with upper respiratory tract infections.

Introduction

Several data suggest that polymeric IgA plays an important role in the pathogenesis of IgA nephropathy. Thus, we have recently described the existence of high levels of polymeric IgA, partially as immune complexes, in the serum and kidneys of patients with IgA nephropathy [1,2], as well as increased rates of polymeric IgA synthesis after polyclonal stimulation in vitro by circulating [3] and by tonsillar lymphoid cells [4]. Since these patients often present macroscopic haematuria following upper respiratory tract infections, the mucosal origin of the IgA deposited in the kidney has been suspected.

Recently we have observed that patients with episodes of macroscopic haematuria present a larger percentage of polymeric IgA-secreting peripheral lymphocytes, after polyclonal stimulation, than patients without these episodes. These facts suggested the tonsils as an important place in the synthesis of polymeric IgA.

As there is a diminution of serum IgA in some normal tonsillectomized subjects and that some authors advise tonsillectomy in patients with IgA nephropathy [5], we decided to study whether this surgical approach produces significant

changes in the synthesis of polymeric IgA by blood lymphocytes and on the immune regulation of IgA, as well as on the clinical activity of this disease.

Material and methods

Eight patients with IgA nephropathy (5 males and 3 females, mean age 18.7± 10) were selected for tonsillectomy due to their high frequency of episodes of haematuria following upper respiratory tract infections. Control group included 21 subjects undergoing routine tonsillectomy, sex and age matched as far as possible with the patients.

Clinical evaluation and urine examination for proteinuria and haematuria, as well as immunological studies, were performed before tonsillectomy and one to two years after the surgical intervention. No patient had upper respiratory tract infections or macroscopic haematuria, three and six months respectively before tonsillectomy.

Peripheral mononuclear cell suspensions were obtained from 100ml of fresh heparinized blood by standard Hypaque-Ficoll gradient centrifugation (Hucoa-Erloss) using the conditions previously published [6]. T cell and B cell fractions were isolated by the rosetting technique of neuraminidase treated erythrocytes. T cell subpopulations were identified in the mononuclear cells by using specific monoclonal antibodies (Ortho). Immunoglobulins bearing lymphocytes were measured by immunobead solid-phase method (Biorad). T and B cells with Fc receptors for IgA (Tα and Bα) were measured by rosetting with Affigel beads treated with IgA (Biorad).

Lymphocytes at $2x10^2$ cells/ml were incubated in the presence or absence of 10μl/ml of Pokeweed mitogen (PWM) for seven days. In other experiments different doses of Concanavalin A (Con A) were added as previously published [4]. At the end of the culture, immunoglobulin synthesis was measured by ELISA assay and polymeric IgA-synthesizing cells were detected by immunofluorescence based upon the affinity of the secretory component for polymeric IgA.

Results

Two years after tonsillectomy the following results were seen: a significant decrease in the incidence of pharyngitis and macrohaematuria per year in relation to a similar period of time before tonsillectomy and in relation to the evolution of the parameters in patients not treated (Figure 1). We also observed improvement in proteinuria and microhaematuria. The eight patients studied presented before tonsillectomy significantly high percentages of the polymeric IgA-secreting peripheral lymphocytes, diminishing after the surgical procedure to the normal levels (Figure 2). In the same way the percentage of Tα cells before tonsillectomy (14.7±2) decreased significantly after tonsillectomy (10.8± 2; $p<0.005$). There were no changes in serum IgA except for those patients with more than 400mg/dl of serum IgA (n=4) in which it decreased in a significant manner. No changes were noted in the spontaneous and PWM-stimulated

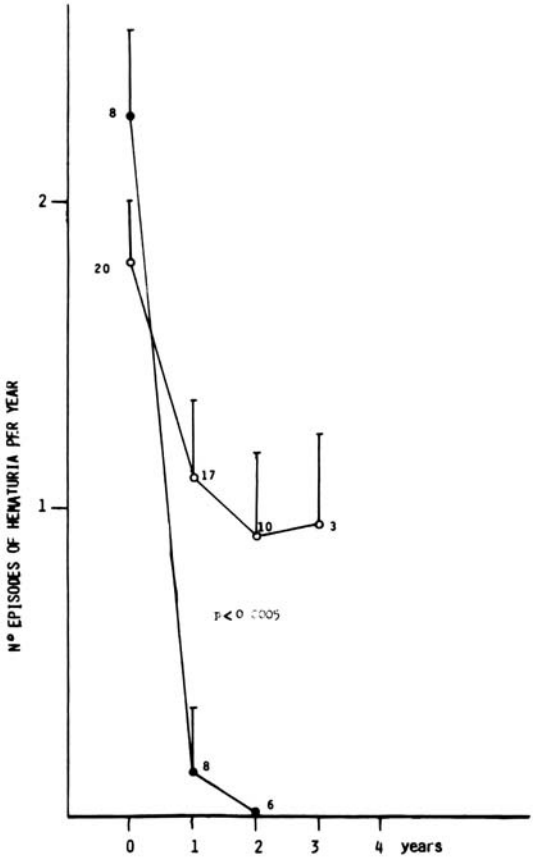

Figure 1. Number of episodes of haematuria per year in patients with IgA nephropathy without treatment (○=control patients or ●=with tonsillectomy). Numbers represent patients studied at each period of time

IgA synthesis in vitro by peripheral lymphocytes, and in the percentage of T helper cells (OKT_4^+) (data not shown).

Discussion

The more important data obtained on clinical grounds was the disappearance of bouts of macroscopic haematuria in the eight patients two years after tonsillectomy. Although it is well known that bouts of haematuria decrease spontaneously in a large number of patients with IgA nephropathy, the rate of diminution in tonsillectomized patients was greater than that observed in untreated patients or those treated with phenytoin [7]. Since renal function has been thought to be relatively well preserved for prolonged periods in patients having recurrent episodes of macroscopic haematuria these episodes have been

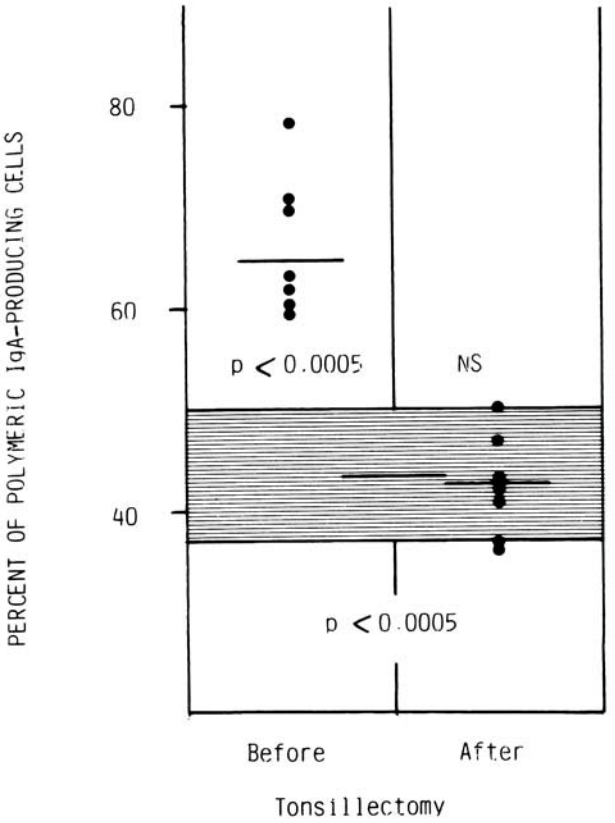

Figure 2. Percentage of polymeric IgA-producing blood lymphocytes in patients with IgA nephropathy before and after tonsillectomy. The shaded area represents mean ± 2 SD

considered to be of little importance. However, recently a striking association of macroscopic haematuria with focal and segmental proliferation, sequential necrosis and their consequences, namely glomerular crescent formation, has been described [8]. In our small series, as in the larger one of Viatel [5], a signficant diminution of microhaematuria and proteinuria was also seen after tonsillectomy.

Several data suggested that polymeric IgA plays an important role in the pathogenesis of IgA nephropathy: 1) the existence of polymeric IgA at mesangial level as shown by the affinity of the immunoglobulin to the secretory component and by the presence of J-chain; 2) the existence of high serum levels of polymeric IgA, probably due to the increased production by blood and tonsil lymphocytes; 3) the presence of polymeric IgA-circulating immune complexes, with a significant correlation with the clinical activity of the disease; 4) the experimental evidence of nephritopathogeneity of these immune complexes containing only polymeric IgA. Tomino et al [9] have demonstrated that the antibodies eluted from renal tissues of patients with IgA nephropathy bind

specifically to the nuclear region of tonsillar cells, suggesting that antibodies to tonsillar antigens might constitute a proportion of the deposited IgA immune complexes. In this context, the finding of a significant decrease of polymeric IgA synthesis by blood lymphocytes two years after tonsillectomy suggests that tonsils could be an important source of this polymeric IgA.

Recent studies from Hoover et al [10] demonstrated that polymeric IgA was able to induce an expansion of Tα cells in vivo as well as in vitro. Then, we can think that the decreased Tα cells after tonsillectomy could be due to the reduction in polymeric IgA. In this sense, we have found a strong correlation between the percentage of polymeric IgA-producing cells and the number of Tα cells, in a large group of patients with IgA nephropathy (in preparation). The absence of effect of tonsillectomy on serum IgA and on the synthesis of IgA by peripheral lymphocytes could be explained, among other reasons, by the fact that polymeric IgA represents only a small proportion of the total IgA.

Although the number of patients studied is small, the recent observation that lymphocytes from patients with IgA nephropathy, having episodes of macroscopic haematuria, produce more polymeric IgA than those without these bouts, suggests that tonsillectomy could be indicated in this group of subjects. If the pathogenetic role of polymeric IgA is further sustained in the next years, manoeuvres directed to decrease the serum levels of this immunoglobulin, including tonsillectomy, should be considered.

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